



Lecture 5

Teratogens and drugs of abuse in pregnancy

Objectives:

- ★ Factors affecting drug placental transfer
 - ★ Harmful effects of drugs during different stages of development
 - ★ FDA classifications of drugs.
 - ★ Teratogenic drugs
 - ★ Adverse effects of drugs
 - ★ Effects of drug abuse
- Additional Notes
 - **Important**
 - Explanation –Extra-

before starting, please check our [Reproductive block correction](#)

For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology434@gmail.com

Medications in Pregnancy

- Most drugs can cross placenta by **passive diffusion**.
- Placental membrane is **semi-permeable**.
- The movement of drugs across the placenta is limited by a single layer of cells called **trophoblasts**.



Factors controlling placental drug transfer

I. Physiochemical properties of the drug

Lipid solubility or diffusion.

Molecular size.

Protein binding.

II. The stage of placental and fetal development

III. Duration of exposure to the drug.

Physiochemical properties of the drugs

Lipid solubility:

Lipophilic drugs: Diffuse readily across the placenta and enter fetal circulation. e.g. **Thiopental** > crosses placenta & causes sedation, apnea in newborn infants.

Ionized drugs*: cross the placenta very slowly > very low conc. in the fetus e.g. **Succinylcholine & pancuronium**

*Ionized means **Polar drug**: is water soluble it cannot cross placental barrier

Molecular Weight:

when the size is decreased it has more chance to go inside the placental barrier and here is the guide:

- 250 - 500 Da* cross placenta easily
- 500 - 1000 Da cross placenta with more difficulty
- –More than 1000 Da cannot cross placenta e.g. **Heparin** (high molecular weight)

*Da: means Dalton molecular weight

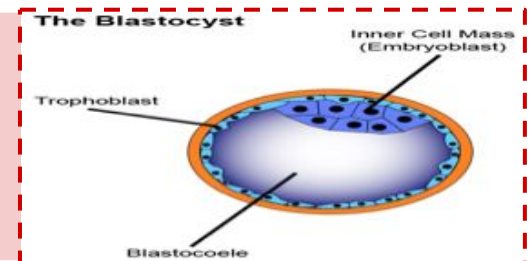
Protein Binding:

- Protein binding in maternal circulation hinders passage of drugs especially . e.g **propylthiouracil and chloramphenicol**
- When protein binding of drug is high it will prevent it to go to placenta

The stages of mammalian fetal development

1-Blastocyst formation (First 2 weeks)

- Occurs from (1-16 days) in the first trimester.
 - Pre-differentiated period (conceptus).
 - Drugs have an **all-or-nothing effect**: If a pregnant woman take a drug cause teratogenesis it will be either abortion (not malformation) or nothing happens.
 - Exposure to harmful drugs during this period cause > **Prenatal death & abortion**
- Period of dividing zygote and implantation



The stages of mammalian fetal development

2-Organogenesis: (2-8 weeks)

- Occurs in (17- 60 days) in the first trimester.
- is the process by which cells specialize and organize to form the tissues and organs of an organism.
- The **most sensitive period** of pregnancy. (**Dangerous period**)
- Exposure to harmful drugs → **Major birth defect in body parts or major congenital malformation.** (because it is the period of organ formation)

3-Histogenesis and functional maturation: (8 weeks onwards)

- Growth and fetal development occur during this stage.
- Fetus depends upon nutrients & hormonal supply.
- Exposure to drugs during 2nd and 3rd will **not** induce major malformation but drugs can produce minor morphologic abnormalities, growth retardation and functional defects.
- “Function problems” rather than “gross malformation”

Summary of stages of mammalian fetal development

- **First trimester: week 1- week 12:**
 - **Organogenesis (week 2- week 8) :**
Major congenital malformations (teratogenesis).
- **Second & Third trimesters (week 13-week 28):**
Affect growth & fetal development
- **Near Term (week 29-week 40):**
Adverse effects on labor or neonates after delivery.

Teratogenesis

- **Teratogenesis:** Occurrence of congenital defects of the fetus.
- **What is a teratogen?**
 - Is any agent that is able to interfere with fetal development and leads to permanent birth defects.
 - This could be severe during critical periods of development e.g. (**organogenesis**).
 - **Agent may be:** medication, street drug, chemicals, disease, environmental agents.

FDA Classification System

Category A	<ul style="list-style-type: none">• Adequate and well-controlled human studies have failed to demonstrate a risk to fetus, Drugs can be used. eg. : Folic acid ,Thyroxine	Controlled human studies show no risk
Category B	<ul style="list-style-type: none">• No risk in animal studies• No adequate and well-controlled human studies• Drugs can be used in pregnancy Example : Paracetamol, Erythromycin	Animal studies ok , No human data
Category C	<ul style="list-style-type: none">• Adverse effects on the fetus in animals only• No adequate and well-controlled studies in humans.• Drug may be used in serious situation despite its potential risk. example: morphine	Animal studies are not ok , No human data , Risk can not be ruled out
Category D	<ul style="list-style-type: none">• Positive evidence of human fetal risk based on adverse reaction data from studies in humans, investigational or marketing experience.• May be used in serious diseases or life threatening situations. example : Antiepileptics	Positive evidence of risk Benefits outweigh risks
Category X	<ul style="list-style-type: none">• Proven fetal abnormalities in animal and human studies• the risks involved in the use of the drug in pregnant women clearly outweigh potential benefits.• Drugs are teratogens and contraindicated in pregnant women or planning to conceive. example: Thalidomides	Contraindicated in pregnancy

Proven teratogens

The following drugs are contraindicated during pregnancy (category X):

- **Thalidomide** (sedative/ hypnotics).
- **Cytotoxic drugs** :
 - Folate antagonists (**methotrexate**).
 - Alkylating agents (**cyclophosphamide**).
- **Lithium**
- **Alcohols**
- **Anticonvulsant drugs** (valproic acid, phenytoin, carbamazepines)
- **Anticoagulants** (warfarin).
- **Antibiotics** (tetracyclines, quinolones)
- **ACEIs**
- **Ionizing radiation** (diagnostic X-ray or radiation therapy).
- **Radioactive iodine** (I^{131}).
- **Corticosteroids.**
- **Hormones**
- **Retinoids e.g :**
 - **vitamin A** (should be limited to 700 µg/day)
 - **isotretinoin** (used in treatment of acne)

Teratogenesis of drugs

Thalidomide

Phocomelia: shortened or absent long bones of the limbs



Alcohol

Fetal Alcohol Syndrome (FAS):

- Microcephaly
- Craniofacial abnormalities
- Intrauterine growth retardation
- CVS abnormalities
- CNS abnormalities (attention deficits, intellectual disability, mental retardation)



Phenytoin

Fetal Hydantoin Syndrome

- Nail & Digital hypoplasia
- Oral Clefts (cleft lip and palate)
- Cardiac Anomalies

Corticosteroids and phenytoin do Cleft lip



Valproic acid

- Neural tube defect (spina bifida)
- Antiepileptic drug Impairs folate absorption



Tetracyclines

- Altered growth of teeth and bones
- Permanent teeth staining
- Enamel hypoplasia



Warfarin

- Hypoplasia of nasal bridge
- CNS malformation

Teratogenesis of drugs

Corticosteroids	Cleft lip and Palate
Hormones: Serious genital malformation	Estrogens: Testicular atrophy in male fetus
	Androgens: Fetal masculinization in female fetus
	Diethylstilbestrol: Vaginal carcinoma of female offspring
Lithium	Ebstein's anomaly Cardiovascular anomalies mainly valvular heart defect involving tricuspid valve
ACE inhibitors captopril, enalapril	Renal damage <ul style="list-style-type: none">● Fetal & neonatal anuria● Fetal hypotension, hypoperfusion, growth retardation● ACE inhibitors disrupt the fetal renin-angiotensin system, which is essential for normal renal development

Adverse effects of drugs

Tetracyclines	Impaired teeth & bone development, yellow-brown discoloration of teeth
Aminoglycosides	Streptomycin, kanamycin → Ototoxicity = 8th Cranial nerve damage
Cloramphenicol	Gray baby syndrome
Corticosteroids	Adrenal atrophy – growth retardation
Propranolol	Bradycardia, neonatal hypoglycemia, placental insufficiency, reduced uterine blood flow, fetal distress
Antithyroid drugs	Iodide, methimazole, carbimazole, propylthiouracil, risk of neonatal hypothyroidism and goiter
Benzodiazepines as Diazepam	Chronic use → neonatal dependence and withdrawal symptoms
ACEIs	Renal damage
warfarin	Risk of bleeding
NSAIDs e.g. Aspirin-indomethacin	Prostaglandin synthesis inhibitors: Constriction of ductus arteriosus (close prematurely), pulmonary hypertension in newborns Increase in gestation time ,prolong labor, neonatal bleeding ,Risk of postpartum hemorrhage
CNS depressants	eg. diazepam, morphine → •Interference with suckling •Respiratory depression •Reduced blood flow, fetal distress
Sulfonamides	• can displace bilirubin from albumin (neonatal hyperbilirubinemia)

During second and third trimesters

- Some drugs can produce adverse effects on the fetus more likely than major malformations due to their pharmacological actions.
- Affect growth & fetal development or toxic effects on fetal tissues

	Probably safe	Contraindicated	Emergency
Hypertension in pregnancy	<ul style="list-style-type: none"> • α- methyl dopa • Labetalol 	<ul style="list-style-type: none"> • ACE inhibitors • Angiotensin II receptor blockers • Thiazide diuretics • Propranolol (not selective) • Calcium channel blockers in mild hypertension 	<ul style="list-style-type: none"> • Hydralazine • Labetalol
Coagulation disorders in pregnancy	<ul style="list-style-type: none"> ▪ Heparin Polar, does not cross placenta The antidote of heparin is <u>protamine sulphate</u> in case of heparin overdose 	<ul style="list-style-type: none"> • warfarin is contraindicated in all trimesters, Cross placenta • 1st trimester: teratogenicity (Chondroplasia) • 2nd, 3rd: risk of bleeding 	-
Antibiotics in pregnancy	<ul style="list-style-type: none"> • Penicillins: (ampicillin, amoxicillin) • Cephalosporins • Erythromycin and azithromycin in case of penicillin-hypersensitivity BUT erythromycin estolate should be avoided (risk of hepatic injury to mother) 	<ul style="list-style-type: none"> • Tetracyclines: Teeth and bones deformity • Quinolones as ciprofloxacin: arthropathy (bone and cartilage damage) • Aminoglycosides: ototoxicity • Sulfonamides: neonatal jaundice-kernicterus • Chloramphenicol: Gray baby syndrome 	-

Antithyroid drugs in pregnancy (used in thyrotoxicosis or Grave's disease)

Examples	-Propylthiouracil -Methylthiouracil (Methimazole) -Carbimazol -Radioactive Iodine (I ¹³¹)
Characteristics	All can cross placenta. All have risk of congenital goiter and hypothyroidism. The lowest dose of antithyroid drugs should be used. Propylthiouracil is preferable over others because of its ability to bound to protein

Drugs of choice in pregnancy

Antihypertensive	<ul style="list-style-type: none">• α-methyl dopa• Labetalol (alpha ,beta Blocker)• Hydralazine (emergency only)
Antibiotics	-penicillin -cephalosporins -erythromycin
Antidiabetics	Insulin, avoids oral antidiabetics
Anticoagulants	Heparin
NSAIDs	Acetaminophen
Antithyroid drugs	Propylthiouracil (protein-bound)
Anticonvulsants	<ul style="list-style-type: none">• All antiepileptics have potential to cause malformations• avoid valproic acid (highly teratogenic)• Folic acid supplementation prevents neural tube defects in women receiving AEDs

Drugs of Abuse in Pregnancy

definition

Habitual use of drugs not for therapeutic purposes but for alteration of one's mood or state of consciousness. most commonly abused drugs are **alcohol, barbiturates, benzodiazepines, opium alkaloids amphetamines, cocaine, nicotine, marijuana.**
 They may lead to organ damage, dependence, addiction, and disturbance of behavior.

Alcohols

- The use of alcohol is **contraindicated** during all trimesters of pregnancy, in 1st trimester Teratogenicity, in 2nd, 3rd trimester mental retardation.
- Fetal Alcohol Syndrome (FAS):**
 Caused by chronic maternal alcohol abuse during early weeks of first trimester of pregnancy.



- Characters:**
1. Microcephaly .
 2. Low weight birth.
 3. Craniofacial abnormalities.
 4. CVS abnormalities.
 5. CNS abnormalities in 2nd and 3rd (attention deficits, intellectual disability, mental retardation)

Cocaine

- Cocaine has **low molecular weight**, easily passes into fetus through placenta.
- Inhibits **re-uptake of sympathomimetics** (epinephrine, NE, dopamine), causing vasoconstriction, rapid heart rate, hypertension (Vascular disruption).
- It decreases blood flow to uterus and fetal oxygenation (**Hypoxia**).
- It increases uterine contractility

- Characters:**
1. Microcephaly.
 2. Prematurity.
 3. Mental retardation .
 4. Growth retardation.
 5. Intrauterine growth retardation.
 6. **Placental abruption** (separation of placenta from uterus wall before delivery).



Tobacco

- Tobacco contains nicotine and carbon monoxide that may harm fetus.
 - No evidence it causes birth defects but **Tobacco can increase risk of :**
1. Spontaneous abortion
 2. Prematurity (Preterm labor)
 3. Reduced blood flow to placenta
 4. Fetal hypoxia
 5. Retarded fetal growth
 6. Low birth weight
 7. Perinatal mortality

MCQs

1- pregnant women in her first trimester was diagnosed with morning sickness the doctor doesn't prescribed her thalidomide because it teratogenic effect on fetus which anomalies this drug can do ?

A-Nail & Digital hypoplasia

B-Neural tube defect (spina bifida)

C-shortened or absent long bones of the limbs (Phocomelia)

•D-neonatal hyperbilirubinemia

2-pregnant women takes a drug and this drug cause abortion which of the following period of pregnancy the woman takes the drug?

A- First 2 weeks (Blastocyst formation)

B- From 2-8 weeks (Organogenesis 2-8 weeks)

C- More than 8 weeks (Histogenesis)

D-29 - 40 weeks (Near term)

3-Pregnant woman takes a drug and this drug cause sedation and apnea to fetus which of the following drug cause this side effect?

•A- Thiopental because it has low molecular weight

•B- Propylthiouracil because it has high protein bound

•C- Thiopental because it is lipid soluble

•D- Propylthiouracil because it is lipid soluble

4- pregnant women have bleeding tendency and the doctor want to prescribe an anticoagulant drug which of the following is a drug of choice ?

A- Warfarin

B- Heparin

C- combination between A&B

D- the doctor should not give anticoagulant

5-Which of the following May be used in serious diseases or life threatening situations despite fetal risk based on data from studies in humans ?

A-Erythromycin

B-Antiepileptics

C-morphine

D-Thalidomides

6-Ototoxicity it's adverse effect of which of the following drug ?

•A-methimazole

•B-erythromycin

•C-cephalosporins

•D-Streptomycin

ANS:1-C, 2-B , 3-D ,4-B, 5-B , 6-D

Good luck!

Done by Pharmacology team

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Done by:

- ★ Abdullah Alhmoodi
- ★ Abdulrhman ALmotairi
- ★ Abdullah Althuniyan

Reviewed by:

- ★ Rawan Ghandour
- ★ Ahmed Alsaleh

