Drugs in Pregnancy, Fetus & Newborn

Transplacental Drug Transfer

- **Most drugs move from the maternal circulation into the fetal circulation by diffusion.**
- **That depends on lipid solubility, electrical charge, molecular weight, and degree of protein binding.**
- **Reduction of maternal albumin, while fetal albumin is increased throughout pregnancy, may result in high concentration of certain protein-bound drugs in the fetus.**

Methods and Resources for Determining Drug Safety During Pregnancy

- Pregnant women are not eligible to participate in clinical trials.
- Therefore, the resources are less than optimal to provide good quality evidence (animal studies, case reports, case-control studies, prospective cohort studies, voluntary reporting ..).
- Thalidomide was found safe in animal studies, but teratogenic in humans. Thus, extrapolation of results of animal studies to humans is not always valid.

Methods and Resources for Determining Drug Safety During Pregnancy

- The listed clinical studies suffer from bias (recall bias), and require large number of subjects.
- Assistance concerning teratogenicity of drugs can be obtained from some data bases:
- WWW.motherisk.org , www.toxnet.nlm.nij.gov
- Pregnancy risk factors categories (A, B, C, D, X).

Reasons for Drug Therapy During Pregnancy

1. Pregnancy-induced conditions such as nausea and vomiting, preeclampsia / eclampsia.
2. Chronic conditions diagnosed before pregnancy such as epilepsy, bronchial asthma, DM, hypertension etc..
3. Acute conditions that may occur during pregnancy such as infections, diabetes mellitus, hypertension, etc..

Reasons for Drug Therapy During Pregnancy

4. Fetal therapy:

- **Fetal therapeutics involves drug administration to the pregnant woman with the fetus as the target of the drug.**

a. Corticosteroids are given to the mother to stimulate fetal lung maturation when preterm birth is expected.

Reasons for Drug Therapy During Pregnancy

b. Phenobarbital, when given to pregnant women near term, can induce fetal hepatic enzymes responsible for the glucuronidation of bilirubin. The incidence of jaundice is lower in newborns when mothers are given phenobarbital than when phenobarbital is not used.

Reasons for Drug Therapy During Pregnancy

c. **Maternal use of zidovudine decreases transmission of HIV from the mother to the fetus. Combinations of three antiretroviral agents can eliminate fetal HIV infection almost entirely.**

Drug Therapy in Pregnancy

- **Most drugs taken by pregnant women can cross the placenta.**
- **The developing embryo and fetus may be exposed to their pharmacologic, toxic and teratogenic effects.**

Factors Affecting Placental Drug Transfer

1. The physicochemical properties of the drug.
2. The duration of exposure to the drug.
3. Pharmacokinetics of the drug in fetal tissues.

Pharmacokinetics

A. Lipid Solubility:

- **Drug passage across the placenta is dependent on lipid solubility and the degree of drug ionization.**
- **Lipophilic drugs tend to diffuse readily across the placenta and enter the fetal circulation.**
- **Thiopental crosses the placenta almost immediately and can produce sedation or apnea in the newborn infant.**

Pharmacokinetics

- **Highly ionized drugs, such as tubocurarine, cross the placenta slowly and achieve very low concentrations in the fetus.**
- **Impermeability of the placenta to polar (or ionized) compounds is relative rather than absolute.**
- **If high enough maternal-fetal concentration gradients are achieved, polar compounds can cross the placenta in measurable amounts.**

Pharmacokinetics

- **Salicylate, which is almost completely ionized at physiologic pH, crosses the placenta rapidly, because the small amount of salicylate that is not ionized is highly lipid-soluble.**

B. Molecular Size:

- **Drugs with molecular weights of 250–500 can cross the placenta easily.**
- **Drugs with molecular weights of 500–1000 cross the placenta with more difficulty.**

Pharmacokinetics

- **Drugs with molecular weights greater than 1000 cross very poorly.**
- **Heparin may be safely given to pregnant women who need anticoagulation. Because of its large size and polarity, it is unable to cross the placenta.**
- **Insulin is indicated for treatment of diabetes during pregnancy because it does not cross the placenta.**

Pharmacokinetics

C. pH

- **Because maternal blood has a pH of 7.4 and that of the fetal blood is 7.3, weakly basic drugs with pKa above 7.4 will be more ionized in the fetal compartment, leading to ion trapping and, hence, to higher fetal levels.**

Pharmacokinetics

D. Placental Transporters:

- **Many drug transporters have been identified in the placental brush border membrane.**
- **P-glycoprotein transporter pumps back into the maternal circulation a variety of drugs, including anticancer drugs (vinblastine, doxorubicin) and other agents (anti-HIV drugs).**

Pharmacokinetics

E. Protein Binding:

- **Binding of drugs to plasma proteins (particularly albumin) may reduce the rate of transfer and the amount transferred.**
- **This might NOT be true if the drug is highly lipid soluble (thiopental used in anesthesia). The transfer of such compounds will depend on placental blood flow.**

Pharmacokinetics

- **Fetal proteins have lower binding affinity than maternal proteins.**
- **This has been shown for sulfonamides, barbiturates, phenytoin, and local anesthetic agents.**
- **Very high maternal protein binding of glyburide is associated with lower fetal levels because it does not cross placenta. This drug is also effluxed from the fetal circulation.**

Pharmacokinetics

F. Placental and Fetal Drug Metabolism:

- **The placenta plays a role as a site of metabolism of some drugs passing through it.**
- **Pentobarbital is oxidized by the placenta.**
- **The metabolic capacity of the placenta may lead to formation of toxic metabolites (ethanol, benz(a)pyrenes).**
- **Drugs that enter the fetal liver may be partially metabolized before reaching the fetal circulation.**

Effects of Drugs on the Product of Conception

There are several possibilities:

1. **No Effect.**
2. **Restricted growth.**
3. **Impairment of functional development.**
4. **Abortion, Death, Placental damage.**
5. **Neonatal problems.**
6. **Congenital malformations (Tertogenicity).**

Drug Selection During Pregnancy

- Most drugs needed by pregnant women are relatively safe, while some have the potential to cause teratogenic effects.
- The baseline risk of congenital malformations is 3-6%.
- 3% of congenital malformations are severe.
- <1% of congenital malformations are due to drugs.
- Genetic causes are responsible for 15-25% of cases.
- Maternal conditions and infections, and environmental factors account for 10% of cases.
- 65-75% of cases are idiopathic.

Causes and Incidence of Congenital Malformations

1. X-Radiation (1920s).
2. UV radiation (skin cancer).
3. Viral Infections (Rubella) (1940s).
4. Drugs and chemicals (Thalidomide and limb deformities) (1960). (defects that can be avoided, should be avoided).

Causes and Incidence of Congenital Malformations

- For more than 90% of available drugs, the human teratogenic risk is not determined.
- Why?

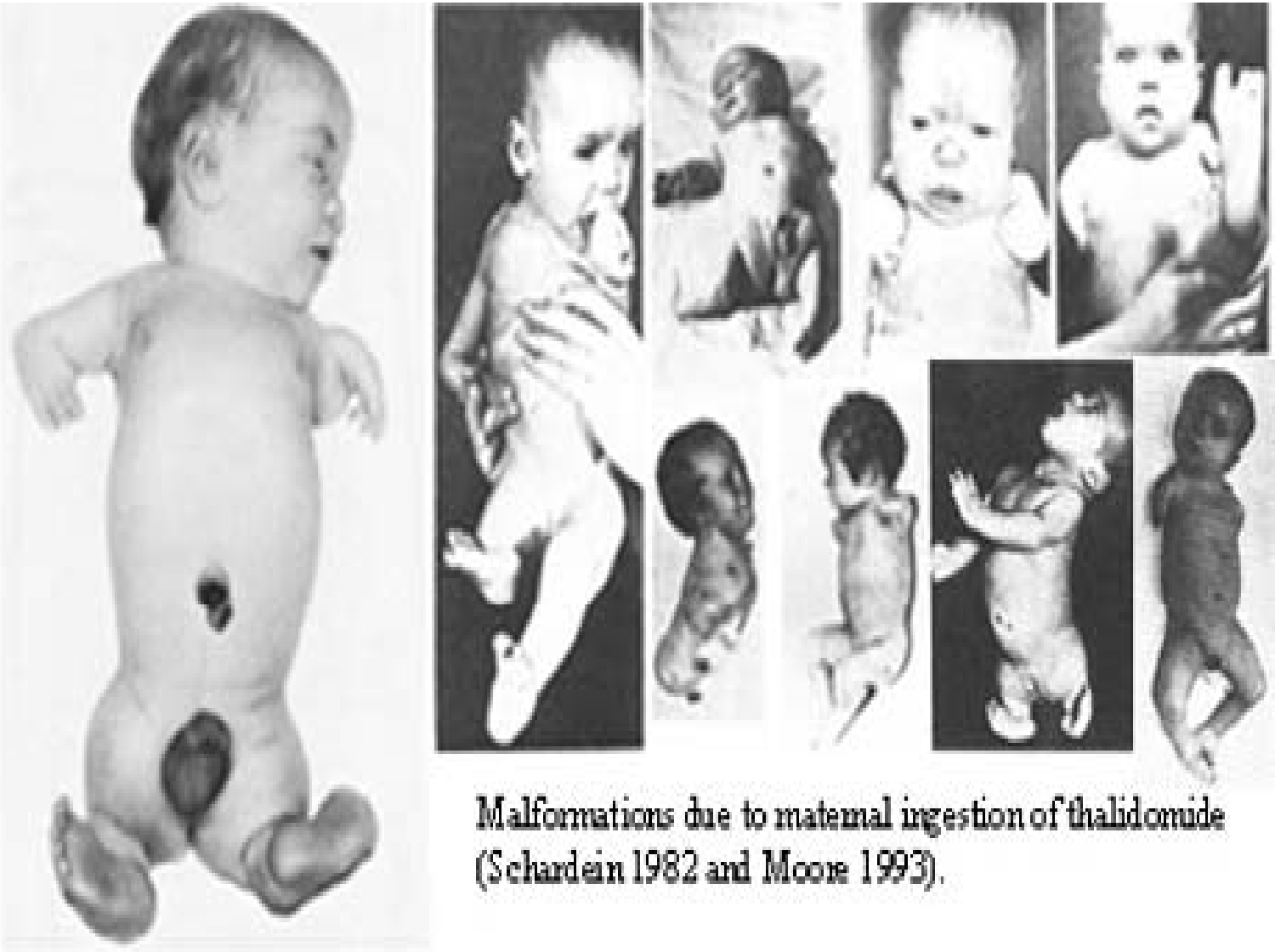
1. Performance of drug experiments during human pregnancy to test for teratogenicity is not allowed.
2. Evidence to support teratogenesis is derived from animal studies.

Causes and Incidence of Congenital Malformations

- Dosage used in animals are much higher than therapeutic doses to women.
- Results in animals do not always extrapolate to humans.

Teratogenic Drug Actions

- A single intrauterine exposure to a drug can affect the fetal structures undergoing rapid growth at the time of exposure.
- This exposure must be at a critical time during development.
- Types of anomalies are determined by the time of exposure during pregnancy.
- The thalidomide phocomelia risk occurs during the 4^{th}-7^{th} weeks of gestation, because it is during this time that the arms and legs develop.



Malformations due to maternal ingestion of thalidomide (Schardein 1982 and Moore 1993).

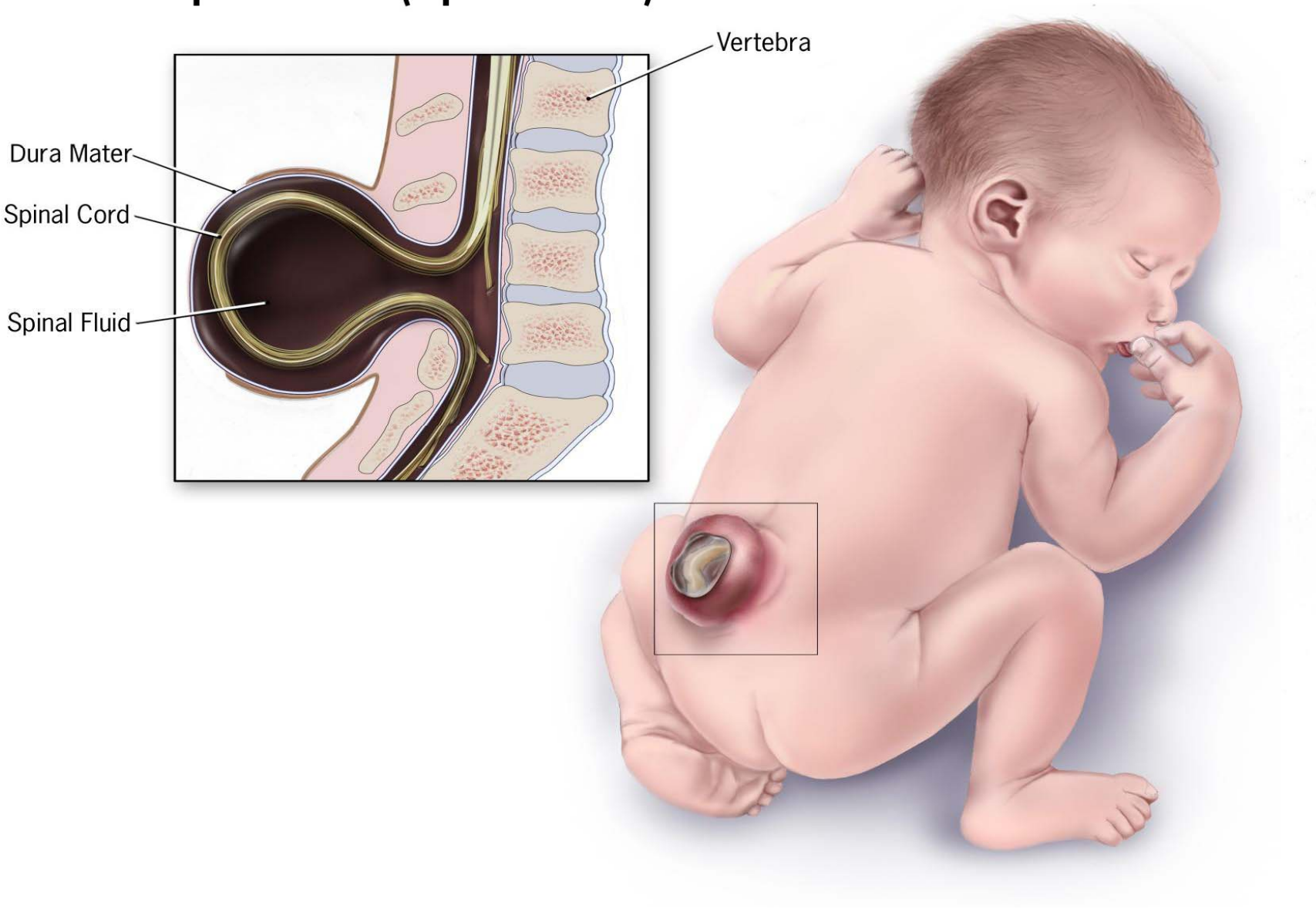
Teratogenic mechanisms

- **They are poorly understood and are probably multifactorial:**

1. **Folic acid deficiency, or use of folic acid antagonists, during pregnancy may produce neural tube defects (Spina bifida).**

- **Folic acid supplementation during pregnancy reduces the incidence of these defects.**
- **Rapidly proliferating tissues require DNA synthesis which requires folate.**

Spina Bifida (Open Defect)



Teratogenic mechanisms

2. **Neural crest cells disruption:**

- **Neural crest cells are pluripoptent cell population that gives numerous structures.**
- **Disruption can be caused by endothelin receptor blockers, folic acid antagonists, and retinoic acid (vitamin A derivative).**

3. **Drugs may alter the normal processes of differentiation. Vitamin A analogs (isotretinoin, etretinate) are powerful teratogens.**

Teratogenic mechanisms

4. **Endocrine disruptions (Sex hormones):**

- **Diethylstilbesterol increases the risk of vaginal adenocarcinoma in daughters, and hypospadius and cryptorchidism in sons.**

5. **Oxidative stress (reactive oxygen species) cause irreversible damage of DNA, proteins and lipids; leading to inactivation of many enzymes and cell death; and alteration of gene expression.**

Teratogenic mechanisms

6. Vascular disruption:

- **Refers to disruption in the circulation which include hypoperfusion, hyperperfusion, hypoxia and obstruction.**
- **Drugs may interfere with the passage of oxygen or nutrients through the placenta and have effects on the most rapidly metabolizing tissues of the fetus.**

Teratogenic mechanisms

7. **Chronic consumption of high doses of ethanol during pregnancy, particularly during the first and second trimesters, may result in the "Fetal Alcohol Syndrome".**

- **In this syndrome, the central nervous system, growth, and facial development may be affected.**

Fetal Alcohol Syndrome Symptoms

- **A small head, a smooth ridge between the upper lip and nose, small and wide-set eyes, a very thin upper lip, or other abnormal facial features, below average height and weight, hyperactivity, lack of focus, poor coordination, delayed development and problems in thinking, speech, movement, and social skills; poor judgment, problems seeing or hearing, learning disabilities, intellectual disability, heart problems, kidney defects and abnormalities, deformed limbs or fingers, mood swings.**


Small head
Low nasal bridge
Epicanthal folds
Small eye openings
Flat midface
Short nose
Thin upper lip
Smooth philtrum
Underdeveloped jaw
ADAM.

Teratogenic mechanisms

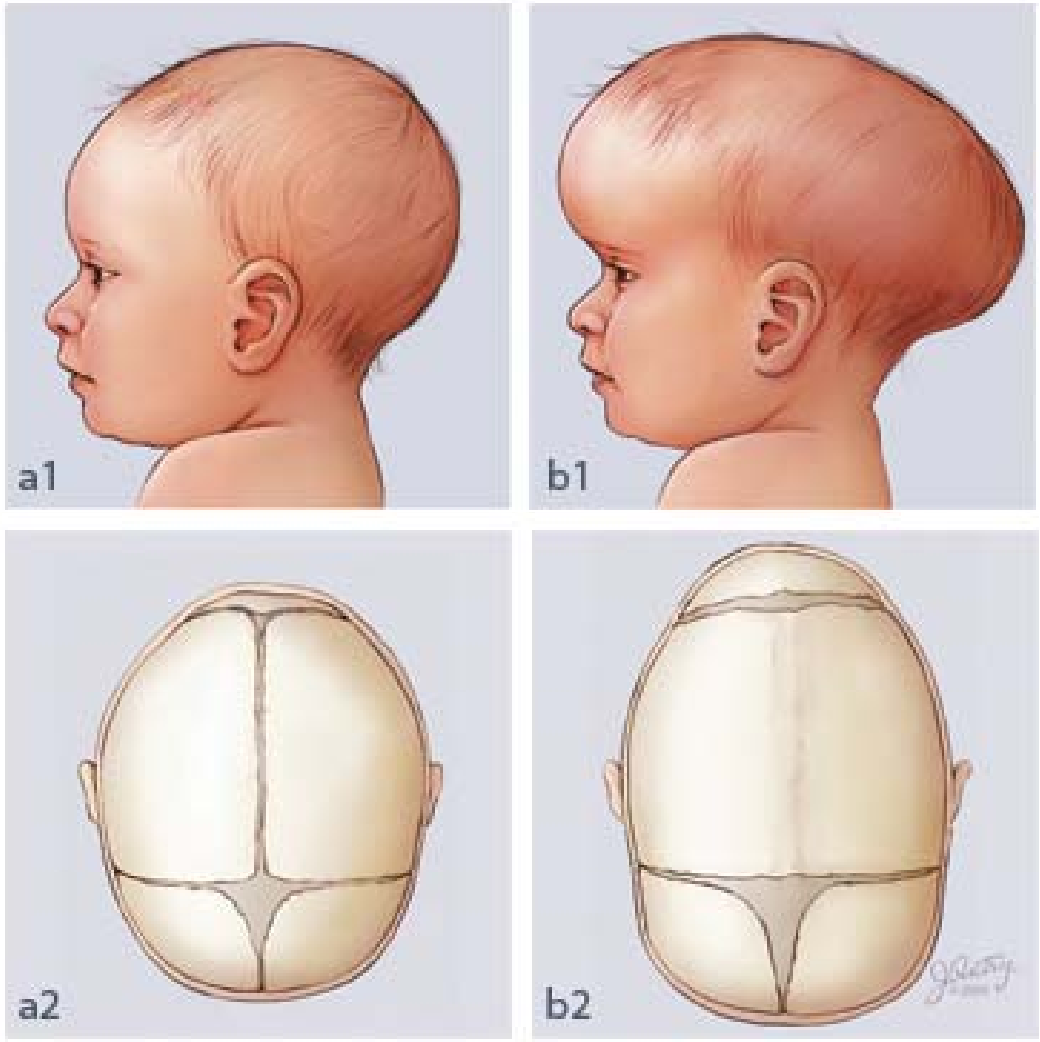
8. Maternal Smoking in Pregnancy:

The Fetus may have the following anomalies:

- **Cardiovascular defects.**
- **Musculoskeletal defects and craniosynostosis.**
- **Facial defects (face, nose, eyes or ears).**
- **Defects of the gastrointestinal system.**
- **Increased risk of early delivery – preterm.**
- **Abortion.**

Teratogenic mechanisms

- **Abruptio placentae.**
- **Slow fetal growth.**
- **Learning disabilities.**
- **Infant death.**
- **Sudden infant death syndrome (SIDS).**
- **Low birth-weight.**
- **Mental retardation.**
- **Cerebral palsy.**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Defining a teratogen

To be considered teratogenic, a drug should:

1. **Result in a characteristic set of malformations, indicating selectivity for certain target organs.**
2. **Exert its effects at a particular stage of fetal development, during the limited time period of organogenesis of the target organs.**
3. **Show a dose-dependent incidence.**

Defining a teratogen

- **Drug effects on the fetus are not limited only to major malformations, but also include intrauterine growth retardation (cigarette smoking), miscarriage (alcohol), stillbirth (cigarette smoke), and neurocognitive delay (alcohol).**

Factors Affecting the Production of Congenital Malformations

A. The Dose of the Teratogen:

The effect is dose-dependent. Therefore, give the lowest effective dose for the shortest possible duration.

B. The developmental stage of the embryo:

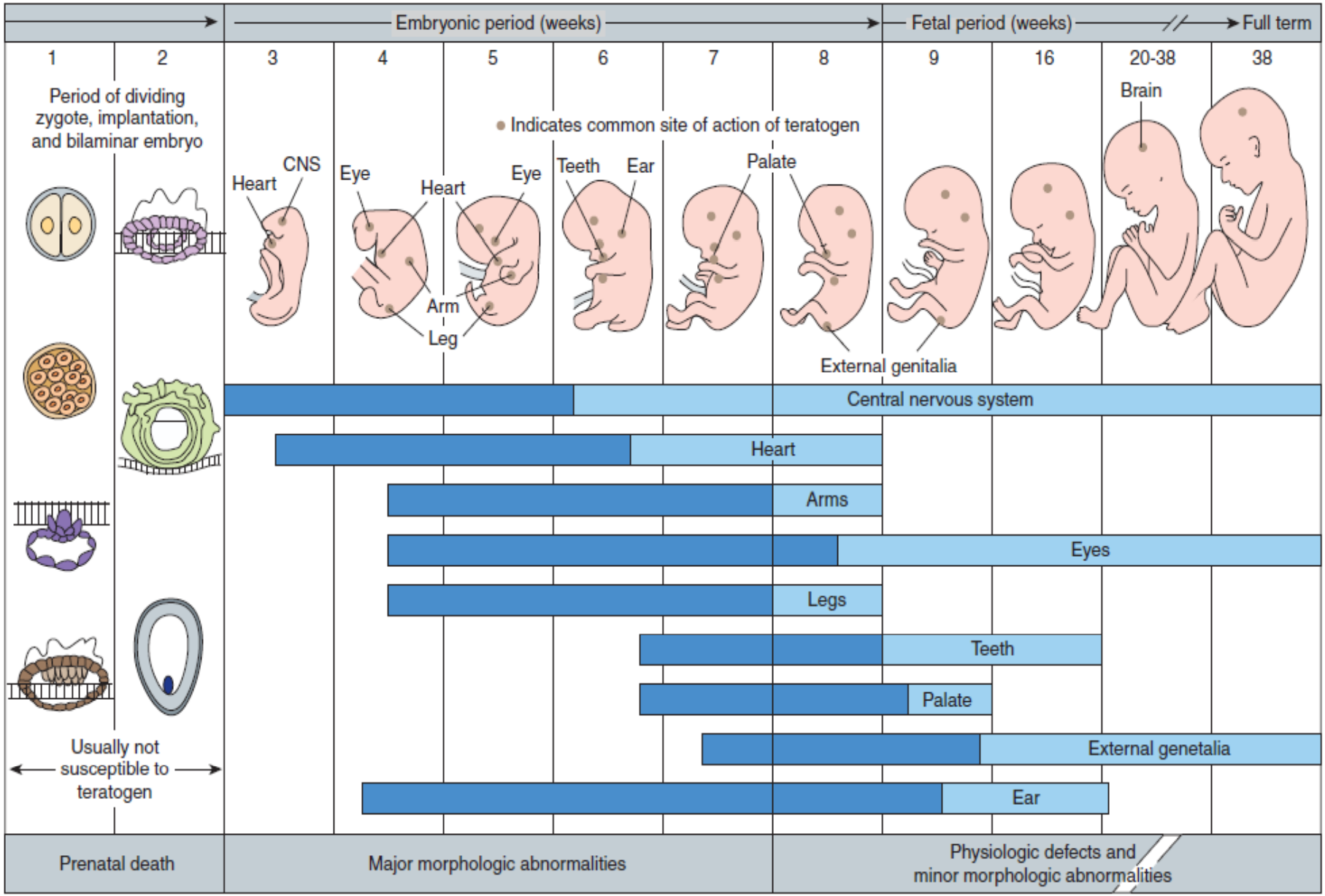

FIGURE 59–1 Schematic diagram of critical periods of human development. (Reproduced, with permission, from Moore KL: *The Developing Human: Clinically Oriented Embryology,* 4th ed. Saunders, 1988.)

Factors Affecting the Production of Congenital Malformations

1. **Blastogenesis:**

   Time of fertilization to implantation, 1-8 days).

- **Exposure may kill blastocyst, no evidence of production of congenital malformations.**
- **Up to 15th day after fertilization, cells are still totipotent and damaged cells can be replaced.**

Factors Affecting the Production of Congenital Malformations

2. **Embryogenesis:**

   Time of implantation to the end of 8th week (2^{nd} – 8^{th} week).

- **The vulnerability of the developing embryo to teratogens is greatest because this is the critical period for organogenesis.**
- **It results in gross malformations or fetal death.**

Factors Affecting the Production of Congenital Malformations

2. **Fetogenesis:**

   End of 8th week to End of pregnancy.

- **The most important events are:**

a. **Differentiation of external genitalia.**

b. **Histogenesis of CNS.**

Results:

a. **Impairment of Differentiation of external genitalia.**

b. **Behavioral changes or impairment of mental development.**

Factors Affecting the Production of Congenital Malformations

C. The Genetic Susceptibility of the Embryo:

- No teratogen produces congenital malformations in all fetuses

D. The physiological and Pathological status of the mother:

a. Age

b. Nutritional status

c. Disease states

Effect of Drugs Late in Pregnancy

- **No congenital malformations.**
- **Examples on effects that are likely to occur:**

1. **Salicylates may increase bleeding or delay labor.**
2. **ACEIs may produce irreversible fetal renal damage.**
3. **Opioids may produce dependence in the fetus.**

Effect of Drugs Very Near Delivery

- **No congenital malformations.**
- **Examples on effects that may occur:**

1. **Thiopental may produce sedation and apnea in the newborn.**
2. **Opioids may produce apnea in the newborn.**

Counseling Women About Teratogenic Risk

1. Few drugs are teratogens compared to the majority of safe drugs during pregnancy.
2. Evidence-based medicine should be practiced when talking about drug teratogenicity.
3. The risk of a neonatal abnormality in the absence of any known teratogenic exposure is about 3%.
4. Pregnancy outcomes are affected by maternal health status, lifestyle, and history prior to conception.

Counseling Women About Teratogenic Risk

5. **The maternal-fetal risks of the untreated condition or if a medication is avoided is high.**

- **Recent studies show serious morbidity in women who discontinued selective serotonin reuptake inhibitor therapy for depression in pregnancy.**
- **The goal of planning is health promotion through modification of behavioral, biomedical and social risks in all women of productive age.**

Drug Associated with Congenital Malformations

- **Examples of drugs associated with congenital anomalies during organogenesis: methotrexate, cyclophosphamide, sex hormones (androgens and progestins, lithium, retinoids, thalidomide, certain antiepileptic drugs, and coumarines.**
- **NSAIDs and tetracycline are likely to produce effects during the second and third trimesters.**

Table 57.2 Some drugs reported to have adverse effects on human fetal development

Agent	Effect(s)	Teratogenicity[a]	See Chapter
Thalidomide	Phocomelia, heart defects, gut atresia, etc.	K	This chapter
Penicillamine	Loose skin etc.	K	26
Warfarin	Saddle nose; retarded growth; defects of limbs, eyes, central nervous system	K	24
Corticosteroids	Cleft palate and congenital cataract—rare	–	32
Androgens	Masculinisation in female	–	34
Oestrogens	Testicular atrophy in male	–	34
Stilbestrol	Vaginal adenosis in female fetus, also vaginal or cervical cancer	20+ years later	34
Phenytoin	Cleft lip/palate, microcephaly, mental retardation	K	44
Valproate	Neural tube defects (e.g. spina bifida)	K	44
Carbamazepine	Retardation of fetal head growth	S	44
Cytotoxic drugs (especially folate antagonists)	Hydrocephalus, cleft palate, neural tube defects, etc.	K	55
Aminoglycosides	Deafness	–	50
Tetracycline	Staining of bones and teeth, thin tooth enamel, impaired bone growth	S	50
Ethanol	Fetal alcohol syndrome	K	48
Retinoids	Hydrocephalus etc.	K	56
Angiotensin-converting enzyme inhibitors	Oligohydramnios, renal failure	K	22

[a]K, known teratogen (in experimental animals and/or humans); S, suspected teratogen (in experimental animals and/or humans).
Adapted from Juchau 1989 Annu Rev Pharmacol Toxicol 29: 165.

Preconception Risk Factor	Potential Adverse Pregnancy Outcomes	Management or Prevention Options
Use of known teratogens		
• Antiepileptic drugs	• Known teratogens; causes craniofacial, cardiac, and limb defects[a] • NTD • Fetal hydantoin syndrome	• Use lowest possible dose to maintain control • Folic acid 4 mg daily
• Isotretinoins	• Miscarriage • Known teratogen; causes CNS, craniofacial, and cardiac defects[a]	• Use effective pregnancy prevention
• Oral anticoagulants	• Fetal warfarin syndrome	• Switch to nonteratogenic anticoagulant (eg, LMWH) before becoming pregnant

Lifestyle factors		
• Alcohol misuse	• Fetal alcohol syndrome	• Cease alcohol intake before conception
• Obesity	• NTD • Preterm delivery • Diabetes, HTN, VTE • Cesarean section	• Weight loss with appropriate nutritional intake before pregnancy
• Tobacco use	• Preterm birth • Low birth weight • Spontaneous abortion • Increased perinatal mortality	• Ideally, cease tobacco use before conception • Nonpharmacologic therapies (eg, CBT, counseling, hypnosis) • No consensus for NRT product, dosing, or frequency: ○ Intermittent forms (eg, gum) ○ Transdermal patch (limit to 16 h/day) • Bupropion risk may be less than risk posed by smoking; efficacy unclear • Varenicline safety unknown

CBT, cognitive behavioral therapy; CNS, central nervous system; HTN, hypertension; LMWH, low-molecular weight heparin; NRT, nicotine replacement therapy; NTD, neural tube defect; VTE, venous thromboembolism.

[a]List is not all-inclusive.

Fetal Hydantoin syndrome

Areas affected	Clinical features
Craniofacial abnormalities	Cleft lip, cleft palate, a broad depressed nasal bridge, low-set abnormal ears, broad alveolar ridges, and long philtrum
Ocular defects	Ocular hypertelorism, strabismus, ptosis of the eyelids, and inner epicanthic folds
Limb abnormalities	Hypoplasia of distal phalanges with small nails, a digital thumb, and dislocation of hip
Growth abnormalities	Impaired psychomotor performance and physical growth retardation
Miscellaneous (less frequent)	Nuchal webbing, a low hairline, rib and sternal anomalies, umbilical and inguinal hernias, cardiovascular anomalies, positional limb deformities, and gastrointestinal abnormalities

FDA Pregnancy Categories

Category A

Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

Category B

Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Category C

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

FDA Pregnancy Categories

Category D

There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category X

Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Meaning of FDA Pregnancy Categories of Drugs

- **Category A: No evidence of fetal risk and is safe to use during in pregnancy.**
- **Category B: Relatively safe.**
- **Category C: Information about fetal risk is not available but risk can NOT be ruled out.**
- **Category D: Positive evidence of fetal risk.**
- **Category X: Definite fetal risk and the drug is contraindicated during pregnancy.**

Principles that Guide Drug Selection During Pregnancy

1. Effective old drugs are preferable to new alternatives.
2. Use the lowest effective dose for the shortest possible duration.
3. Discourage pregnant ladies from taking over-the-counter medications, supplements or herbs by themselves.
4. No drug is absolutely safe during pregnancy and at high doses categories can change.

Drug Selection During Pregnancy

Strategies to optimize the health of the mother while minimizing the risk to the fetus:

1. **Identification of the pattern of medication use before conception.**
2. **Eliminating nonessential medications.**
3. **Discouraging self medication.**
4. **Minimizing exposure to medications known to be harmful.**
5. **Adjusting medication dosing.**