

# 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, tretinate, 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<br>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  |
|---|--|--|---|
| <b>ACE inhibitors:</b> 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                |
| <b>Amiodarone</b>   | Thyroid disorder   | 10 wk-term   | Neonatal thyroid dysfunction or goitre  |
| <b>Aminopterin</b> (≥ 1–3 mg/d)   | Cancer   | Organogenesis (18–60 d)  | CNS, limb and skeletal defects  |
| <b>Antiepileptic drugs:</b> 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  |
| <b>Coumarin derivatives:</b> 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 |
| <b>Cyclophosphamide</b>   | Cancer, transplant rejection                                     | Organogenesis (18–60 d)  | Skeletal and ocular defects, cleft palate   |
| <b>Danazol</b> (≥ 200 mg/d)   | Endometriosis, fibrocystic breast disease, hereditary angioedema | Unknown  | Virilization of external genitalia in female fetuses  |
| <b>Diethylstilbestrol</b> (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

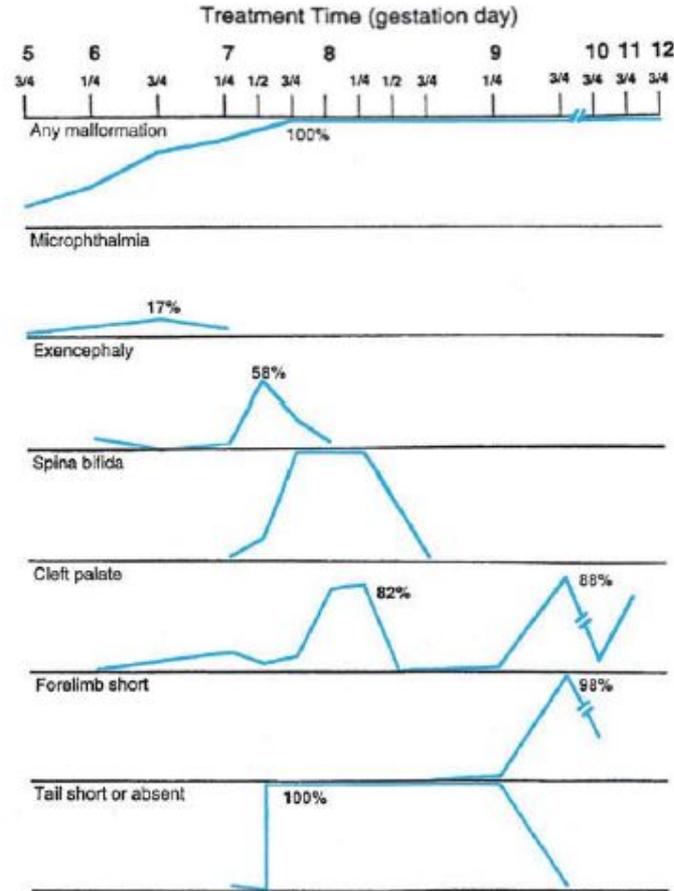
| Drug  | Maternal condition  | Most susceptible period, post conception                   | Nature of adverse effect   |
|---|---|--|--|
| <b>Methotrexate</b><br>(≥ 12.5 mg/wk)   | Cancer, rheumatic disease   | Organogenesis (18–60 d)                                    | Large fontanelles, abnormal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

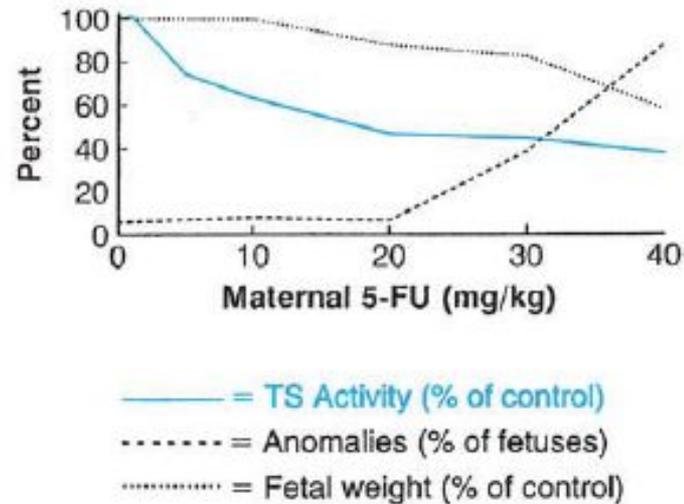
| Exposure  | Indication for treatment                                       | Most susceptible period, post conception                                     | Risk in embryo or fetus   | Comments  |
|---|--|--|---|---|
| <b>Fluconazole</b><br>(chronic, parenteral doses, 400–800 mg/d) | Mycotic infection  | 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  | <p>1) Risk appears to be more likely with high-dose, chronic, parenteral use</p> <p>2) A single, oral dose of fluconazole (150–200 mg) is unlikely to pose a substantial teratogenic risk</p>   |
| <b>Methimazole</b><br>(usual therapeutic doses)                 | Hyperthyroidism  | <p>First trimester (1–12 wk)</p> <p>Second–third trimesters (10 wk–term)</p> | <p>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</p> <p>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</p> | <p>1) Risk of fetal goitre or congenital anomalies is minimal to small</p> <p>2) Untreated or inadequately treated maternal hyperthyroidism during pregnancy may lead to life-threatening complications of thyrotoxicosis and an increased risk of fetal death</p> <p>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</p> |
| <b>Misoprostol</b><br>(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   | <p>1) The risk of congenital anomalies resulting from vascular disruptions has been associated with unsuccessful attempts to induce abortion early in pregnancy</p> <p>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</p>  |
| <b>Trimethoprim</b><br>(usual therapeutic doses)                | Bacterial infection, <i>pneumocystis carinii</i> 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

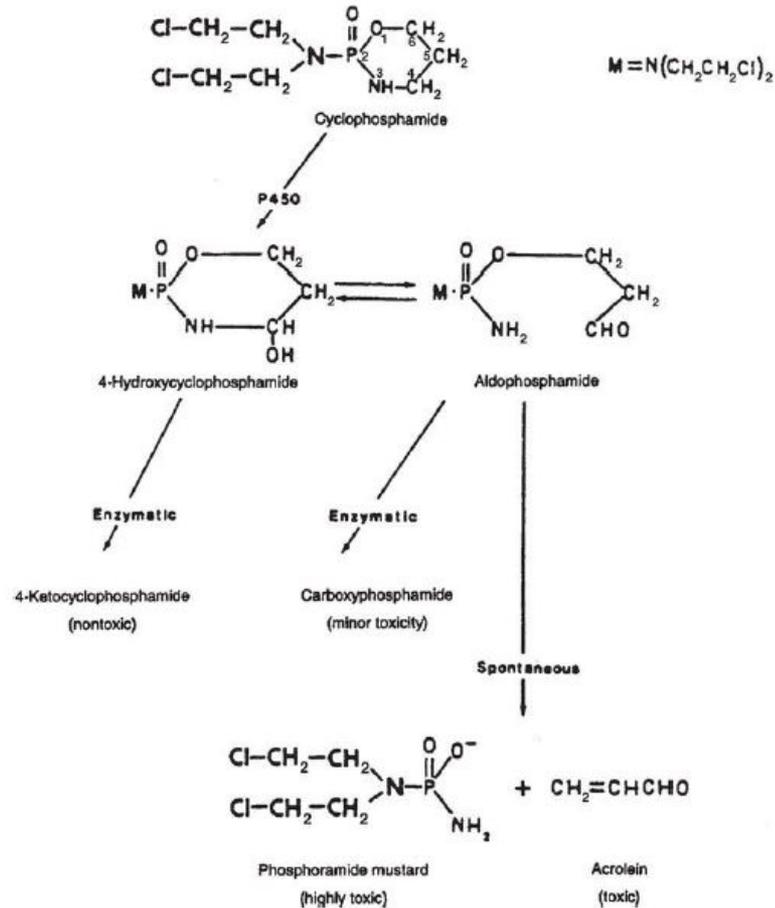


# Эффекты 5-ФУ на развитие крыс

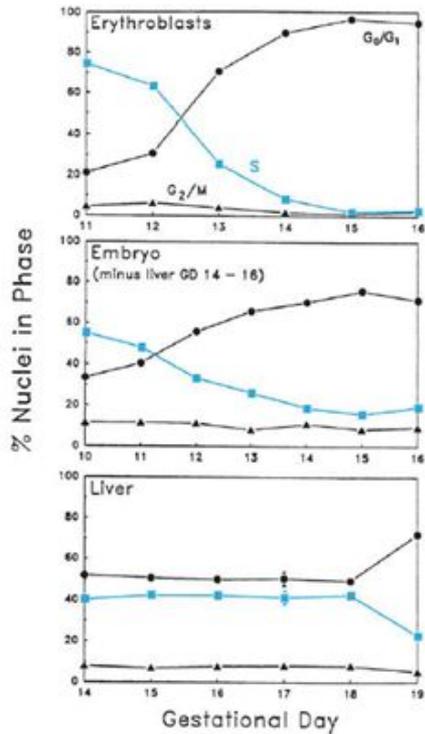


*Relationship between inhibition of embryonal thymidylate synthetase (TS) and adverse fetal outcome following maternal 5-fluorouracil (5-FU) administration on gestation day 14 in the rat.*

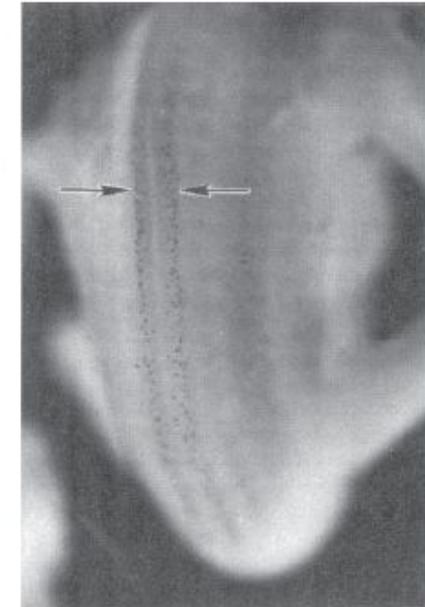
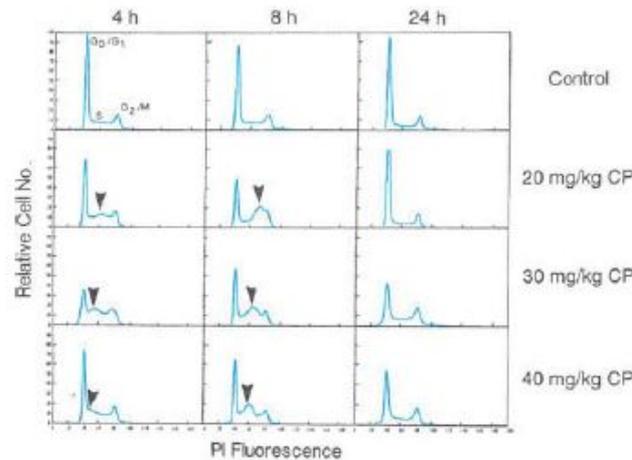
# Метаболизм тератогена циклофосфамида



# Влияние ФА на клеточный цикл эмбрионов крыс и морфогенез мышей



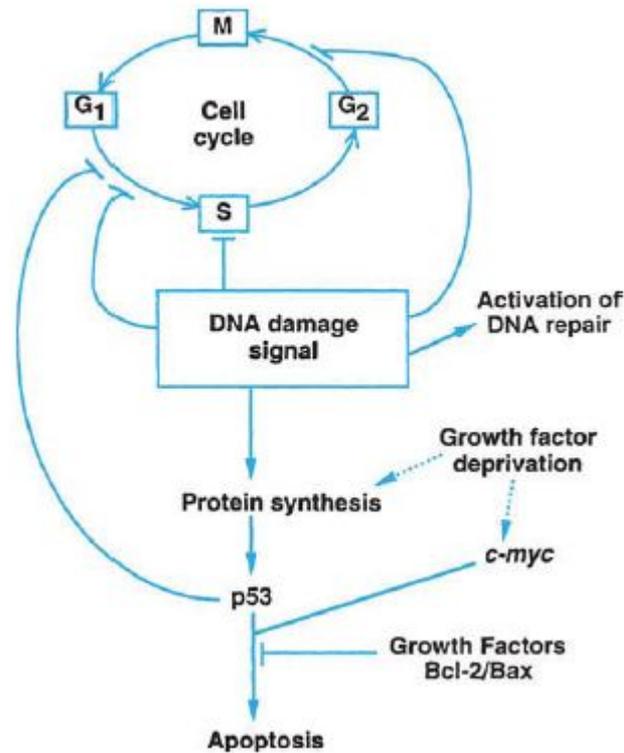
Normal developmental changes in cell cycle distributions in erythroblasts, embryo (minus the liver after GD 13), and fetal liver. Percentages of cells in: ● G<sub>0</sub>/G<sub>1</sub>; ■ S; and ▲ G<sub>2</sub>/M are shown for rat embryos between gestation days 10 and 19 (note changing x-axis range).



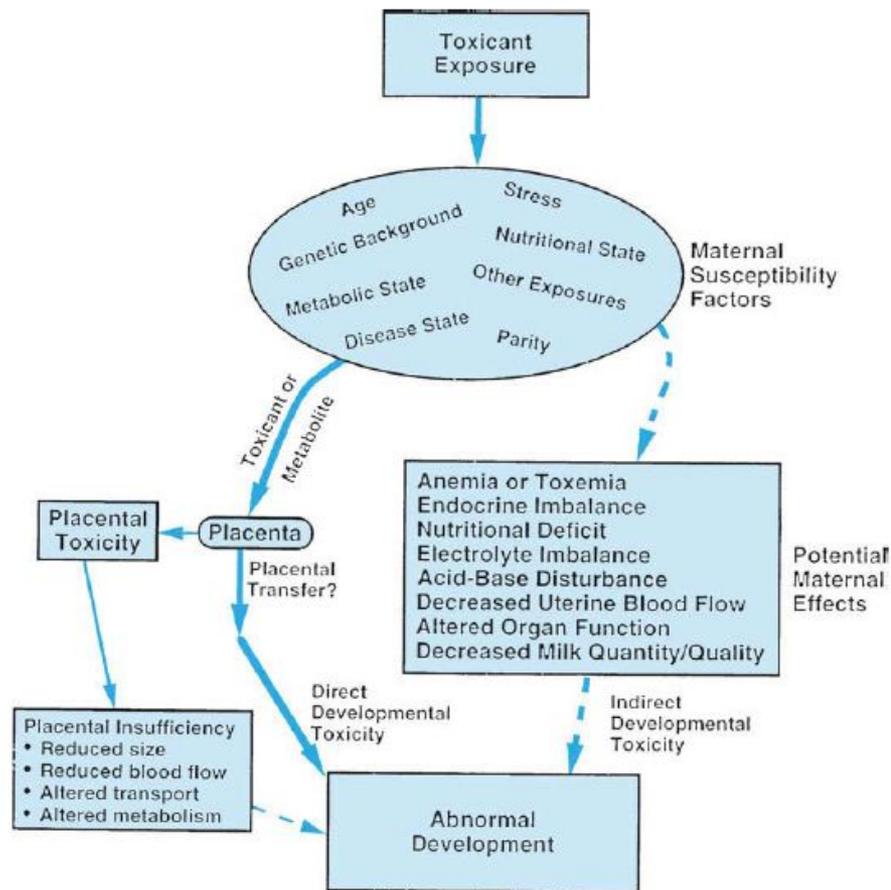
Maternal cyclophosphamide (CP) administration on gestation day 10 in CD-1 mice produces perturbations of

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<sub>0</sub>/G<sub>1</sub>, S, and G<sub>2</sub>/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



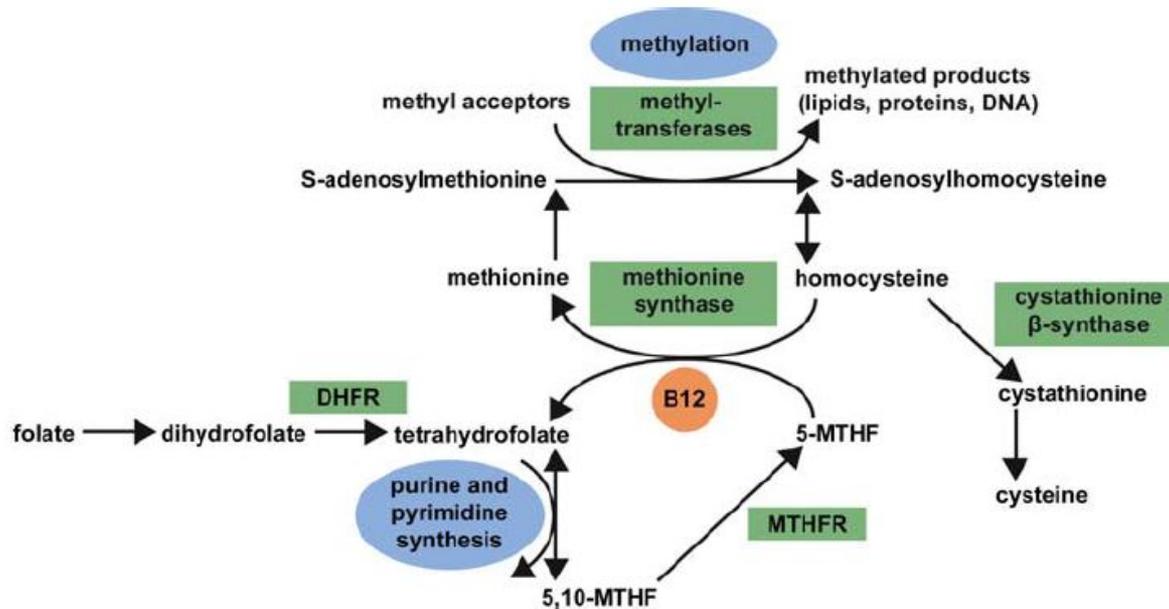
# Взаимодействие мать-плод



# 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<sub>12</sub>; 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 <sub>12</sub> absorption  |
| Cyclosporine   | Transplants, psoriasis, atopic dermatitis                           | Possible interference folate dependent remethylation  |
| Lamotrigine    | Epilepsy, bipolar disorder  | Inhibition DHFR   |
| Metformin      | Diabetes  | Interference vitamin B <sub>12</sub>  |
| Methotrexate   | Cancer, some auto-immune diseases (rheumatoid arthritis, psoriasis) | Inhibition DHFR   |
| Nicotinic acid | Hypercholesterolemia  | Decrease activity 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

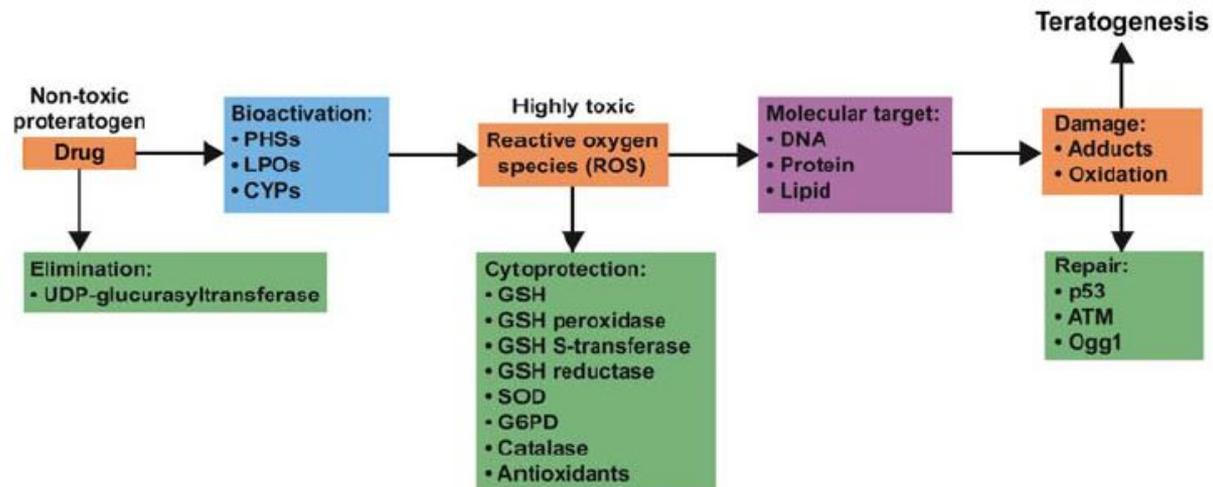
# Endocrine Disruption: Sex Hormones

- 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

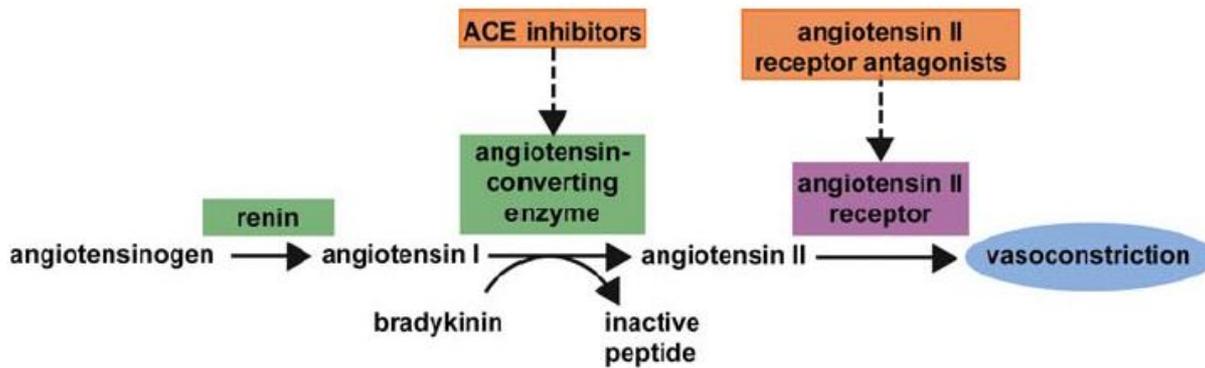


ATM, ataxia telangiectasia mutated; CYP, cytochrome P450; G6PD, glucose-6-phosphate dehydrogenase; GSH, glutathione; LPO, lipoxygenase; Ogg1, oxoguanine glycosylase I; PHS, prostaglandin H synthase; SOD, superoxide dismutase; UDP, uridine diphosphate. Modified from Winn and Wells (1995) with kind permission 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 гистонов Cyclooxygenase-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 CO<sub>2</sub> into the bicarbonate ion and protons. This reaction
- is involved in many biological processes, including pH homeostasis,
- respiration, biosynthetic reactions and bone resorption.
- 2.  $\gamma$ -Aminobutyric acid receptors
- In vertebrates,  $\gamma$ -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

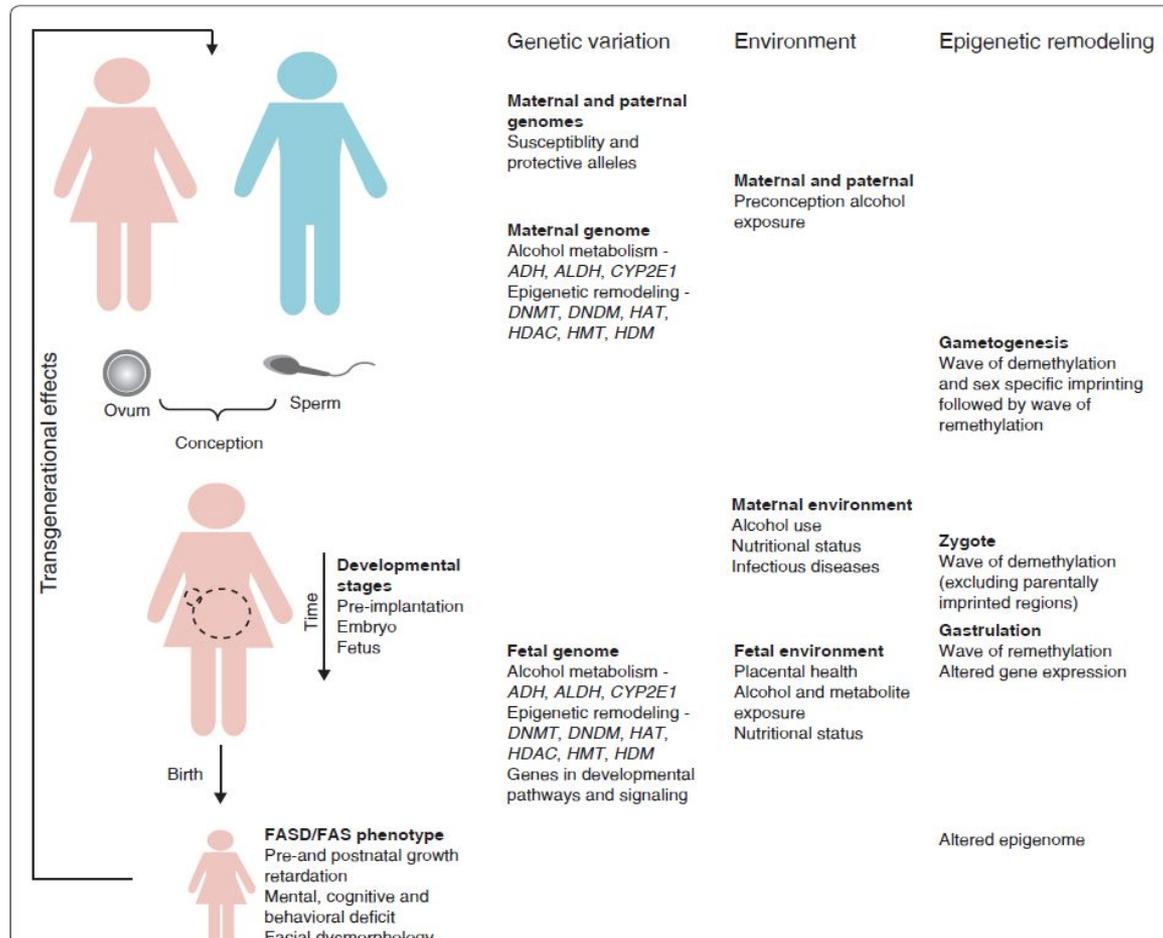
# Результат применения лекарств



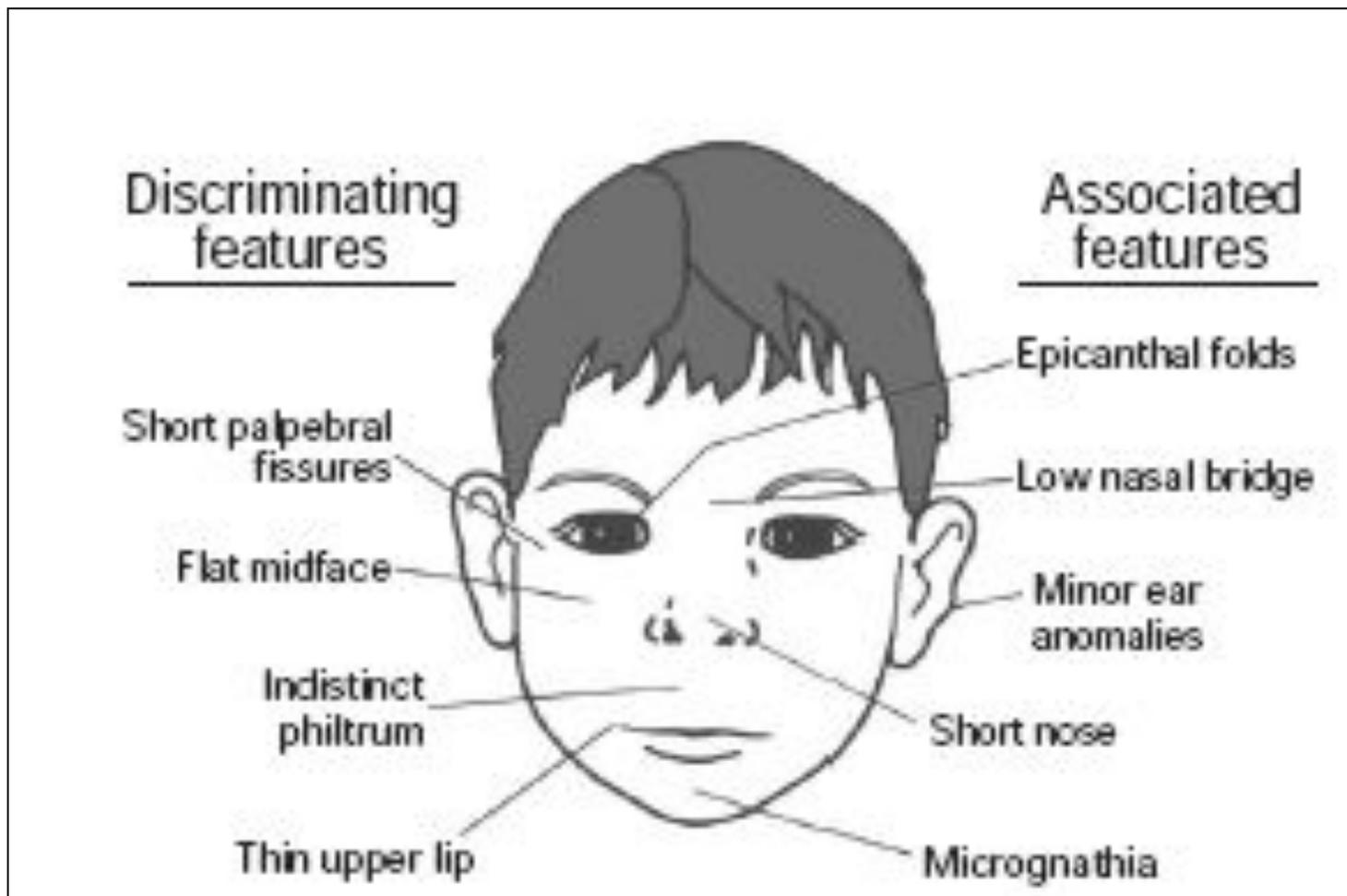
Fig. 1: Minor facial anomalies in a 3-year-old boy whose mother was treated with carbimazole (a prodrug that is completely metabolized to methimazole) for the treatment of Graves' disease during pregnancy (picture provided by Drs. L.C. Wilson, B.A. Kerr, R. Wilkinson, C. Fossard and D. Donnai). Reprinted 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 <sup>1</sup> | 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 $\beta$ 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  |
|---|---|---|---|
| <b>Segment I:</b><br>Fertility and general reproduction study                                   | Males: 10 weeks prior to mating<br>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.   |
| <b>Segment II:</b><br>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. |
| <b>Segment III:</b><br>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.   |
| <b>ICH 4.1.1:</b><br>Fertility protocol   | Males: 4 weeks prior to mating<br>Females: 2 weeks prior to mating  | Males: Reproductive organ weights and histology, sperm counts and motility<br>Females: Viability of conceptuses at mid-pregnancy or later                                     | Improved assessment of male reproductive endpoints; shorter treatment duration than Segment I.  |
| <b>ICH 4.1.2:</b><br>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) |   |
| <b>ICH 4.1.3:</b><br>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).   |
| <b>OECD 414</b><br>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;<br>20/33; 11/15<br>Specificity: 17/19;<br>18/18; 8/10<br>Accuracy: 79% | Flint and Orton, 1984<br>Renault <i>et al.</i> , 1989<br>Uphill <i>et al.</i> , 1990<br>Genschow <i>et al.</i> , 2000<br>Spielmann <i>et al.</i> , 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%<br>Specificity: 68%<br>Accuracy: 79%                                      | Scholz <i>et al.</i> , 1999<br>Genschow <i>et al.</i> , 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<br>Specificity: 14/17   | Daston <i>et al.</i> , 1991<br>Daston <i>et al.</i> , 1995a<br>(concordances combined)  |
| <i>Drosophila</i>                       | 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<br>Specificity: 4/5   | Lynch <i>et al.</i> , 1991<br>Palermo <i>et al.</i> , 2004  |
| FETAX                                   | Mid-blastula stage <i>Xenopus</i> embryos exposed for 96 h and evaluated for viability, growth, morphology.  | Sensitivity: 6/7<br>Specificity: 2/2   | Bantle, 1995<br>Fort <i>et al.</i> , 2000<br>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 <i>et al.</i> , 1997<br>Genschow <i>et al.</i> , 2000<br>Piersma <i>et al.</i> , 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<br>Specificity: ND   | Frayssé <i>et al.</i> , 2006<br>Love <i>et al.</i> , 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<br>Specificity: 28/34   | Hardin <i>et al.</i> , 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 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  $\mu$ M) 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.

**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):**

Marleen van Gelder was supported by the Netherlands Organisation for Scientific Research/NWO (grant no. 021.001.008). No competing interests are declared. TRIAL REGISTRATION NUMBER: N/A.