



PT 431 team pharmacology

Reproductive Block

Lecture 4

Teratogens and drugs of abuse in pregnancy

Done by :

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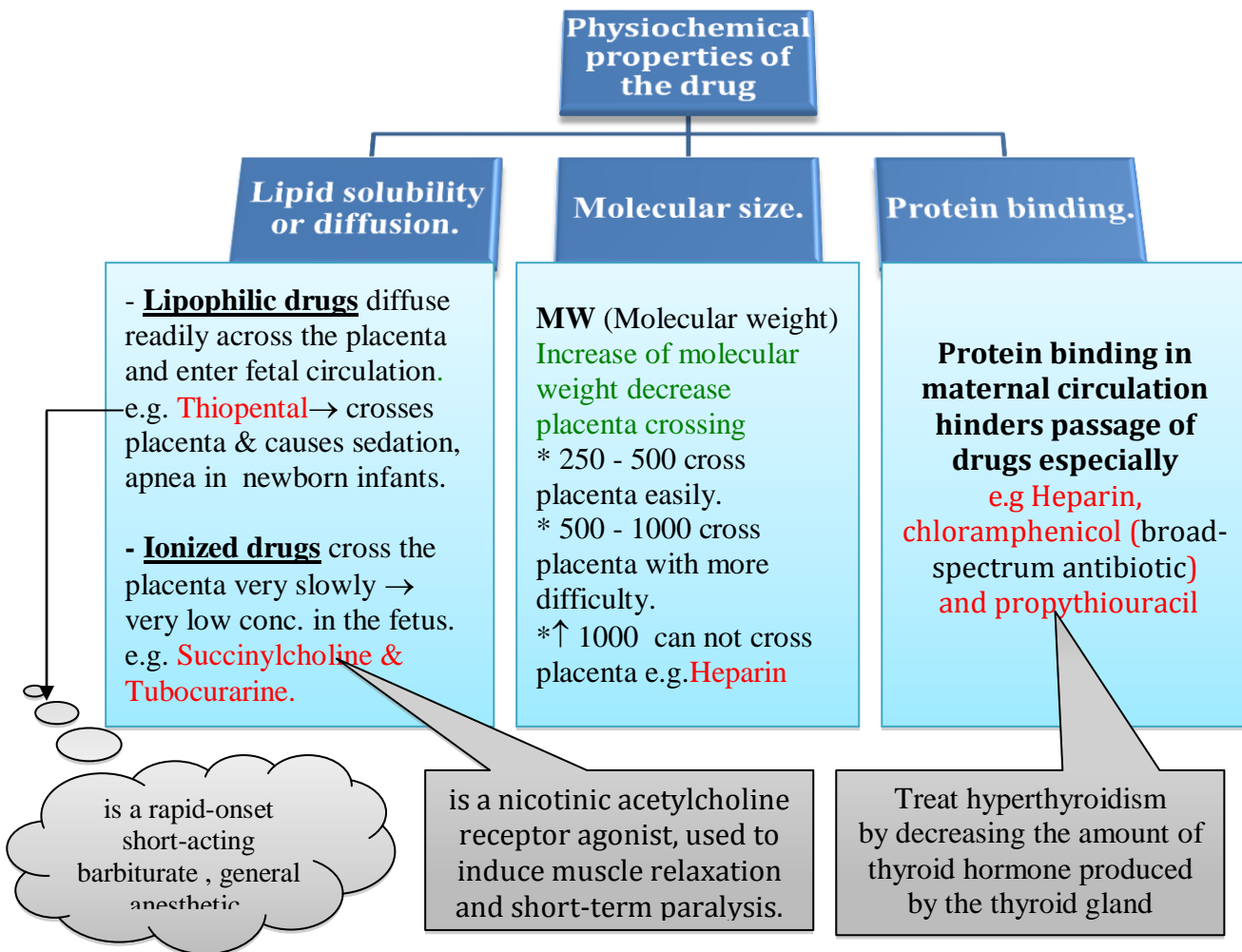


Introduction:

- PLACENTAL MEMBRANE IS SEMI-PERMEABLE.
- MOST DRUGS CAN CROSS PLACENTA BY PASSIVE DIFFUSION.
- THE MOVEMENT OF DRUGS ACROSS THE PLACENTA IS LIMITED BY A SINGLE LAYER OF CELL CALLED TROPHOBLASTS.

FACTORS CONTROLLING PLACENTAL DRUG TRANSFER:

1. Physiochemical properties of the drug :



2. The stage of placental and fetal development at the time of exposure to the drug.
3. Duration of exposure to the drug.

THREE TRIMESTERS OF PREGNANCY ARE :

- **First trimester:** week 1- week 12
- **Second trimester:** week 13-week 28
- **Third trimester:** week 29-week 40

The stage of mammalian fetal development:

Harmful action of drugs depend upon **stage of fetal development** at **time of drug exposure**.

MAMMALIAN FETAL DEVELOPMENT PASSES THROUGH THREE PHASES:

	Blastocyst formation	Organogenesis	Histogenesis and functional maturation
Duration:	1-16 days (First Trimester)	17- 60 days – 2 to 8 weeks (First Trimester)	8 weeks onwards (2 nd , 3 rd Trimester)
Characteristics of the phase :	<ul style="list-style-type: none"> * Period of dividing zygote, implantation *Pre-differentiated period (conceptus). *Drugs have an all-or-nothing effect. (That mean the drug may cause death or not cause anything to the fetus) *Exposure to drugs during this period → death of the embryo → abortion. 	<ul style="list-style-type: none"> *The most sensitive period of pregnancy because major body organs and systems are formed. *Exposure to harmful drugs during organogenesis → major birth defect or gross malformation (Teratogenesis) 	<ul style="list-style-type: none"> *Maturation occurs during this stage & fetus depends upon nutrients & hormonal supply. *Will not induce major malformation but drugs can produce minor morphologic abnormalities, growth retardation and functional defect. *However, CNS is sensitive to toxic effects throughout pregnancy.

Teratogenesis :

Congenital defects of the fetus occur due to teratogen .

Teratogen is any agent (*medication, street drug, chemicals, disease, environmental agents*) that is able to interfere with fetal development by placenta barrier (trophoblas) and leads to permanent birth defects. This could be more severe during critical periods of development e.g. (**organogenesis**).

FDA: Classification systems

Category A	Category B	Category C	Category D	Category X
<p>* Controlled human studies with no risk to fetus.</p> <p>*Drugs can be used.</p>	<p>*Adverse effects on animal studies only.</p> <p>Adequate human studies lacking its affect or not shown similar results.</p> <p>Drug can be used in pregnancy.</p>	<p>*Adverse effects on animal studies only.</p> <p>No human studies, human fetal risk is unknown.</p> <p>Drug may be used in serious situation despite its potential risk.</p>	<p>*Evidence of human fetal risk.</p> <p>May be used in serious diseases or life threatening situations e.g phenytoin</p> <p>Phenytoin = antiepileptic drug</p>	<p>*Fetal abnormalities in animal and human studies</p> <p>Drugs are teratogens and contraindicated in pregnant women or planning to conceive.</p>

PROVEN TERATOGENS:

1. **Thalidomide** (sedative/ hypnotics).
2. **Cytotoxic drugs**
 - a. Folate antagonists (methotrexate).
 - b. Alkylating agents (cyclophosphamide).
 - c. All others : smaller risk.
3. **Lithium** (valvular heart abnormality)
4. **Alcohols** (fetal alcohol syndrome).
5. **Anticonvulsant drugs** (valproic acid, phenytoin)
6. **Anticoagulants** (warfarin has low MW).
7. **Antibiotics** (tetracyclines, quinolones)
8. **Retinoids** :
 - a. vitamin A (should be limited to 700 µg/day)
 - b. isotretinoin (used in treatment of Acne)
9. **Angiotensin converting enzyme inhibitors (ACEIs)**
10. **Ionizing radiation** (diagnostic X-ray or radiation therapy like **Radioactive iodine (I131)**).
11. **Corticosteroids.**
12. **Hormones**

is an anti-nausea and sedative drug , quickly discovered to help pregnant women with the effects of morning sickness

Drug use to treat a cancer , they inhibit cell proliferation which will

In the treatment of bipolar disorder, lithium compounds continue to be the standard against which newer medications are measured and helpful for related diagnoses, such as schizoaffective disorder and cyclic major depression.

Use to treat hyperthyroidism and thyrotoxicosis

It is group of drug used to treat Hypertension

TERATOGENESIS OF DRUGS:

Thalidomide	<i>Phocomelia</i> And it is symptoms:	<ol style="list-style-type: none"> 1. shortened or absent long bones of the limbs 2. Anorectal stenosis 3. Absence of External Ears
Alcohol	<i>Fetal Alcohol Syndrome (FAS),</i> And it is symptoms:	<ol style="list-style-type: none"> 1. Microcephaly 2. Intrauterine growth retardation 3. Craniofacial abnormalities 4. CVS abnormalities 5. CNS abnormalities (<i>attention deficits, intellectual disability, mental retardation</i>)
Phenytoin	<i>Fetal Hydantoin Syndrome,</i> And it is symptoms:	<ol style="list-style-type: none"> 1. Nail & Digital hypoplasia 2. Oral Clefts (cleft lip and palate) 3. Cardiac Anomalies 4. Mental & growth retardation
Corticosteroids	<i>Cleft lip and Palate</i>	
Tetracyclines	<ul style="list-style-type: none"> • Permanent teeth staining • Enamel hypoplasia • altered growth of teeth and bones. 	
Warfarin	<ul style="list-style-type: none"> • Hypoplasia of nasal bridge • CNS malformation 	
Finasteride	<i>Abnormal development of genitalia of male fetuses</i>	
Valproic acid	<ul style="list-style-type: none"> • Antiepileptic drug • Neural tube defect (spina bifida) • Impair folate absorption 	<p>Use to treat Prostatic Hypertrophy , It is a type II 5α-reductase inhibitor. 5α-reductase is an enzyme that converts testosterone to dihydrotestosterone (DHT).</p>
Hormones: (Estrogens, Androgens, diethylstilbestrol)	<ul style="list-style-type: none"> • Serious genital malformation • Testicular atrophy in male • Fetal masculinization in female • Vaginal carcinoma of female offspring 	
Lithium	<i>Cardiovascular anomalies mainly valvular heart defect involving tricuspid valve Called <i>Ebstein's anomaly</i></i>	
ACE inhibitors (captopril, enalapril)	<ul style="list-style-type: none"> • Fetal & neonatal anuria • Renal damage , ACE inhibitors disrupt the fetal renin-angiotensin system, which is essential for normal renal development. • Fetal hypotension, hypoperfusion • growth retardation 	

ADVERSE EFFECTS OF DRUGS :

During second and third trimesters : Some drugs can produce adverse effects on the fetus more likely than major malformations due to their pharmacological actions.

Adverse effects of drugs prior to labor:

<i>Tetracyclines</i>	Impaired teeth bone development yellow-brown discoloration of teeth
<i>Aminoglycosides</i>	(Streptomycin, kanamycin) Ototoxicity = 8 th Cranial nerve damage
<i>Cloramphenicol</i>	Gray baby syndrome
<i>Corticosteroids</i>	Adrenal atrophy and growth retardation
<i>Propranolol</i>	Bradycardia neonatal hypoglycemia placental insufficiency reduced uterine blood flow fetal distress
<i>Antithyroid drugs (Iodide, Methimazole ,Carbimazole, Propylthiouracil)</i>	Risk of hypothyroidism and goitre
<i>NSAIDs</i> 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
<i>Benzodiazepines as Diazepam</i>	Chronic use → neonatal dependence and withdrawal symptoms
<i>ACEIs</i>	Renal damage
<i>warfarin</i>	Risk of bleeding
<i>CNS depressants</i> e.g. diazepam, morphine	Interference with suckling Respiratory depression Reduced blood flow fetal distress
<i>Sulfonamides</i>	Displacement of bilirubin from plasma protein (neonatal hyperbilirubinemia)

DRUGS USED IN PREGNANCY:

Disease	Contraindication Drug	Safty Drug
Hypertension	<ul style="list-style-type: none"> • ACE inhibitors • Angiotensin II receptor blockers • Thiazide diuretics • Propranolol • Calcium channel blockers in mild hypertension 	<ul style="list-style-type: none"> ▪ α- methyl dopa ▪ Labetalol <p>And can use in Emergency :</p> <ul style="list-style-type: none"> ▪ Hydralazine ▪ Labetalol
Coagulation disorders	<p>Warfarin is contraindicated in all trimesters ,because it is : Cross placenta 1st trimester : Teratogenicity (Chondroplasia) 2nd, 3rd : risk of bleeding</p>	<ul style="list-style-type: none"> ▪ Heparin : <p>Polar, does not cross placenta (not lipophilic)</p> <ul style="list-style-type: none"> ▪ Protamine sulphate : as antidote for neutralization
Antithyroid	<ul style="list-style-type: none"> • Propylthiouracil • Methylthiouracil (Methimazole) • Carbimazol • Radioactive Iodine (I131) <p>All can cross placenta All have risk of congenital goiter and hypothyroidism The lowest dose of antithyroid drugs should be used.</p>	<p>Propylthiouracil is preferable over others</p>
Antibiotics	<ul style="list-style-type: none"> • Aminoglycosides: ototoxicity • Tetracyclines: Teeth and bones deformity • Sulfonamides: neonatal jaundice-kernicterus • Chloramphenicol: Gray baby syndrome • Quinolones as ciprofloxacin: bone and cartilage damage (arthropathy) 	<ul style="list-style-type: none"> ▪ Penicillins (ampicillin, amoxicillin) ▪ Cephalosporins ▪ Erythromycin and azithromycin as alternative in penicillin-sensitive individuals BUT erythromycin estolate should be avoided (<i>risk of hepatic injury to mother</i>).

Summary of Drugs used in Pregnancy :

Antihypertensive	<ul style="list-style-type: none">▪ α-methyl dopa▪ Labetalol (α - β Blocker)▪ Hydralazine (emergency only)
Antibiotics	<ul style="list-style-type: none">▪ Penicillin▪ Cephalosporins▪ Erythromycin
Antidiabetics	<ul style="list-style-type: none">▪ Insulin is safe▪ Avoids oral antidiabetics
Anticoagulants	<ul style="list-style-type: none">▪ Heparin
Analgesics	<ul style="list-style-type: none">▪ Acetaminophen
Antithyroid drugs	<ul style="list-style-type: none">▪ Propylthiouracil (protein-bound)
Anticonvulsants	<ul style="list-style-type: none">▪ All antiepileptics have potential to cause malformations▪ avoid valproic acid.▪ Folic acid should be supplied.

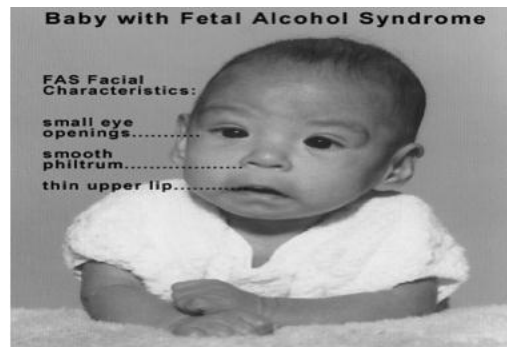
DRUGS OF ABUSE IN PREGNANCY:

DRUG ABUSE: *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; cocaine; nicotine; marijuana; amphetamines; barbiturates; opium alkaloids, benzodiazepines.**
- **Drug abuse may lead to organ damage, addiction, and disturbance of behavior.**

1. **Alcohol** : The use of alcohol is contraindicated during all trimesters of pregnancy → **Fetal Alcohol Syndrome (FAS) Caused by chronic maternal alcohol**

Abuse during early weeks of **first trimester of pregnancy** , Its characters said before .



2-Cocaine :

-Cocaine is **low MW**, water-soluble

-**easily pass** to placenta

- Inhibits re-uptake (increase concentration) of sympathomimetics (epinephrine, NE, dopamine), **causing vasoconstriction, rapid heart rate, hypertension (Vascular disruption).**

-It **decreases blood flow to uterus, fetal oxygenation** and intestinal blood flow.

It increases uterine contractility

It is will cause :

- **Microcephaly**
- **Prematurity**
- **Low birth weight.**
- **Abruptio placentae (separation of placenta from uterus wall before delivery)**
- **Growth retardation**
- **Mental retardation**
- **Withdrawal symptoms**

3-Tobacco:

-It is contains **nicotine and carbon monoxide** that may **harm fetus.**

Tobacco can produce:

- Decreased blood flow to placenta
- **Fetal hypoxia**
- Retarded fetal growth
- Low birth weight
- Increased spontaneous abortion
- Preterm labor and stillbirth

Conclusion:

1-The use of drugs during pregnancy should be avoided unless absolutely necessary.

2-Most drugs cross the placenta to some extent.

3-Birth defects are of great concern.

4-Drugs can harm the embryo or foetus depending upon the stage of foetal development.

Lipid solubility of the drug	Molecular size of the drug	Protein binding.
- More lipid soluble → cross placenta → affect fetus	- Low MW → easy to diffuse placenta → affect fetus.	- more protein binding → less diffusion in placenta.
- Less lipid soluble → less crossing placenta → less affect on fetus.	- High MW → no diffusion in placenta → no affect on fetus.	- less protein binding → more diffusion in placenta

5-The most critical period of pregnancy is organogenesis (17 days - 8 weeks).

Alcohol, nicotine and other addicting drugs should be avoided.

Questions:

1. Which one of the following drugs should be avoided during lactation :

- Chloramphenicol
- Insulin
- Erythromycin
- Penicillin

2. Which one of the following drugs can be given during lactation :

- Quinolones
- Sulphonamides
- L-dopa
- Heparin

3. All of the following antibiotics can be used to treat syphilis in pregnant women except :

- a. Penicillin
- b. Macrolides
- c. Tetracycline
- d. Ceftriaxone

4. the drug of choice in case of pregnancy with need of anticoagulants :

- a. warfarine
- b. Phenindione
- c. Low molecular weight Heparine
- d. High molecular weight Heparine

5. Regarding Fetal Alcohol Syndrome :

- a. Caused by chronic maternal alcohol abuse
- b. Macrocephaly
- c. Big eye openings
- d. All of the above

6. antimalarial drug to be avoided in pregnancy ?

- a. chloroquine
- b. quinine
- c. primaquine
- d. anti-folates
- e. tetracyclines

1- A

2- D

3- C

4- D

5- A

6- C & E

GOOD LUCK