

Drugs Use During Pregnancy

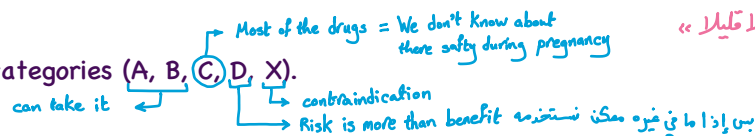
- Most drugs move from the maternal circulation into the fetal circulation by diffusion.
- Some of them may attain high enough concentrations in the fetal circulation to be detrimental to the fetus.
- Reduction of maternal albumin, while fetal albumin is increased throughout pregnancy, may result in 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. → Epidemic of phocomelia: congenital malformation in the limbs (either lack of a limb, short limbs, hands stuck to the shoulder ..)
- Thus, extrapolation of results of animal studies to humans is NOT always valid.
- 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.nih.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..
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.
 - 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.
 - 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.

- 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: → affect passage of drugs through membranes in the body نفس ال factors التي

1. The physicochemical properties of the drug. (water/lipid soluble)
2. The duration of exposure to the drug. → كلما زاد ، يزيد ال passage
3. Pharmacokinetics of the drug in fetal tissues.

Pharmacokinetics

* if water soluble it will penetrate very little; can't pass through membranes.

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.
- 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.
- 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.
- 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. Warfarin crosses the placenta & can damage the fetus (can be toxic & can produce congenital malformations)
- Insulin is indicated for treatment of diabetes during pregnancy because it does NOT cross the placenta.

C. pH

- Maternal blood has a pH of 7.4 and that of fetal blood is 7.3. (a little more acidic)
- 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.

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).

efflux pump

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.
- Fetal proteins have lower binding affinity than maternal proteins. → more of it can be free → act
- 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. by: P-glycoprotein

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. *associated with low birth weight*
3. Impairment of functional development.
4. Placental damage, Abortion & Death.
5. Neonatal problems.
6. Congenital malformations (Teratogenicity). *like DM*

Drug Selection During Pregnancy

- Some drugs have the potential to be teratogenic.
- The baseline risk of congenital malformations is 36%.
- 3% of congenital malformations are severe.
- < 1% of congenital malformations are due to drugs. (*preventable*)
- 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. « وما أوتيتم من العلم إلا قليل »

سبحان العليم الحكيم

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!

→ Ethical agreement in pregnant ladies is not taken only from the mother, but also from father.

ثمن الولد لهما، وليس لها لحالها أوله لحاله

تسكّر آية: « لا تقهار والدة بولدها ولا مولود له بولده » الحمد لله!

→ Category C

- 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 4th-7th 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.

Monopotent
Pluripotent → more than one type of cell can develop from them : like neural crest cells
Totipotent → cells can develop into any kind of tissue / most types of tissues : like stem cells or early cells

2. Neural crest cells disruption:

- Neural crest cells are **pluripotent** 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.

↳ Retinoic acid derivatives

4. Endocrine disruptions (Sex hormones):

- Diethylstilbesterol increased the risk of vaginal adenocarcinoma in daughters, and hypospadias and cryptorchidism in sons of mothers taking it during pregnancy. (historic example) → No one use diethylstilbesterol as estrogen now.

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.

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.

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.

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.

- 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:

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.

لكن ممكن تموت كل الخلايا
وبين مع السيدة إنه بي
Delay in the period

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. *may result from drugs at any stage*
- Exposure results in gross malformations or fetal death. *of pregnancy*

3. Fetogenesis:

(End of 8th week - end of pregnancy).

The most important events are:

- Differentiation of external genitalia.
- Histogenesis of CNS.

ما بيسر والاني ٣ أماكن
CNS
Eyes
External Genitalia

Results:

- Impairment of differentiation of external genitalia.
- Behavioral changes or impairment of mental development.

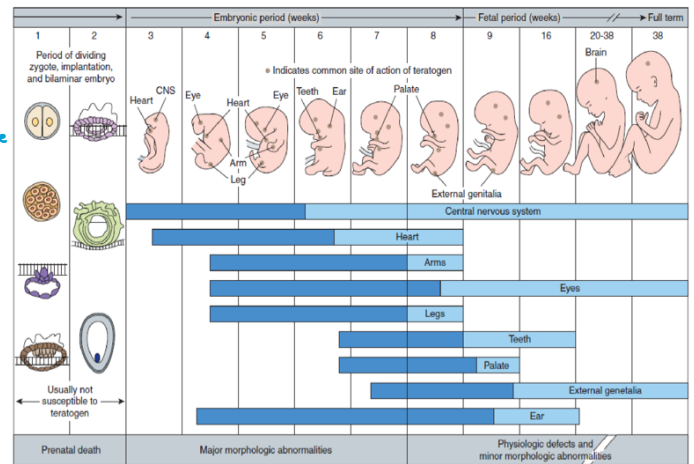


FIGURE 59-1 Schematic diagram of critical periods of human development. (Reproduced, with permission, from Moore KL: The Developing Human: Clinically Oriented Embryology, 4th ed. Saunders, 1988.)

C. The Genetic Susceptibility of the Embryo:

- No teratogen produces congenital malformations in all fetuses

D. The physiological and Pathological status of the mother:

- Age (< 18 and > 35 years → higher risk) → الدكتور لا يتبنى هذا الومضوع ولا يرفضه
- Nutritional status - malnutrition
- Disease states - DM

Effect of Drugs Late in Pregnancy:

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

Examples:

- Salicylates may increase bleeding or delay labor → low birth weight. *aging of placenta → No transfere of nutrients*
- ACEIs may produce irreversible fetal renal damage. *Teratogenic in the first 3 weeks; like agenesis of kidney*
- Opioids may produce dependence in the fetus. *Late in pregnancy result in renal damage*
بجسر عنده withdrawal symptoms بس ينولد

Effect of Drugs Very Near Delivery:

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

Examples:

- Thiopental may produce sedation and apnea in the newborn.
- Opioids may produce apnea in the newborn.

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.

Counseling Women About Teratogenic Risk:

- بعضها مع بعضها
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.
 6. The maternal-fetal risks of the untreated condition (if a required medication is avoided) is high.
- Recent studies have shown serious morbidity in women who discontinued selective serotonin reuptake inhibitor therapy for depression during pregnancy.

Drug Associated with Congenital Malformations:

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

Agent	Effect(s)	Teratogenicity*	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

*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.

- 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.

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.

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.

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