Drugs Use During Pregnancy

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Drugs use During Pregnancy

- **Most drugs move from the maternal circulation into the fetal circulation by diffusion.**
- **Some of them may attain high enough concentrations in the fetal circulation to be detrimental to the fetus.**
- **Reduction of maternal albumin, while fetal albumin is increased throughout pregnancy, may result in high concentration of certain protein-bound drugs in the fetus.**

Determining Drug Safety During Pregnancy

- **Pregnant women are NOT eligible to participate in clinical trials.**
- **Therefore, There is less than optimal sources to provide good quality of evidence for efficacy and safety of drugs during pregnancy (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.**

Determining Drug Safety During Pregnancy

- **The available 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:**

1. **WWW.motherisk.org**
2. **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 to benefit the fetus.**

A. **Corticosteroids are given to mothers to stimulate fetal lung maturation (surfactant) 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, although to variable concentrations.**
- **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. Therefore, it should NOT be used for induction of anesthesia in case of Cesarean section.**

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 un-ionized is highly lipid-soluble.**

B. Molecular Size:

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

Pharmacokinetics

- **Drugs with molecular weights greater than 1000 daltons 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

- **Maternal blood has a pH of 7.4 and that of fetal blood is 7.3.**
- **Therefore, 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 blood 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 induction of 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 blood 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).**
- **Some 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. **Placental damage, Abortion & Death.**
5. **Neonatal problems.**
6. **Congenital malformations (Tertogenicity).**

Drug Selection During Pregnancy

- Some drugs have the potential to be teratogenic.
- 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 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 of Congenital Malformations

- **For > 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 unethical and prohibited.**
2. **Evidence to support teratogenesis is derived from animal studies.**

- **Dosage used in animals are much higher than therapeutic doses to women. Therefore, results in animals do not always extrapolate to humans.**

Teratogenic Drug Actions

- **A single intrauterine exposure to a drug, at a critical time during development, can affect the fetal structures undergoing rapid growth**
- **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.**

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 neural tube defects.**
- **Rapidly proliferating tissues require DNA synthesis, which requires folate.**

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 (bosentan), folic acid antagonists, and retinoic acid.**

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

Teratogenic mechanisms

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

- **Diethylstilbesterol increased the risk of vaginal adenocarcinoma in daughters, and hypospadius and cryptorchidism in sons of mothers taking it during pregnancy. (historic example)**

5. **Oxidative stress (reactive oxygen species) causes 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 high consumption 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.**

Teratogenic mechanisms

8. Maternal Smoking During Pregnancy:

The Fetus may have the following anomalies:

a) **Cardiovascular defects.**

b) **Musculoskeletal defects and craniosynostosis.**

c) **Facial defects (face, nose, eyes or ears).**

d) **Increased risk of early delivery – preterm.**

e) **Abortion.**

g) **Slow fetal growth.**

h) **Cerebral palsy.**

i) **Learning disabilities.**

j) **Mental retardation.**

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, miscarriage, stillbirth and neurocognitive delay.**

Factors Affecting the Production of Congenital Malformations

A. The Dose of the Teratogen:

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

B. The developmental stage of the embryo:

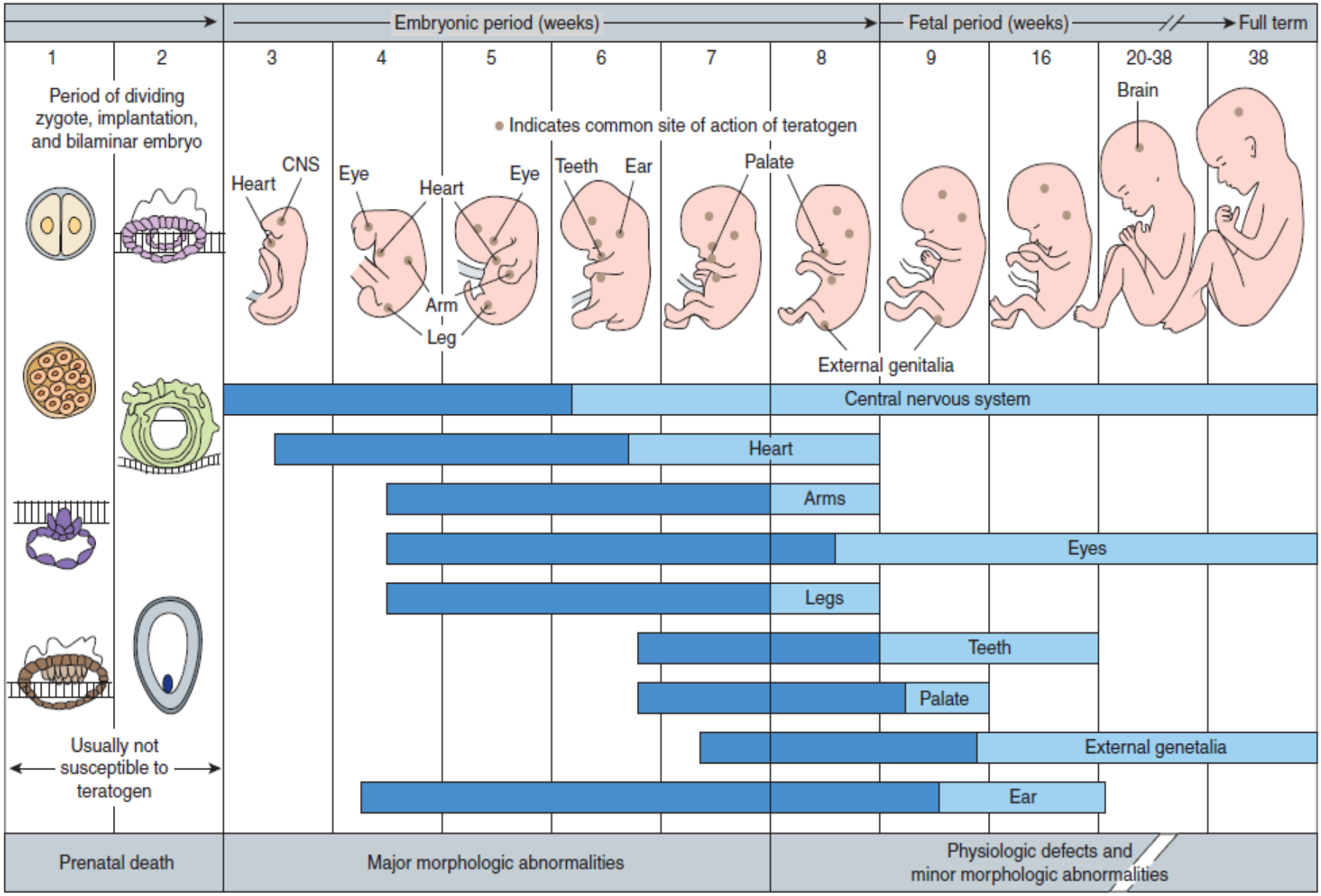

FIGURE 59–1 Schematic diagram of critical periods of human development. (Reproduced, with permission, from Moore KL: *The Developing Human: Clinically Oriented Embryology*, 4th ed. Saunders, 1988.)

Factors Affecting the Production of Congenital Malformations

1. **Blastogenesis:**

   (Time of fertilization - 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 - the end of 8th week (2nd – 8th week).

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

Factors Affecting the Production of Congenital Malformations

3. **Fetogenesis:**

   (End of 8th week - 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:

1) Age (< 18 and > 35 years → higher risk)
2) Nutritional status - malnutrition
3) Disease states - DM

Effect of Drugs Late in Pregnancy

- **No congenital malformations, but adverse effects are likely to occur.**

Examples:

1. **Salicylates may increase bleeding or delay labor → low birth weight.**
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, but adverse effects are likely to occur.**

Examples:

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 known teratogens.
2. For most drugs, teratogenicity is unknown.
3. Evidence-based medicine should be practiced when talking about drug teratogenicity.
4. The risk of a neonatal abnormality in the absence of any known teratogenic exposure is about 3%.
5. Pregnancy outcomes are affected by maternal health status, life-style, and history prior to conception.

Counseling Women About Teratogenic Risk

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

- ***Recent studies have shown <u>serious morbidity</u> in women who discontinued selective serotonin reuptake inhibitor therapy for depression during pregnancy.***

Drug Associated with Congenital Malformations

- **Examples of drugs associated with congenital anomalies during organogenesis: methotrexate, cyclophosphamide, sex hormones (androgens, estrogens and progestins), lithium, retinoids, thalidomide, certain antiepileptic drugs, and coumarins.**
- **NSAIDs and tetracycline are likely to produce adverse 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.

Meaning of FDA Pregnancy Categories of Drugs

1. **Category A: No evidence of fetal risk and is safe to use during in pregnancy.**
2. **Category B: Relatively safe.**
3. **Category C: Information about fetal risk is not available but risk can NOT be ruled out.**
4. **Category D: Positive evidence of fetal risk.**
5. **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.**