Тератогенез

- Факторы внешней среды (тератогены)
- Вирусы
- Воспаление
- Эндокринные нарушения
- Генетические нарушения

Токсикология развития

Human Developmental Toxicants

Radiation
- Atomic fallout
- Radioiodine
- Therapeutic

Infections
- Cytomegalovirus
- Herpes simplex virus I and II
- Parvovirus B-19 (erythema infectiosum)
- Rubella virus
- Syphilis
- Toxoplasmosis
- Varicella virus
- Venezuelan equine encephalitis virus

Maternal trauma and metabolic imbalances
- Alcoholism
- Amniocentesis, early
- Chorionic villus sampling (before day 60)
- Cretinism
- Diabetes
- Folic acid deficiency
- Hyperthermia
- Phenylketonuria
- Rheumatic disease and congenital heart block
- Sjogren's syndrome
- Virilizing tumors

Drugs and chemicals
- Aminoglycosides
- Androgenic hormones
- Angiotensin converting enzyme inhibitors: captopril, enalapril
- Angiotensin receptor antagonists: sartans
- Anticonvulsants: Diphenylhydantoin, trimethadione, valproic acid, carbamazepine
- Busulfan
- Carbon monoxide
- Chlorambucil
- Cocaine
- Coumarins
- Cyclophosphamide
- Cytarabine
- Diethylstilbestrol
- Danazol
- Ergotamine
- Ethanol
- Ethylene oxide
- Fluconazole
- Folate antagonists: aminopterin, methotrexate
- Iodides
- Lead
- Lithium
- Mercury, organic
- Methimazole
- Methylene blue
- Misoprostal
- Penicillamine
- Polychlorobiphenyls
- Quinine (high dose)
- Retinoids: Accutane, isotretinoin, etretinate, acitretin
- Tetracyclines
- Thalidomide
- Tobacco smoke
- Toluene
- Vitamin A (high dose)

Время развития дефектов (дни)

	RAT	RABBIT	MONKEY	HUMAN
Blastocyst formation	3–5	2.6–6	4–9	4–6
Implantation	5–6	6	9	6–7
Organogenesis	6–17	6–18	20–45	21–56
Primitive streak	9	6.5	18–20	16–18
Neural plate	9.5	—	19–21	18–20
First somite	10	—	—	20–21
First branchial arch	10	—	—	20
First heartbeat	10.2	—	—	22
10 Somites	10–11	9	23–24	25–26
Upper limb buds	10.5	10.5	25–26	29–30
Lower limb buds	11.2	11	26–27	31–32
Testes differentiation	14.5	20	—	43
Heart septation	15.5	—	—	46–47
Palate closure	16–17	19–20	45–47	56–58
Urethral groove closed in male	—	—	—	90
Length of gestation	21–22	31–34	166	267

*Developmental ages are days of gestation

Принципы тератологии

Wilson's General Principles of Teratology

I.	Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this interacts with adverse environmental factors.
II.	Susceptibility to teratogenesis varies with the developmental stage at the time of exposure to an adverse influence.
III.	Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate sequences of abnormal developmental events (pathogenesis).
IV.	The access of adverse influences to developing tissues depends on the nature of the influence (agent).
V.	The four manifestations of deviant development are death, malformation, growth retardation, and functional deficit.
VI.	Manifestations of deviant development increase in frequency and degree as dosage increases, from the no effect to the totally lethal level.

Лекарства с тератогенным эффектом

Drug	Maternal condition	Most susceptible period, post conception	Nature of adverse effect
ACE inhibitors: benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril	Hypertension	Second or third trimester (13th wk–term)	Oligohydramnios, intrauterine growth retardation, neonatal renal failure, hypotension, pulmonary hypoplasia, hypocalvaria, joint contractures, death
Amiodarone	Thyroid disorder	10 wk–term	Neonatal thyroid dysfunction or goitre
Aminopterin (≥ 1–3 mg/d)	Cancer	Organogenesis (18–60 d)	CNS, limb and skeletal defects
Antiepileptic drugs: carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, trimethadione, valproic acid	Epilepsy	Organogenesis (18–60 d)	CNS, cardiac, eye, gastrointestinal and genitourinary defects, facial dysmorphism and digital hypoplasia, growth retardation
Coumarin derivatives: dicumarol, warfarin	Thromboembolic disorders	For CNS defects: unknown; for other defects: second part of first trimester (6–9 wk)	Nasal hypoplasia, stippled epiphyses, vertebral abnormalities, CNS and ocular defects, cutaneous hematomas, intracranial hemorrhage, growth retardation, stillbirth
Cyclophosphamide	Cancer, transplant rejection	Organogenesis (18–60 d)	Skeletal and ocular defects, cleft palate
Danazol (≥ 200 mg/d)	Endometriosis, fibrocystic breast disease, hereditary angioedema	Unknown	Virilization of external genitalia in female fetuses
Diethylstilbestrol (1.5–150 mg/d)	Ovarian insufficiency, postcoital	First and second trimesters (1–24 wk)	Vaginal/cervical carcinoma in females and genital tract abnormalities in males and females

Продолжение

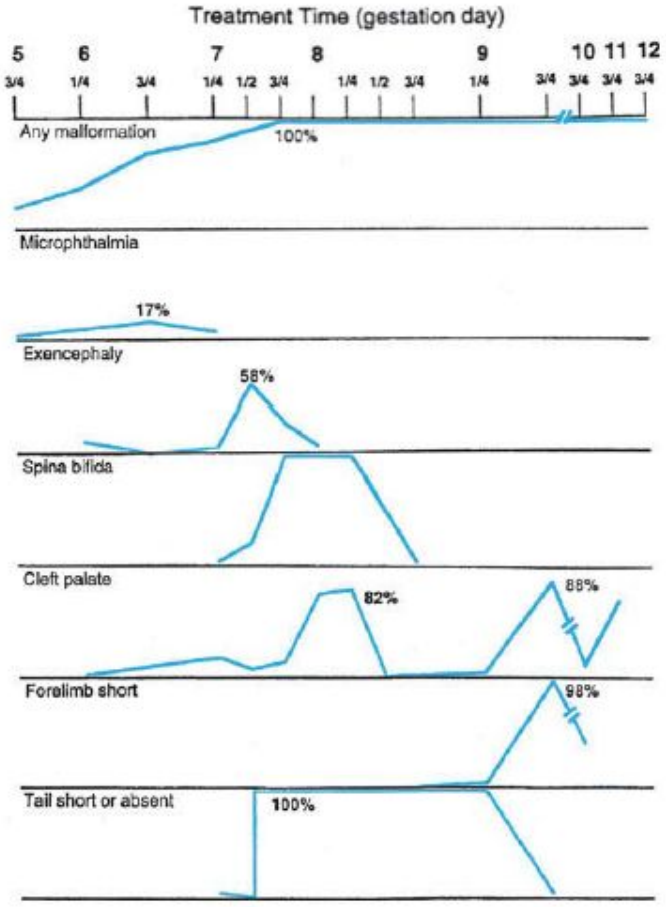
Drug	Maternal condition	Most susceptible period, post conception	Nature of adverse effect
Methotrexate (≥ 12.5 mg/wk)	Cancer, rheumatic disease	Organogenesis (18–60 d)	Large fontanelles, abnormal head shape, craniosynostosis, ocular and skeletal defects
Methylene blue (Intra-amniotic injection)	Twin pregnancy (as an aid to amniocentesis)	Second trimester when amniocentesis is generally performed	Jejunal atresia
Penicillamine	Cystinuria, rheumatoid arthritis	Unknown	Connective tissue abnormalities resembling cutis laxa with loose skin, hernias, loose joints, flat face, small jaw
Quinine (≥ 2 g/d)	Leg cramps, malaria	First–third trimesters (1 wk–term)	Deafness, abortion
Radioiodine (296–8325 MBq)	Thyroid carcinoma, thyroid disorder	End of first–third trimester (10 wk–term)	Fetal hypothyroidism and goitre
Retinoids (oral): acitretin, eretinate, isotretinoin	Dermatologic disease	Organogenesis (18–60 d)	CNS and ear defects, microagnathia, cleft lip/palate, cardiac and great vessel defects, thymic abnormalities, eye anomalies, limb defects
Tetracycline derivatives: chlortetracycline, demeclocycline, doxycycline, methacycline, minocycline, oxytetracycline, tetracycline	Infection	Second or third trimester (13th wk–term)	Staining of primary dentition
Thalidomide	Insomnia, oropharyngeal and esophageal ulcers associated with AIDS, immuno-pathologic disease, graft-versus-host disease	Organogenesis (27–40 d)	Limb reduction, cardiac, urogenital, renal, orofacial, ocular and gastrointestinal defects, cranial nerve anomalies, microtia

Недавно выявленные тератогены

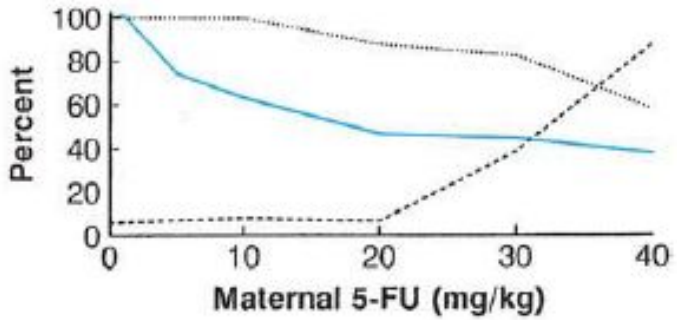
Exposure	Indication for treatment	Most susceptible period, post conception	Risk in embryo or fetus	Comments
Fluconazole (chronic, parenteral doses, 400–800 mg/d)	Mycotic infection	First trimester (1–12 wk)	Four children have been described with a similar and rare pattern of congenital anomalies. The features seen in these children are brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis and congenital heart disease	1) Risk appears to be more likely with high-dose, chronic, parenteral use 2) A single, oral dose of fluconazole (150–200 mg) is unlikely to pose a substantial teratogenic risk
Methimazole (usual therapeutic doses)	Hyperthyroidism	First trimester (1–12 wk)	Aplasia cutis congenita, skull hypoplasia, dystrophic nails and supernumerary nipples. Three children exhibited a characteristic pattern of malformations including facial dysmorphism, scalp defects, severely hypoplastic nipples, choanal atresia, esophageal atresia, psychomotor delay and growth retardation	1) Risk of fetal goitre or congenital anomalies is minimal to small 2) Untreated or inadequately treated maternal hyperthyroidism during pregnancy may lead to life-threatening complications of thyrotoxicosis and an increased risk of fetal death
		Second–third trimesters (10 wk–term)	Infants of women who are treated for Graves' disease during pregnancy with methimazole are at increased risk of hyperthyroidism due to placental transfer of thyroid-stimulating immunoglobulins as well as of hypothyroidism and goitre due to the medication	3) Fetal hypothyroidism and goitre are unlikely to be caused by methimazole treatment before about 10 wk after conception when the fetal thyroid begins to function
Misoprostol (usual therapeutic oral doses)	Peptic ulcer disease, cervical ripening, pregnancy termination	First–second trimesters (1–24 wk)	Moebius anomaly, terminal transverse limb reduction defects, arthrogryposis multiplex congenita and talipes equinovarus	1) The risk of congenital anomalies resulting from vascular disruptions has been associated with unsuccessful attempts to induce abortion early in pregnancy 2) No consistent adverse effect has been observed in newborns of women who were given misoprostol for cervical ripening and induction of labour near term
Trimethoprim (usual therapeutic doses)	Bacterial infection, *pneumocystis carinii* pneumonia	First trimester (1–12 wk)	Neural tube defects, oral clefts, hypospadias and cardiovascular defects	The absolute risk of neural tube defects in infants of women treated with trimethoprim during the first 2 months of pregnancy is about 1%

Механизмы тератогенного действия химических соединений

Чувствительность эмбрионов хомяков на ретиноевую кислоту

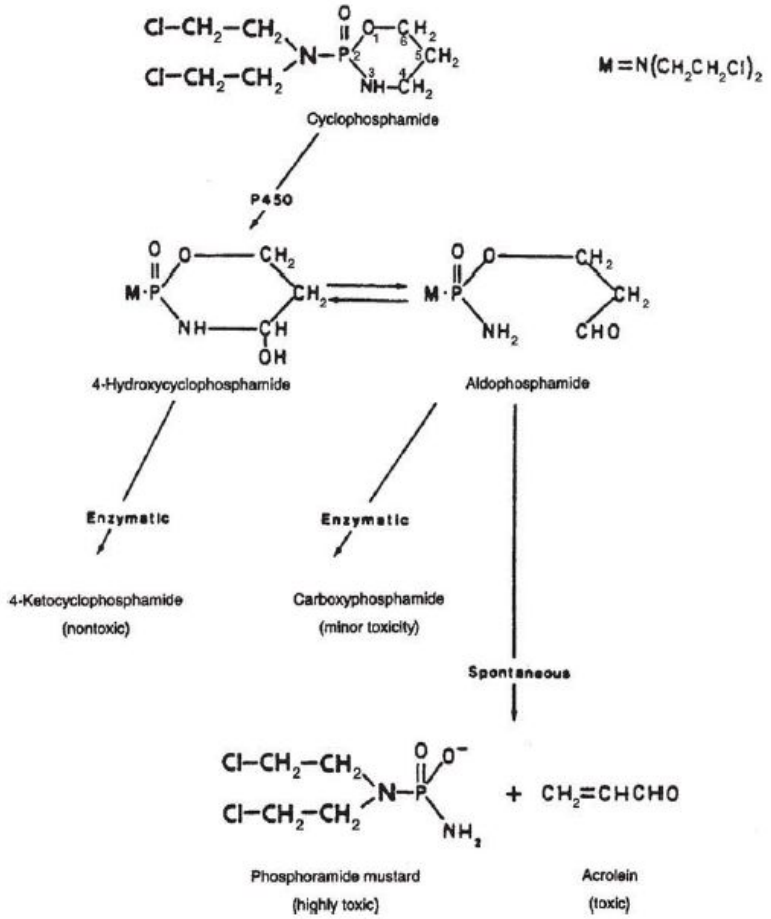


Эффекты 5-ФУ на развитие крыс

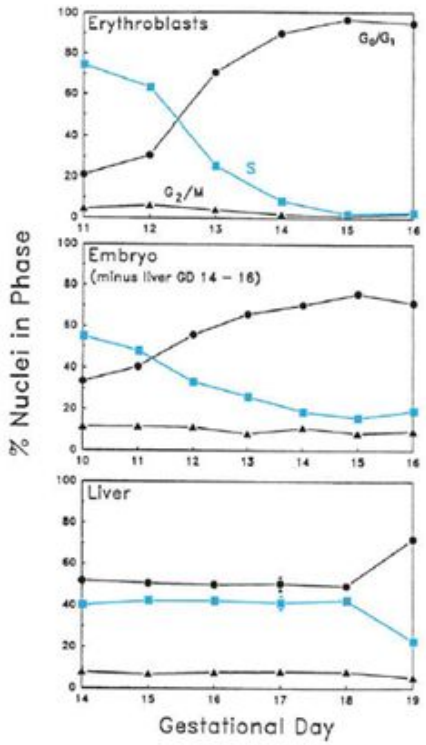


Relationship between inhibition of embryonal thymidylate synthetase (TS) and adverse fetal outcome following maternal 5-fluorouracil (5-FU) administration on gestation day 14 in the rat.

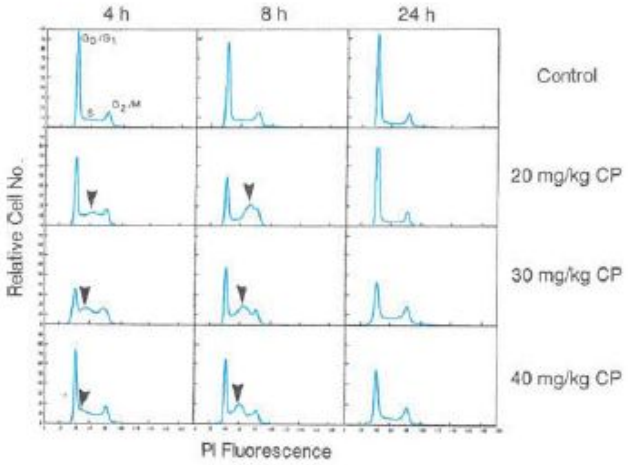
Метаболизм тератогена циклофосфамида

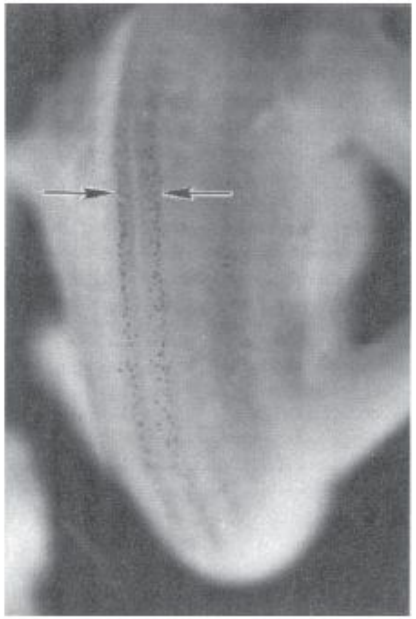


Влияние ФА на клеточный цикл эмбрионов крыс и морфогенез мышей



Normal developmental changes in cell cycle distributions in erythroblasts, embryo (minus the liver after GD 13), and fetal liver. Percentages of cells in: ● G_0/G_1; ■ S; and ▲ G_2/M are shown for rat embryos between gestation days 10 and 19 (note changing x-axis range).

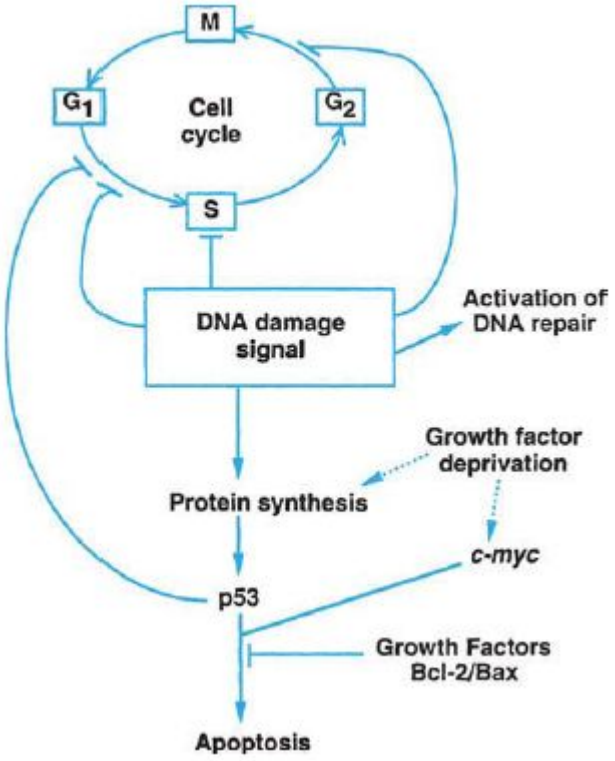




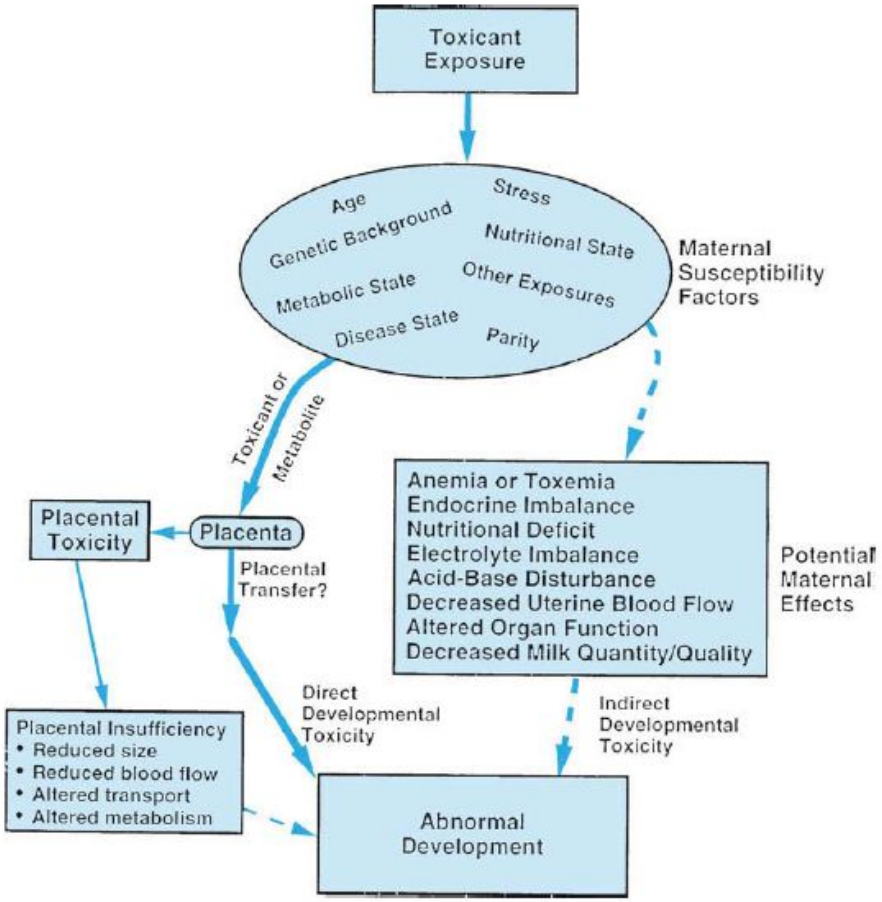
Maternal cyclophosphamide (CP) administration on gestation day 10 in CD-1 mice produces perturbations of

Left: Cells are inhibited from progressing through the S (DNA synthetic) phase of the cell cycle, indicated by the abnormal population of cells (*arrowheads*) accumulating at progressively earlier stages of S phase 4 hours and 8 hours after increasing maternal CP dosages. The upper panels show the normal GD 10-11 distributions, with the G_0/G_1, S, and G_2/M peaks identified in the upper left panel. By 24 hour postdosing, cell cycle distributions have returned to normal at 20 mg/kg, but remain abnormal at higher dosages. *Right*: Nile blue sulfate staining of a mouse embryo 24 hours after maternal CP dosing shows cell death (*stippling along either side of the midline, arrows*) in the neural tube, one of the most sensitive target sites for CP.

Связь между повреждением ДНК и индукцией клеточного цикла и апоптоза



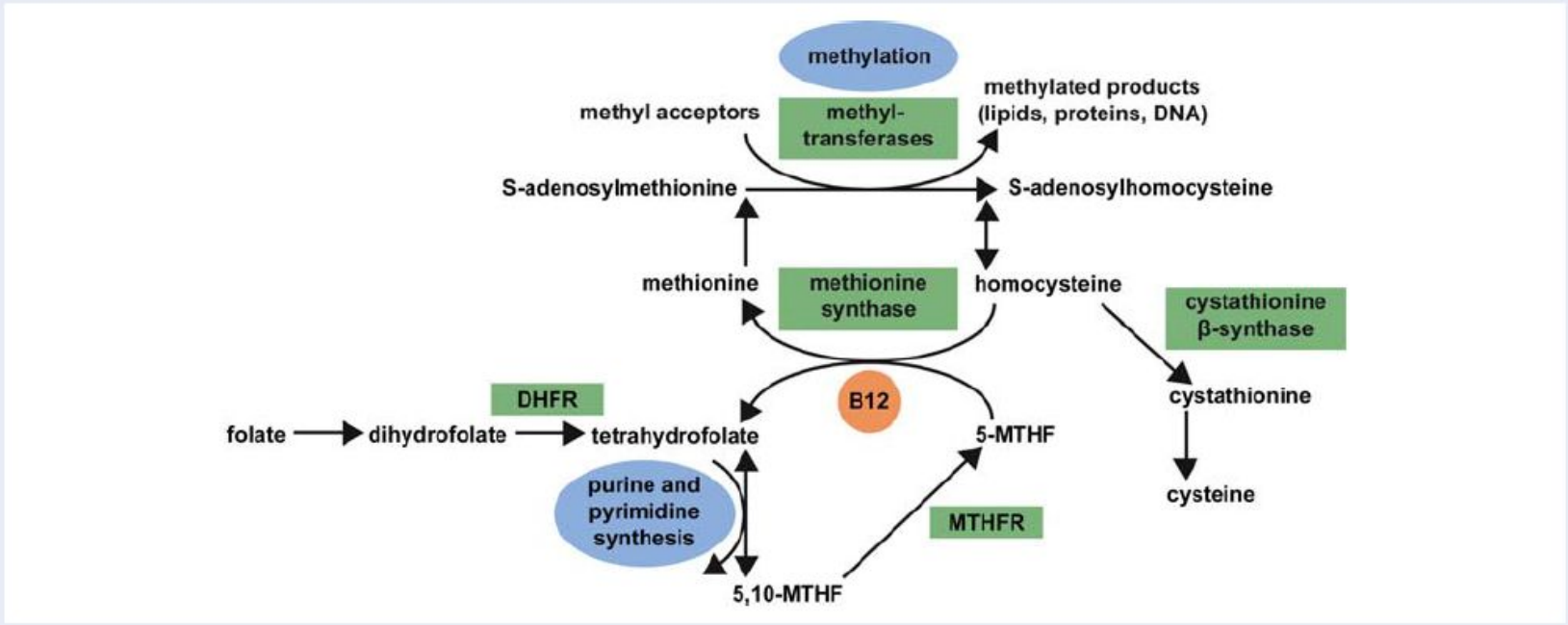
Взаимодействие мать-плод



Фолатный антагонизм

- water-soluble B vitamin, occurs in high
- concentrations in certain natural foods (fruits, leafy green vegetables,
- beans and liver) as polyglutamate. The synthetic form, folic acid (a
- monoglutamic acid), is used in food fortification and vitamin preparations.
- Folic acid has a higher bioavailability than food folate

Folate–homocysteine–methionine метаболизм



B12, vitamin B_{12}; DHFR, dihydrofolate reductase; MTHF, methyltetrahydrofolate; MTHFR, methyltetrahydrofolate reductase.

Лекарства, связанные с фолатным антагонизмом

Medical drugs associated with folate antagonism

Medication	Main indication	Interference with folate metabolism
Carbamazepine	Epilepsy, bipolar disorder	Impairment folate absorption
Cholestyramine	Hypercholesterolemia	Impairment folate and vitamin B_{12} absorption
Cyclosporine	Transplants, psoriasis, atopic dermatitis	Possible interference folate dependent remethylation
Lamotrigine	Epilepsy, bipolar disorder	Inhibition DHFR
Metformin	Diabetes	Interference vitamin B_{12}
Methotrexate	Cancer, some auto-immune diseases (rheumatoid arthritis, psoriasis)	Inhibition DHFR
Nicotinic acid	Hypercholesterolemia	Decrease acitivity CBS
Phenobarbital	Epilepsy	Impairment folate absorption
Phenytoin	Epilepsy	Impairment folate absorption, decrease activity methionine synthase, possible decrease activity MTHFR
Primidone	Epilepsy	Impairment folate absorption
Pyrimethamine	Malaria	Inhibition DHFR
Sulfasalazine	Inflammatory bowel disease, rheumatoid arthritis	Inhibition DHFR
Triamterene	Hypertension, edema	Inhibition DHFR
Trimethoprim	Urinary tract infection	Inhibition DHFR
Valproic acid	Epilepsy, migraine headache	Antimetabolite of folate

CBS, cystathione β-synthase; DHFR, dihydrofolate reductase; MTHFR, methyltetrahydrofolate reductase.

Neural Crest Cell Disruption

- - нарушения в аорте
- - нарушения в развитии нервной системы
- и др. нарушения

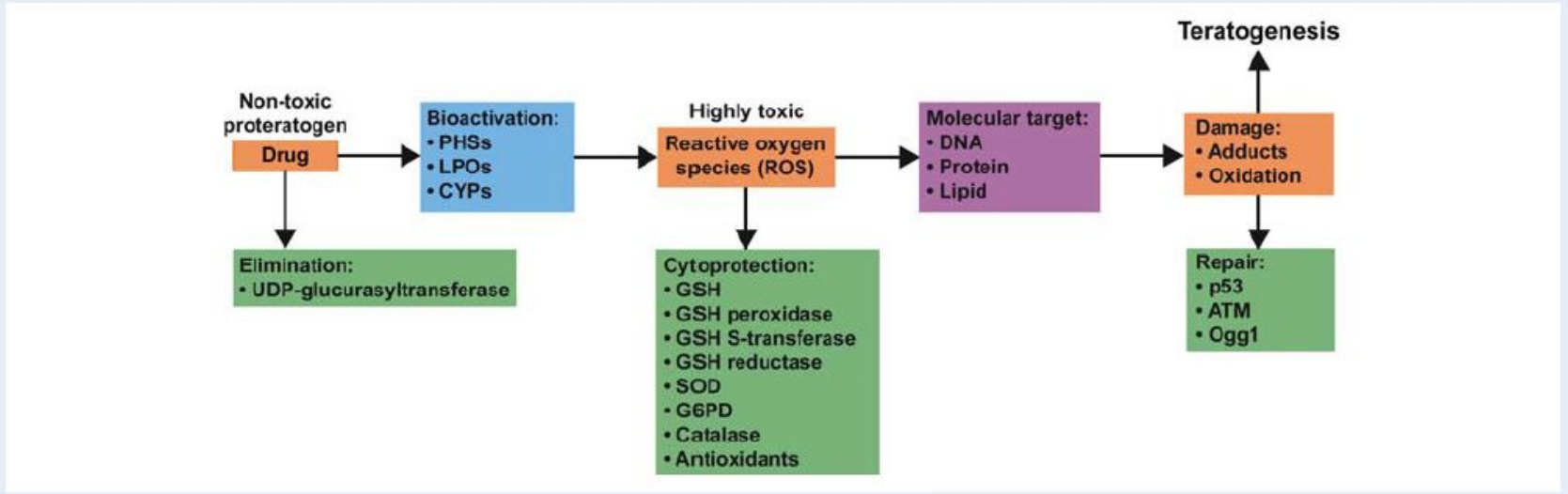
Endocrine Disruption: Sex Hormones

- diethylstilbestrol (DES) – нарушения в гормональном балансе
- - множественные нарушения

Окислительный стресс

- *In vivo*, некоторые лекарства, известные как агенты восстановительного цикла, используются, в том числе, для лечения эпилепсии, аритмии и рака, проходит реакцию одно-электронного восстановления с выходом свободных радикалов.

Молекулярные и биохимические основы тератогенеза, индуцированного ОС

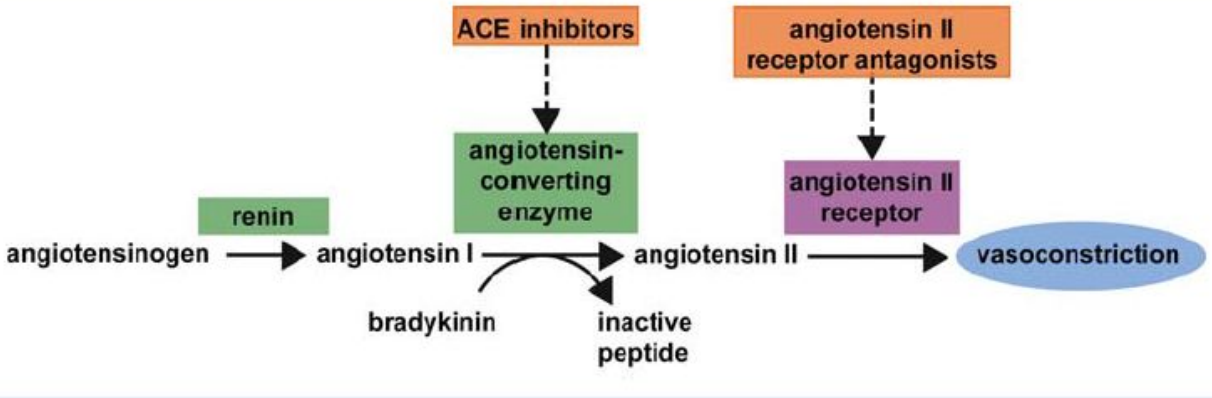


ATM, ataxia telangiectasia mutated; CYP, cytochrome P450; G6PD, glucose-6-phosphate dehydrogenase; GSH, glutathione; LPO, lipoxygenase; Ogg1, oxoguanine glycosylase 1; PHS, prostaglandin H synthase; SOD, superoxide dismutase; UDP, uridine diphosphate. Modified from Winn and Wells (1995) with kind permission from Wiley-Blackwell.

Васкулярные нарушения

- В первые 3 месяца развития
- Нарушение циркуляции крови в uterine-placental unit, the placental-fetal unit

Специфические рецепторы или тератогенез, опосредованный ферментами



The renin–angiotensin system. ACE, angiotensin-converting enzyme.

Другие механизмы

- Hydroxymethylglutaryl-coenzyme A Reductase
- Ацетилаза гистоновCyclooxygenase-1 (Non-steroidal anti-inflammatory drugs)
- N-methyl-D-aspartate receptors (миграция нейронов)
- 5-Hydroxytryptamine receptors
- and transporters (Serotonin (5-hydroxytryptamine, 5-HT) is a monoamine neurotransmitter)

Другие механизмы

- 1. Carbonic anhydrase. Carbonic anhydrases are metalloenzymes that catalyze the reversible hydration of CO2 into the bicarbonate ion and protons. This reaction
- is involved in many biological processes, including pH homeostasis,
- respiration, biosynthetic reactions and bone resorption.
- 2. g-Aminobutyric acid receptors
- In vertebrates, g-aminobutyric acid (GABA) is the major inhibitory
- neurotransmitter, which binds to specific transmembrane GABA
- receptors. Extraneuronal GABA-ergic systems are thought to be
- present in other tissues as well, including the testis

Результат применения лекарств

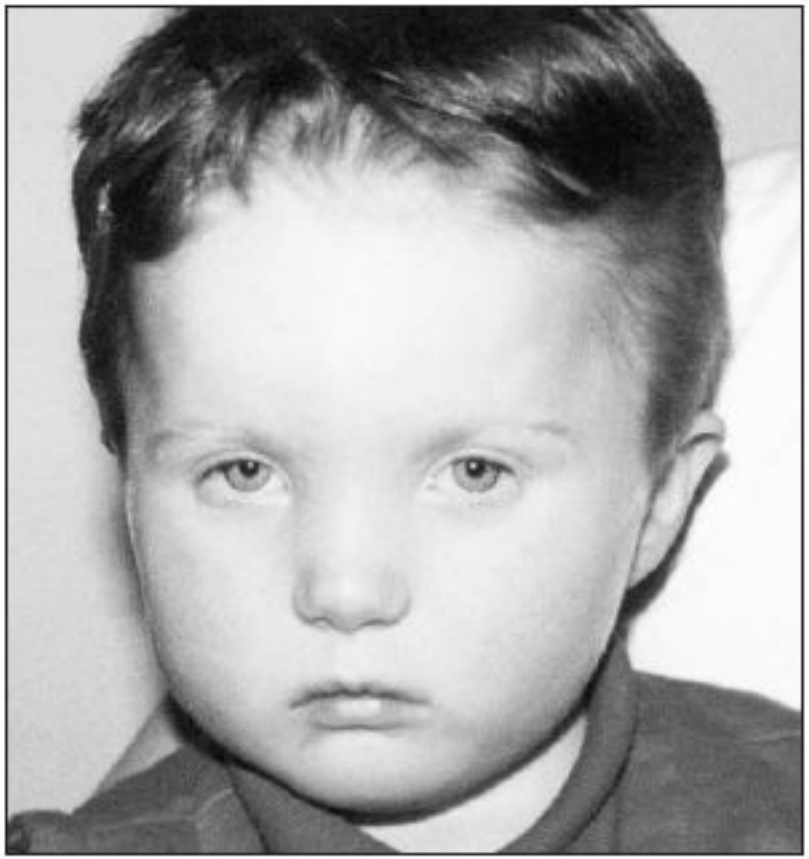
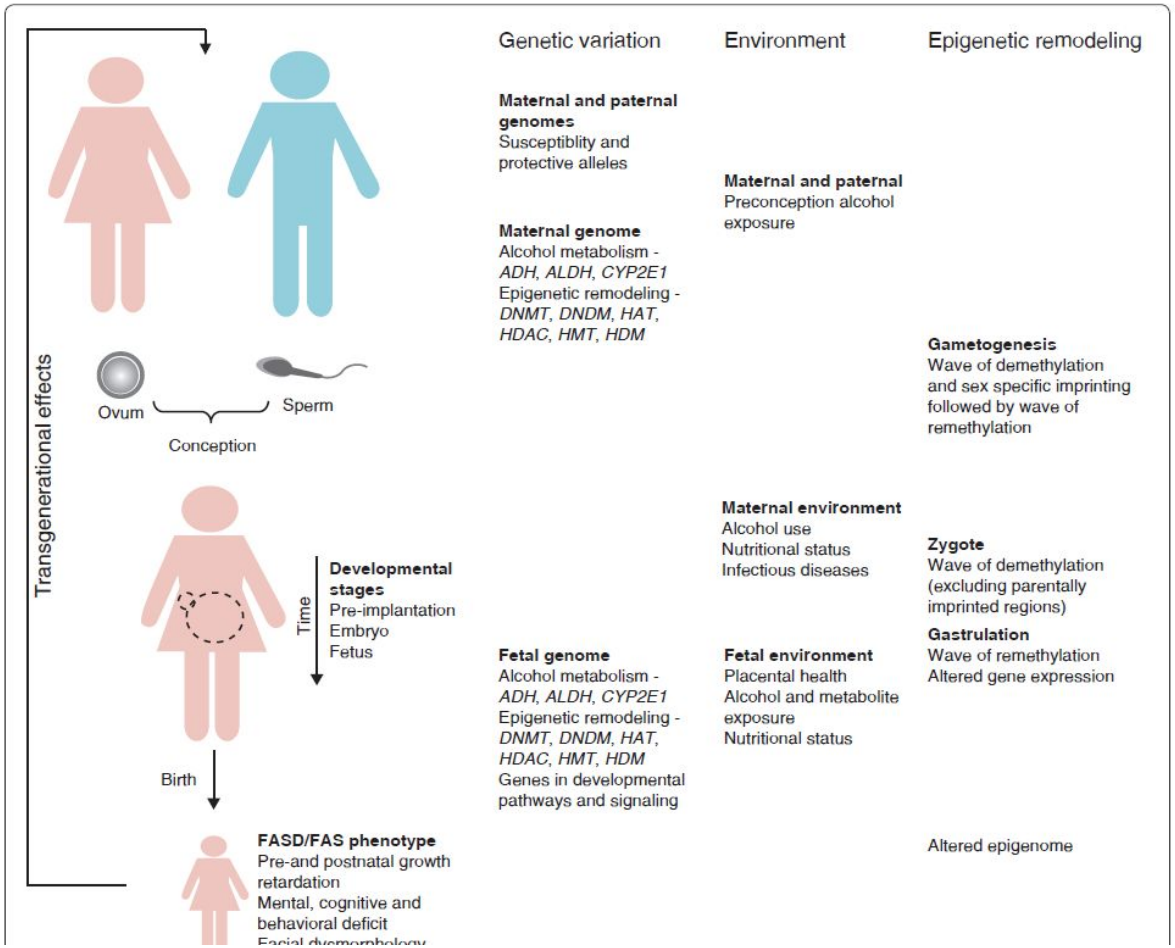


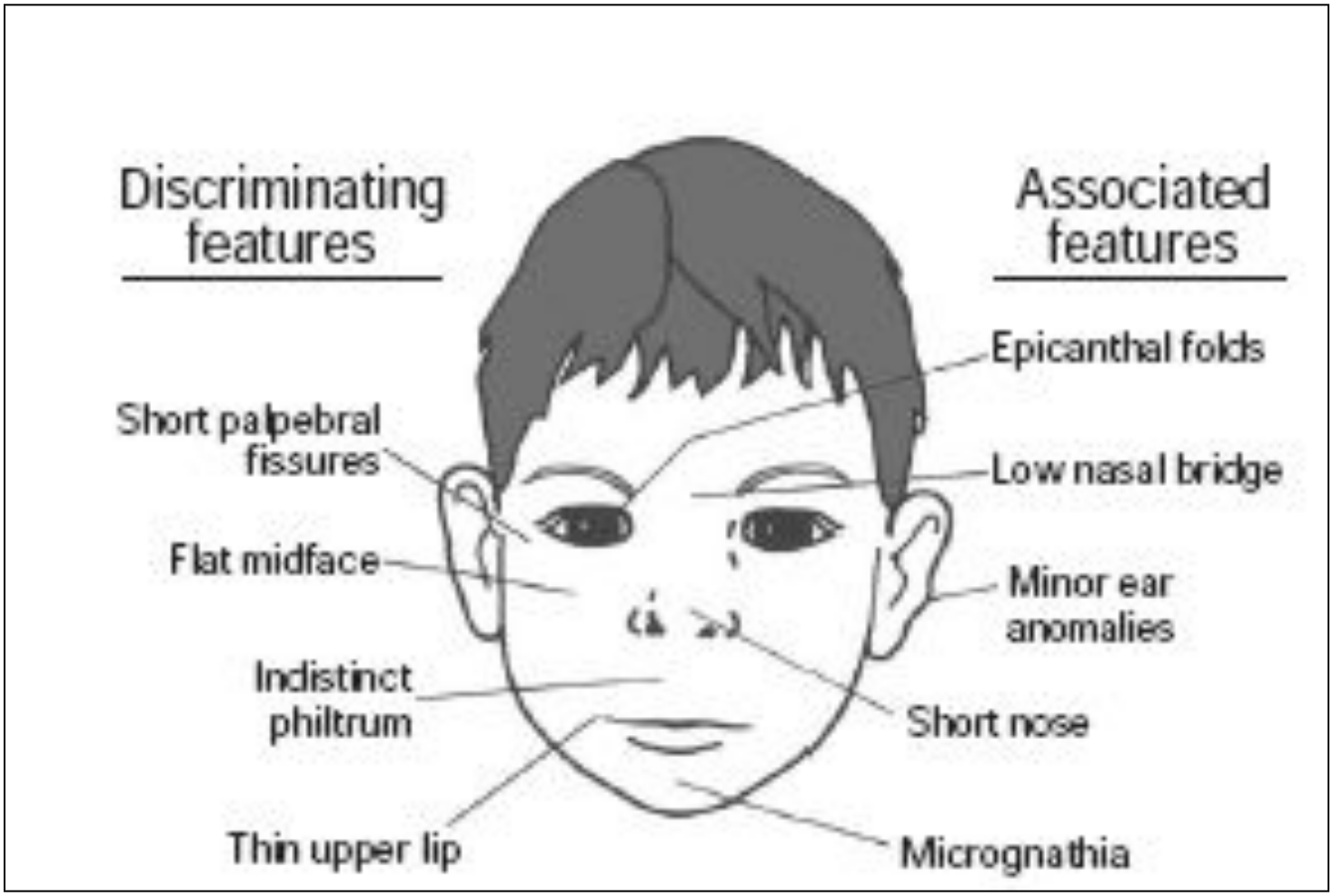
Fig. 1: Minor facial anomalies in a 3-year-old boy whose mother was treated with carbimazole (a prodrug that is completely metabolized to methimazole) for the treatment of Graves' disease during pregnancy (picture provided by Drs. L.C. Wilson, B.A. Kerr, R. Wilkinson, C. Fossard and D. Donnai). Reprinted with permission from Wiley-Liss, Inc. (*Am J Med Genet* 1998;75:220-2).

Фетальный алкогольный синдром

Развитие ФАС



Признаки фетального алкогольного синдрома (FAS)



Интерпретация данных, полученных на животных

Predictiveness of Animal Data for 51 Potential Human Developmental Toxicants

		MOUSE	RAT	MONKEY	RABBIT	HAMSTER
Potential human developmental toxicants tested (%)		86	96	33	61	26
Concordance by class	G[1]	61	57	65	39	39
	D	75	71	53	52	54
	M	71	67	65	65	62
	All	91	98	82	77	85
False positives	G	25	33	6	19	8
	D	11	16	18	10	0
	M	14	12	6	7	15
False negatives	G	10	14	29	39	54
	D	14	12	29	39	46
	M	11	25	29	29	23

KEY: G, growth retardation; D, death of conceptus; M, malformation; All, either growth, death, or malformations.
SOURCE: Adapted from Schardein and Keller (1989), with permission.

The 17 Intercellular Signaling Pathways Used in Development by Most Metazoans

PERIOD DURING DEVELOPMENT	SIGNALING PATHWAY
Before organogenesis; later for growth and tissue renewal	1. Wingless-Int pathway
	2. Transforming growth factor β pathway
	3. Hedgehog pathway
	4. Receptor tyrosine kinase pathway
	5. Notch-Delta pathway
	6. Cytokine pathway (STAT pathway)
Organogenesis and cytodifferentiation; later for growth and tissue renewal	7. Interleukin-1-toll nuclear factor-kappa B pathway
	8. Nuclear hormone receptor pathway
	9. Apoptosis pathway
	10. Receptor phosphotyrosine phosphatase pathway
Larval and adult physiology	11. Receptor guanylate cyclase pathway
	12. Nitric oxide receptor pathway
	13. G-protein coupled receptor (large G proteins) pathway
	14. Integrin pathway
	15. Cadherin pathway
	16. Gap junction pathway
	17. Ligand-gated cation channel pathway

Summary of In Vivo Regulatory Protocol Guidelines for Evaluation of Developmental Toxicity

STUDY	EXPOSURE	ENDPOINTS COVERED	COMMENTS
Segment I: Fertility and general reproduction study	Males: 10 weeks prior to mating Females: 2 weeks prior to mating	Gamete development, fertility, pre- and post implantation viability, parturition, lactation	Assesses reproductive capabilities of male and female following exposure over one complete spermatogenic cycle or several estrous cycles.
Segment II: Teratogenicity test	Implantation (or mating) through end of organogenesis (or term)	Viability, weight, and morphology (external, visceral, and skeletal) of conceptuses just prior to birth	Shorter exposure to prevent maternal metabolic adaptation and to provide high exposure to the embryo during gastrulation and organogenesis. Earlier dosing option for bioaccumulative agents or those impacting maternal nutrition. Later dosing option covers male reproductive tract development and fetal growth and maturation.
Segment III: Perinatal study	Last trimester of pregnancy through lactation	Postnatal survival, growth and external morphology	Intended to observe effects on development of major organ functional competence during the perinatal period, and thus may be relatively more sensitive to adverse effects at this time.
ICH 4.1.1: Fertility protocol	Males: 4 weeks prior to mating Females: 2 weeks prior to mating	Males: Reproductive organ weights and histology, sperm counts and motility Females: Viability of conceptuses at mid-pregnancy or later	Improved assessment of male reproductive endpoints; shorter treatment duration than Segment I.
ICH 4.1.2: Effects on prenatal and postnatal development, including maternal function	Implantation through end of lactation	Relative toxicity to pregnant versus non-pregnant female; postnatal viability, growth, development and functional deficits (including behavior, maturation, and reproduction)	
ICH 4.1.3: Effects on embryo/fetal development	Implantation through end of organogenesis	Viability and morphology (external, visceral, and skeletal) of fetuses just prior to birth.	Similar to Segment II study. Usually conducted in two species (rodent and nonrodent).
OECD 414 Prenatal developmental	Implantation (or mating) through day prior to cesarean section	Viability and morphology (external, visceral, and skeletal) of fetuses just prior to birth.	Similar to Segment II study. Usually conducted in two species (rodent and nonrodent).

Brief Survey of Alternative Test Methodologies for Developmental Toxicity

ASSAY	BRIEF DESCRIPTION AND ENDPOINTS EVALUATED	CONCORDANCE*	REFERENCE(S)
Micromass culture	Midbrain or limb bud cells dissociated from rat embryos and grown in micromass culture for 5 days. Cell proliferation and biochemical markers of differentiation assessed.	Sensitivity: 25/27; 20/33; 11/15 Specificity: 17/19; 18/18; 8/10 Accuracy: 79%	Flint and Orton, 1984 Renault *et al.*, 1989 Uphill *et al.*, 1990 Genschow *et al.*, 2000 Spielmann *et al.*, 2004
Mouse embryonic stem cell (EST) test	Mouse ESTs and 3T3 cells in 96 -well plates assessed for viability after 3 and 5 days. ESTs grown for 3 days in hanging drops form embryoid bodies which are plated and examined after 10 days for differentiation into cardiocytes.	Sensitivity: 84% Specificity: 68% Accuracy: 79%	Scholz *et al.*, 1999 Genschow *et al.*, 2000, 2004
Chick embryo neural retina cell culture	Neural retinas of day 6.5 chick embryos dissociated and grown in rotating suspension culture for 7 days. Endpoints include cellular aggregation, growth, differentiation, and biochemical markers.	Sensitivity: 36/41 Specificity: 14/17	Daston *et al.*, 1991 Daston *et al.*, 1995a (concordances combined)
Drosophila	Fly larvae grown from egg disposition through hatching of adults. Adult flies examined for specific structural defects (bent bristles and notched wing).	Sensitivity: 10/13 Specificity: 4/5	Lynch *et al.*, 1991 Palermo *et al.*, 2004
FETAX	Mid-blastula stage *Xenopus* embryos exposed for 96 h and evaluated for viability, growth, morphology.	Sensitivity: 6/7 Specificity: 2/2	Bantle, 1995 Fort *et al.*, 2000 Fort and Paul, 2002
Rodent whole embryo culture	Postimplantation rodent embryos grown in vitro for up to two days and evaluated for growth and development.	Accuracy: 88%	Webster *et al.*, 1997 Genschow *et al.*, 2000 Piersma *et al.*, 2004
Zebrafish	Zebrafish eggs or blastulae exposed to chemical in water (can be in multi-well plates) for up to four days and evaluated for growth, development and (in some cases) gene expression.	Sensitivity: ND Specificity: ND	Fraysse *et al.*, 2006 Love *et al.*, 2004
Chernoff/Kavlock assay	Pregnant mice or rats exposed during organogenesis and allowed to deliver. Postnatal growth, viability and gross morphology of litters assessed.	Sensitivity: 49/58 Specificity: 28/34	Hardin *et al.*, 1987

Развитие исследований в 2013 г.

- Reprod Toxicol. 2013 Jan;35:117-24. doi: 10.1016/j.reprotox.2012.10.007. Epub 2012 Oct 23.
- **Teratogenic effects of diabetic conditions in chick heart in ovo and in micromass culture may be prevented by addition of vitamin C and folic acid.**
- Memon SMemon S, Pratten MK.
- **Source**
- Centre for Integrated Systems Biology and Medicine, School of Biomedical Sciences, Queen's Medical Centre, University of Nottingham, Nottingham, UK.
- **Abstract**
- Maternal diseases like diabetes mellitus may cause developmental defects. Supplementation with folic acid and vitamin C during the periconceptional period has been shown to prevent some neural tube and congenital heart defects. Hearts were dissected from 5 days-old White Leghorn chick embryos, the cells isolated and cultured in micromass under diabetic conditions, with and without folic acid and vitamin C. Contractile activity, cell viability (resazurin reduction) and protein assays were performed. Results indicated diabetic conditions reduced contractile activity and cell viability, whilst vitamin C (100 μM) and folic acid (1 mM) administered concurrently significantly improved them to values comparable with the control. Day 3 chick embryos in ovo were injected with glucose+hydroxybutyrate or a combination of these and vitamins. Diabetic conditions caused gross and histological malformations, but these effects were abrogated by vitamin supplement. Teratogenic effects on heart development could possibly be prevented by vitamin supplementation during pregnancy.

Hum Reprod. 2013 Oct 9. [Epub ahead of print]

Drugs associated with teratogenic mechanisms. Part II: a literature review of the evidence on human risks.

van Gelder MM, de Jong-van den Berg LT, Roeleveld N.

Abstract

STUDY QUESTION:

What is the current state of knowledge on the human risks of drugs suspected to be associated with teratogenic mechanisms?

SUMMARY ANSWER:

Evidence for the presence or absence of human risks of birth defects is scarce or non-existent for the majority of drugs associated with teratogenic mechanisms.

WHAT IS KNOWN ALREADY:

Medical drugs suspected to be associated with teratogenic mechanisms are dispensed to a significant proportion of women in the first trimester of pregnancy. However, an overview of the current state of knowledge on the human teratogenic effects of these drugs is lacking.

STUDY DESIGN, SIZE, DURATION:

We performed an extensive literature review of studies in the English language which examined the associations between selected drugs and specific birth defects. The literature was identified from MEDLINE and EMBASE from database inception (January 1946 and January 1974, respectively) through December 2012 using 287 terms for the drugs of interest. We only included studies if they specified birth defect subtypes and, specifically for cohort studies, involved live born infants.

PARTICIPANTS/MATERIALS, SETTING, METHODS:

Of 14 406 potentially relevant articles, 556 full-text articles were assessed for eligibility and 250 met the inclusion criteria. The studies included were divided into four categories according to their design to increase the validity of our study.

MAIN RESULTS AND THE ROLE OF CHANCE:

Epidemiologic studies assessing teratogenic risks were identified for less than half of the drugs included in the review. A substantial variation in study design and data collection methods was observed. When the data collection method is of questionable validity, study quality may be affected considerably. For only 15 drugs of interest, birth defects were assessed in at least 1000 infants in cohort studies, and 13 of these were associated with one or more specific birth defects. The majority of associations observed in case-control studies are as yet unconfirmed. For most drugs and drug groups, however, the numbers of exposed infants studied were too small to draw any conclusions regarding their human teratogenic risks.

LIMITATIONS, REASONS FOR CAUTION:

The validity of our review is limited by the validity and reporting of the studies from which the data were extracted. Some relevant studies might have been missed owing to the exclusion of articles not in the English language and publication bias.

WIDER IMPLICATIONS OF THE FINDINGS:

It is a cause of concern that the drugs most often dispensed in the first trimester of pregnancy are not necessarily the drugs for which teratogenic risks have been studied. Future studies should focus on those drugs that are most commonly used during pregnancy and for which the teratogenic risks are unknown, such as iron preparations, serotonin receptor agonists or antagonists, drugs used in fertility treatment, dihydrofolate reductase inhibitors.

STUDY FUNDING/COMPETING INTEREST(S):

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