Pharmacology 439

MED439

pharmacology Team 438

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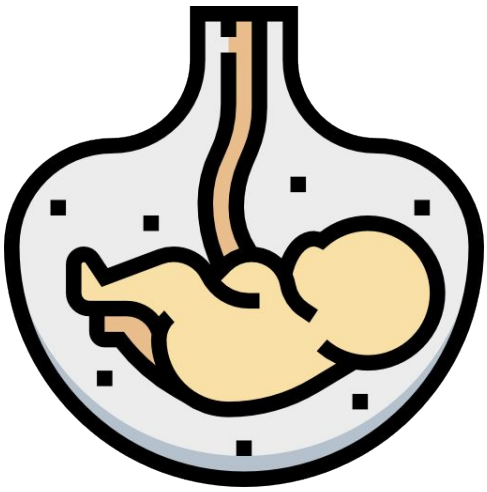


Reproduction Block

Pharmacology team 439

Teratogens & Drugs of Abuse in Pregnancy

Objectives:

By the end of the lecture , you should know:

- Factors affecting placental transfer
- Harmful effects of drugs during different stages of development
- FDA classifications of drugs
- Teratogenic Drugs
- Keep on vibin
- Adverse effects of drugs
- Drugs of abuse

Color index:

Black : Main content
Red : Important
Blue: Males' slides only

Pink : Females' slides only
Grey: Extra info or explanation
Yellow: Dr. notes (439)

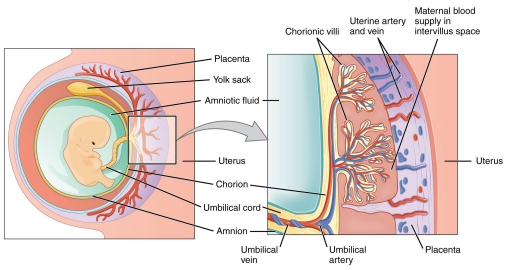
Green: Dr. notes (438)

Medications in Pregnancy

- Majority of pregnant women are exposed to medications during pregnancy.
- Unless absolutely necessary, drugs should not be used during pregnancy because many can harm the fetus.
- Fetal effects of most of the therapeutic agents are unknown for about one-half of medications.
- About 2 to 3 % of all birth defects result from the use of drugs.

How do drugs cross the placenta?

1. Most drugs can cross the placenta by passive diffusion
2. Placental membrane is semi-permeable
3. Thus drugs in the mother's blood can cross this membrane into fetal blood vessels in the villi and pass through the umbilical cord to the fetus by crossing a single layer of trophoblast cells



Factors controlling placental drug transfer

- Physiochemical properties
- Stage of development
- Duration of exposure

1- Physiochemical Properties of the Drug

Lipid solubility and Ionization

- **Lipophilic drugs** diffuse readily across the placenta and enter fetal circulation[1]
  - Example: **Thiopental** → crosses placenta and causes **sedation and apnea** in infants
- **Ionized drugs** cross the placenta slowly leading to very low concentration in fetus
  - Example: **Succinylcholine**, **Tubocurarine** and **Pancuronium** (skeletal muscle relaxants).

Molecular Size

Numbers were skipped by the Females doctor

- MW of 250-500 → cross the placenta easily [2]
- MW of 500-1000 → crosses the placenta more difficulty
- MW >1000 → can NOT cross the placenta
  - Example: **Heparin** for thromboembolic disorders

Protein Binding

- Protein binding in the maternal circulation hinders the passage of drugs[3]
  - Example: **Propylthiouracil**, **Chloramphenicol** and **heparin**

1) lipid soluble drugs should not be used at all during pregnancy. Ionized drugs are preferable due to their slow rate of transfer.
2) High molecular weight drugs are preferable during pregnancy. Because if the MW is high, the ability to cross the placenta is less.
3) High protein binding drugs are preferable during pregnancy.

Factors controlling placental transfer

Dr.ishfaq: this whole page is **not important** for the exam

2- Stage of Placental and Fetal Development; they are 3 stages

First Trimester Week 1-12		2nd & 3rd Trimesters Week 13 - 28	Near Term Weeks 29-40
Blastocyst formation Week 1-2	**Organogenesis** Week 2 - 8	**Histogenesis and functional maturation** Weeks 8 onwards	

1 Blastocyst Formation (First 2 weeks):

- Occurs from 1-16 days in the first trimester
- Period of **dividing zygote and implantation** (pre-differentiation, conceptus)
- Drugs have **all-or-nothing effect** [1]
- ★ Exposure to drugs during this period ⟶ leads to prenatal death and **abortion**

2 Organogenesis:

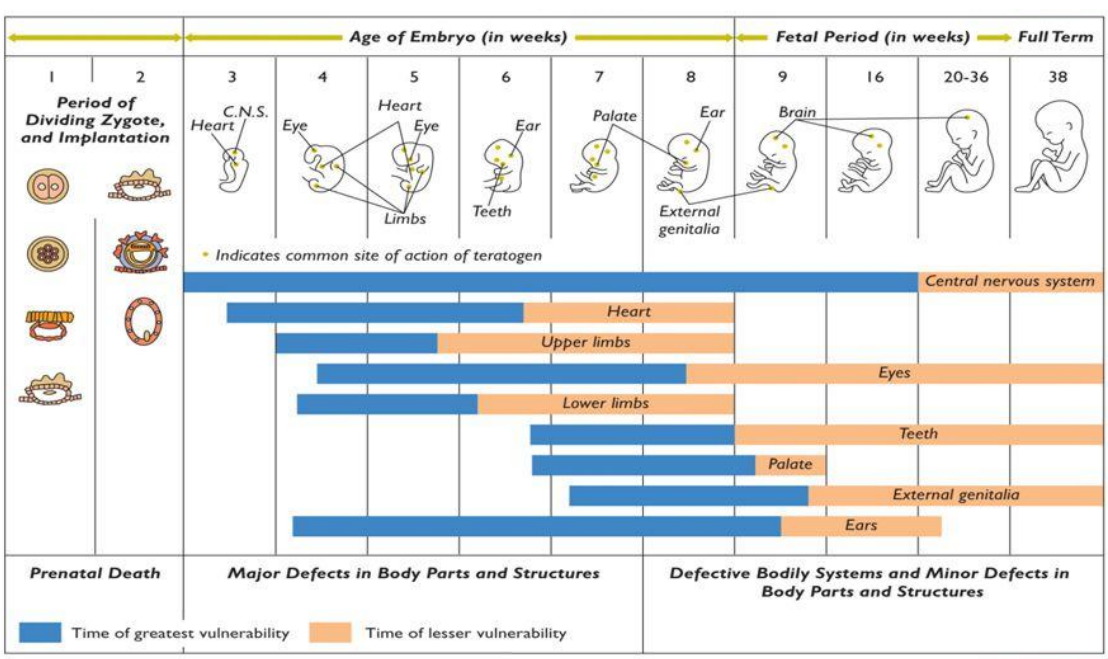
- Occurs in 17-60 days in the first trimester
- Is the process where **cells specialize** to form tissues and organs
- It is the **most sensitive** [2] period of pregnancy (critical period).
- ★ Exposure to harmful drugs during this period⟶ leads to major birth defects or gross malformation **(teratogenesis)** (تشوهات)

3 Histogenesis and Functional Maturation

- Growth and fetal development (maturation) occur at this stage (2nd and 3rd trimesters)
- Fetus depends on nutrients and hormonal supply
- ★ Exposure to drugs during this period ⟶ lead to **functional problems rather than gross malformations**, **minor morphological abnormalities, growth retardation** and functional defects (the function not the structure)
  - However, **CNS** is sensitive to toxic effects throughout pregnancy

4 Near term

- Occurs between 29th and 40th weeks
- Exposure to drugs ⟶ lead to adverse effect on labor or neonates after delivery



1) If exposed to a harmful drug during this stage there are 2 possibilities:
   1- The drugs is safe, nothing will happen and the pregnancy will continue normally.
   2- Perinatal death and abortion.
2) Avoid drugs during this stage.

Teratogenesis

It is the occurrence of congenital defects on the fetus

What is a teratogen?

- Are substances that may cause **permanent birth defects and interferes with fetal development** via a toxic effect on an embryo or fetus.
- **Examples:** medications, street drugs, chemicals, diseases and environmental agents.
- Could be severe during critical periods of development e.g. (**organogenesis**)

★ FDA Classification System

Category	Characteristics	Examples Prof:you should know the examples
A	• Adequate and well-controlled human studies have failed to demonstrate a risk to fetus • **Drugs can be used** in pregnancy	**Folic acid Thyroxine**
B	• No risk in animal studies • No adequate and well-controlled human studies • **Drugs can be used** in pregnancy	**Paracetamol Erythromycin**
C	• Adverse effects on the fetus in **animals only** • No adequate and well-controlled studies in humans. • Risk cannot be ruled out (you have to balance between the benefits and the harmful actions) • **Drug may be used in serious situation despite its potential risk**	**Morphine**
D	• 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** • Used in cases were **benefits outweigh risks**	**Antiepileptics**
X	• 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.	**Thalidomide (sedative)**

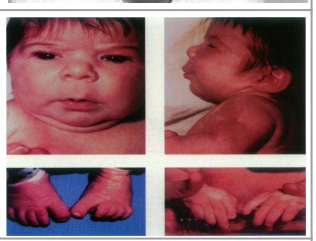
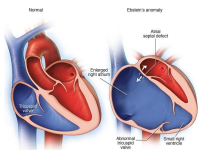
Proven Teratogens (Category X)

1. Retinoids
   - Vitamin A (limit to 700 ug/day)
   - Isotretinoin (used to treat acne)[1]
2. Thalidomide (sedative/hypnotic)
3. Lithium
4. Alcohol
5. Cytotoxic agents (anti cancer):
   - Folate antagonists (methotrexate)
   - Alkylating agents (cyclophosphamide)
6. Anticonvulsants
   - Valproic acid & phenytoin
7. Anticoagulant (warfarin)
8. Antibiotics (tetracyclines, quinolone)
9. ACEIs and ARBs
10. Ionizing radiation (diagnostic x-ray\radiating therapy)
11. radioactive Iodine (I^{131})
12. Corticosteroids
13. Hormones

1) If a patient completed her Isotretinoin treatment and is planning on getting pregnant, one year should elapse before getting pregnant.
   - Just because a drug is harmful doesn't mean you can't use it. The physician should compare the risk vs benefit and decide

Teratogenesis of Drugs
(1st trimester)

Prof. Hanan: I put the most important drugs in the first

Teratogen	Teratogenic Effect
★**Thalidomide** [1] The most notorious human teratogen	**Phocomelia:** • Shortened or absent long bones of the limbs • Absence of external ear 
Alcohol	**Fetal Alcohol Syndrome:** • Microcephaly • Craniofacial abnormalities • Intrauterine growth retardation • CVS abnormalities • CNS abnormalities 
★ **Phenytoin**	**Fetal Hydantoin Syndrome:** • Nail and digital hypoplasia • Oral cleft (cleft lip and palate) • Cardiac anomalies • Mental and growth retardation 
★ **Valproic acid**	• **Neural tube defect** (spina bifida) **(IMPORTANT)** • Antiepileptic drug **Impaired folate absorption** [2] 
Tetracyclines [3]	• Altered growth of feet and bones • Permanent teeth staining • Enamel hypoplasia 
Warfarin	• Hypoplasia of nasal bridge • CNS malformation • **Chondrodysplasia punctata**: abnormal calcification in the cartilage of developing bones and has been seen in association with deranged vitamin K metabolism
Corticosteroids	• Cleft lip and palate 
Lithium	**Ebstein's anomaly:** • CVS anomalies mainly • Valvular heart defect involving tricuspid valve 
ACE inhibitors: **Captopril** **Enalapril** Not important	• Renal damage - ACEIs disrupt fetal RAAS system which is essential for renal development • Fetal & neonatal anuria • Fetal hypotension • Hypoperfusion • Growth retardation
Hormones (Cause serious genital malformation)	
Estrogens	• Testicular atrophy in male fetus
Androgens	• Fetal masculinization in female fetus
Diethylstilbestrol	• Vaginal carcinoma of female offspring (Delayed action, it happens at 10 years old)

1) Thalidomide was used for morning sickness in the past.
2) Folic acid supplements should be prescribed if the pregnant female is on antiepileptics.
3) Tetracyclines deposit in teeth and bones which causes the mentioned teratogenic effects, It likes Ca

Adverse Effects of Drugs
(2nd & 3rd trimesters)

- During the 2nd and 3rd trimesters, some drugs can produce adverse effects on the fetus more likely than major malformations **due to their pharmacological actions** of the drug
- They affect growth and fetal development or may have toxic effects on fetal tissues

Drug	Adverse Effect
Tetracyclines	• Impaired teeth and bone development • Yellow-brown discoloration of teeth
Aminoglycosides	• Ototoxicity (8th cranial nerve damage) - **Examples**: Streptomycin and Kanamycin
★**Chloramphenicol**	• Gray baby syndrome
Corticosteroids	• Adrenal atrophy • Growth retardation
★**Propranolol** And beta-blockers in general	• Bradycardia • Neonatal hypoglycemia • Placental insufficiency → poor uterine blood flow → **fetal distress**
Antithyroids	• Risk for neonatal hypothyroidism and goiter - **Examples**: Methimazole, Carbimazole, Iodide and Propylthiouracil
★**NSAIDs**	• Prostaglandin synthesis inhibitors ★ Constriction of ductus arteriosus • Pulmonary Hypertension in newborns ★ Increase in gestation time (prolonged contraction) • Prolong labor, neonatal bleeding ★ Increase risk for postpartum hemorrhage - **Examples**: Aspirin-indomethacin
Benzodiazepines	• Chronic use → neonatal dependence and withdrawal symptoms after delivery the baby will develop withdrawal symptoms - **Examples**: Diazepam
ACE inhibitors	• Renal damage
Warfarin	• Risk of bleeding
CNS depressants	• Interference with suckling ★ Respiratory depression • Reduced blood flow → Fetal distress - **Examples**: Diazepam and morphine
Sulfonamides	• Displace bilirubin from albumin → neonatal jaundice (neonatal hyperbilirubinemia) (kernicterus: irreversible brain damage)

Drugs of Choice During Pregnancy

Prof. Hanan: **IMPORTANT** to know the safe drugs that can be used in pregnancy, (she skipped the C.I)

Hypertension in Pregnancy

Probably Safe	Contraindicated
• α -Methyl dopa • Labetalol **Emergency ONLY** (injection)**:** • Hydralazine • Labetalol	• ACE inhibitors • Angiotensin II receptor blockers • Thiazide diuretics • Propranolol • Ca^{2+} channel blockers in mild HTN

Coagulation Disorders in Pregnancy

Probably Safe	Contraindicated
• Heparin - It is polar ⟶ doesn't cross the placenta - There's an antidote (protamine sulphate)	• **Warfarin in all trimesters** - Cross the placenta - 1st trimester: teratogenicity - 2nd/3rd trimesters: risk of bleeding

Antibiotics in Pregnancy [1]

Probably Safe	Contraindicated
• Penicillins (ampicillin, amoxicillin) • Cephalosporins • Macrolides (erythromycin, azithromycin) - As an alternative in penicillin-sensitive patients but erythromycin estolate should be avoided (risk of hepatic injury to mother)	• Tetracyclines ⟶ teeth and bones deformities • Quinolones (ciprofloxacin)⟶ arthropathy (bone and cartilage damage) • Aminoglycosides ⟶ ototoxicity • Sulfonamides ⟶ neonatal jaundice and kernicterus • Chloramphenicol ⟶ Gray baby syndrome

Antithyroid Drugs in Pregnancy[2]

- Are used in thyrotoxicosis or Grave's disease
  - Propylthiouracil
  - Methylthiouracil
  - Carbimazole
  - Radioactive iodine
- All can cross the placenta
- All have risk for congenital hypothyroidism and goiter
- The **lowest dose** of antithyroid drugs should be used
- **Propylthiouracil** is preferable over others [3]

Other Drugs

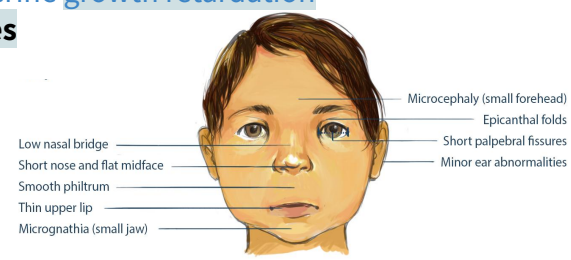
Antidiabetics	• Regular Insulin is the best choice #Endo • Avoid oral antidiabetics
Analgesics	• **Acetaminophen** is the best choice
Anticonvulsants [4]	• All antiepileptics have potential to cause malformations ★ **Avoid valproic acid because it's highly teratogenic** • Folic acid supplementations can prevent neural tube defects associated with antiepileptics **(IMPORTANT)**

1) **Rule: All antibiotics are contraindicated EXCEPT Beta lactams and Macrolides**
2) All antithyroid drugs are risky but Propylthiouracil is the best choice for pregnant women
3) Has high protein binding ability
4) Monotherapy is preferred during pregnancy.

Drugs of Abuse During Pregnancy

What is a drug abuse?

- It is the habitual use of drugs not for therapeutic purposes but for alteration of one's mood or state of consciousness.
- The most commonly abused drugs are alcohol, barbiturates, benzodiazepines, opium alkaloids, amphetamines, cocaine, nicotine and marijuana
- Drug abuse may lead to organ damage, dependence, addiction and behavioral disturbance

Abused Drug	Description
Alcohol **FAS:** **F**acial malformation **A**ttention deficit disorder **S**eptal defects	• The use of Alcohol is contraindicated in all trimesters • Chronic use of alcohol during early weeks of the 1st trimester leads to **Fetal Alcohol Syndrome (FAS)** which is characterized by: 1. Microcephaly 2. Low birth weight / Intrauterine growth retardation **3. Craniofacial abnormalities** 4. CVS abnormalities 5. CNS abnormalities - Attention deficits - Intellectual disability - Mental retardation 
Cocaine	• Cocaine has low MW, so it can easily pass through the placenta ★ It inhibits the reuptake of epinephrine, norepinephrine and dopamine causing: 1. Vasoconstriction 2. Rapid heart rate (tachycardia) 3. Hypertension (vascular disruption) • It decreases blood flow to uterus and fetal oxygenation (hypoxia) ★ It increases uterine contractility • Gross malformations include: 1. Microcephaly 2. Prematurity 3. Growth retardation 4. Intrauterine growth retardation 5. Mental retardation 6. **Placental abruption** (early separation of the placenta from the uterus before delivery) 7. Withdrawal symptoms 
Tobacco	• Tobacco contains nicotine and carbon monoxide which may harm the fetus (cause hypoxia) and there is no evidence that it causes birth defects but it increases the risk of: 1. Decreased blood flow to the placenta 2. Fetal hypoxia 3. Retarded fetal growth **4. Low birth weight** 5. Increased Spontaneous abortion **6. Prematurity (preterm labor)** 7. Perinatal mortality (stillbirth)

Quiz

MCQ

Q1- A 19-year-old G1P0 woman lost her eyeglasses for a day. Constant squinting causes her to develop a headache, for which she takes ibuprofen. Which of the following poses the greatest risk to her fetus?

A- Acute tubular necrosis B- Decreased pulmonary surfactant at birth C- Low birth weight
D- Loss of physiologic heart shunt E- No risk—ibuprofen is a safe drug for pregnancy

Q2- A 33-year-old pregnant woman begins taking a new drug, Drug X, for morning sickness. Drug X has not been found to have adverse maternal or fetal effects in animal models, but no human studies have been done. Under which FDA Pregnancy Category would Drug X fall?

A- Category A B- Category B C- Category C D- Category D E- Category X

Q3- A 17-year-old pregnant woman asks her doctor what she can do about her acne. The doctor prescribes a topical benzoyl peroxide preparation, but the patient is unsatisfied with the results. She has a close friend taking isotretinoin for acne control, and her friend often tells her how well it works. She begins taking her friend's pills and is pleased with the reduction in her acne. In which FDA Pregnancy Category does this drug belong?

A- Category A B- Category B C- Category C D- Category D E- Category X

Q4- A 19-year-old woman is 24 weeks pregnant. She has received no prenatal care. She presents to the emergency department complaining of an intermittent headache and fatigue during her pregnancy. Her blood pressure has been at least 150/110 mm Hg. What is the most appropriate treatment of this patient?

A- Hydralazine B- Propranolol C-Methyl dopa D- Prazosin E- Sodium nitroprusside

Q5- A 26-year-old G2P1001 woman at 33 weeks gestation presents to the emergency department with pain and swelling in her right calf. On physical examination, Homans sign is positive. A duplex of the right calf confirms the presence of a deep vein thrombosis (DVT). What is the most appropriate treatment for the rest of her pregnancy?

A- Streptokinase B- Aspirin C- Heparin D- Acetaminophen E- Warfarin

Q6- A 23-year-old woman with lifelong epilepsy controlled with medication has just found out that she is pregnant. She has seizures once a month but seem to be controlled at present. Which of the following statements about epilepsy in pregnancy is true?

A- Barbiturates should be considered
B- Divalproex is considered a drug of choice
C- Maintenance medication doses should be increased
D- She should be taking high doses of folic acid
E- She will likely have no change in seizure activity during pregnancy

Answers:

Q1	**D**; ibuprofen is a NSAID, which constricts the ductus arteriosus and cause pulmonary hypertension
Q2	**B**; the study was done in animals but not humans
Q3	**E;** isotretinoin is a well known teratogen during pregnancy
Q4	**A**; Hydralazine is the drug of choice in hypertensive emergencies during pregnancy
Q5	**C**; Heparin has a high MW and hugh polarity which prevents it from crossing the placenta
Q6	**D**; antiepileptic impairs folic acid absorption and might cause a neural tube defect

Thank you for all the love and support you gave the team in those two years!

Hope we made the context much easier to study.
God bless you, Future doctors.

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