King Saud University

College of Medicine

2nd Year,

Reproduction Block

PHARMACOLOGY 433

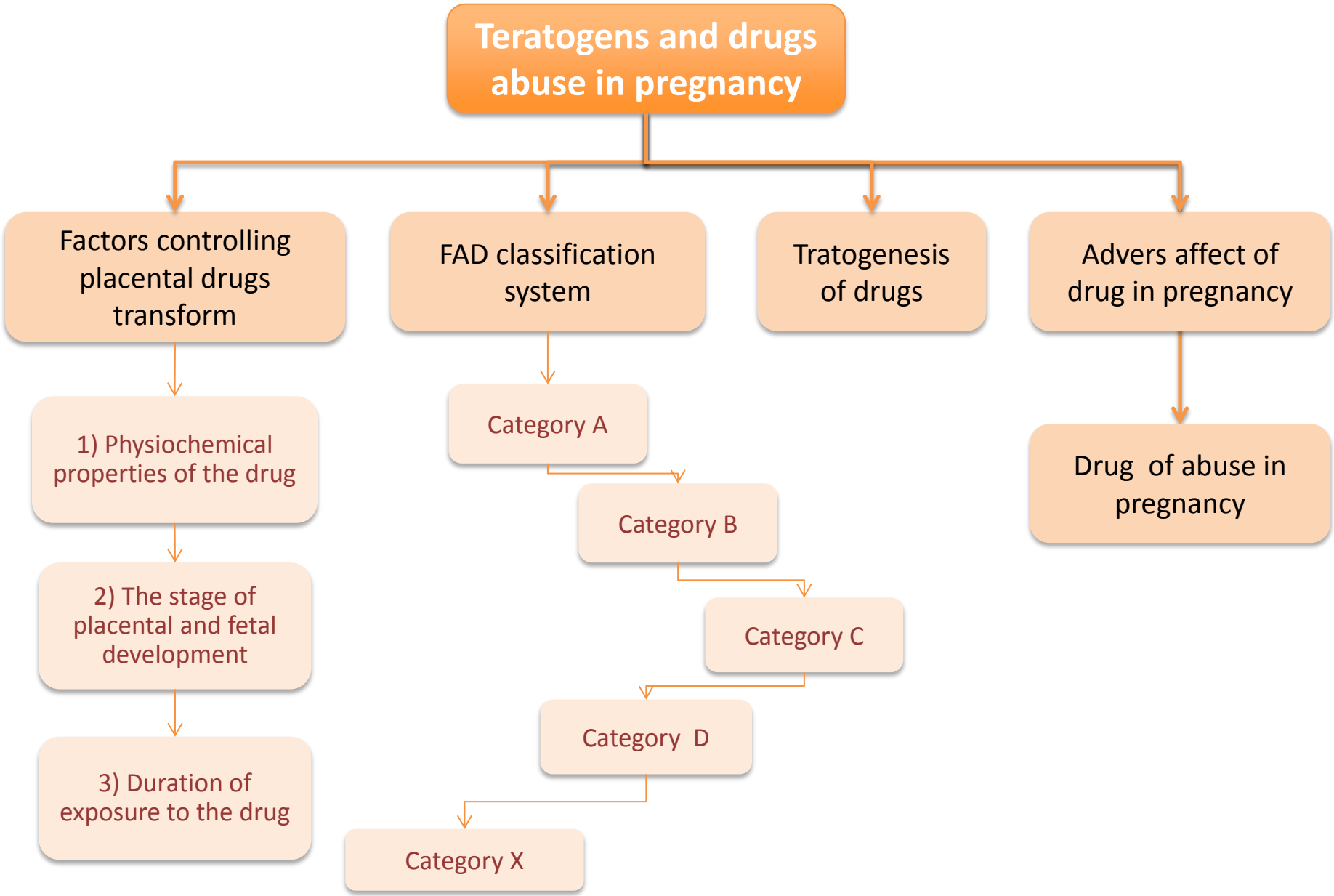
MED 433 Teams

L6-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.

Mind Map


Teratogens and drugs abuse in pregnancy
Factors controlling placental drugs transform
FAD classification system
Tratogenesis of drugs
Advers affect of drug in pregnancy
1) Physiochemical properties of the drug
2) The stage of placental and fetal development
3) Duration of exposure to the drug
Category A
Category B
Category C
Category D
Category X
Drug of abuse in pregnancy

Introduction

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

- 1)Physiochemical properties of the drug
  - Lipid solubility or diffusion
  - Molecular size
  - Protein binding
- 2)The stage of placental and fetal development
  - Blastocysts formation
  - Organogenesis
  - Histogenesis & maturation of function
- 3)Duration of exposure to the drug

1)Physiochemical properties of the drug

Properties	Explanation	
Lipid solubility of drugs	**Lipophilic drugs** Diffuse readily across the placenta and enter Fetal circulation. e.g. Thiopental (Barbiturate)→ crosses placenta & causes sedation, apnea in newborn infants.	**Ionized drugs (Polar)** cross the placenta very slowly → very low con. in the fetus. e.g.Succinylcholine&pancuronium (Neuromuscular blocking agent)
Molecular size of drugs	MW affects the rate of transfer: ❖ 250-500 cross placenta easily. ❖ 500-1000 cross placenta with more difficulty. ❖ ↑1000 can not cross placenta e.g. Heparin (Anticoagulant).	
Protein binding	Protein binding in maternal circulation hinders passage of drugs especially e.g propylthiouracil (Antithyroxin) and chloramphenicol (Antibiotic).	

Better use drugs have ↑MW, binding to protein and water soluble

lipid soluble, low molecular weight, free drugs should not be used

slide | doctor's note | important | explanation

2)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:-

1) Blastocyste formation (up to 16 days).
2) Organogenesis (17-60 days).
3) Histogenesis & maturation of function.

- 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.

2)The stage of mammalian fetal development

Stages	Explanation
Blastocyst formation (First 2 weeks)	▪ Occurs from (1-16 days) in the first trimester. ▪ Period of dividing zygote and implantation ▪ Pre-differentiated period (conceptus). ▪ Drugs have an all-or-nothing effect. All or nothing mean Abortion or nothing well happened ▪ Exposure to harmful drugs during this period → Prenatal death & abortion.
Organogenesis (2-8 weeks)	▪ Is the process by which cells specialize and organize to form the tissues and organs of an organism. ▪ Occurs in (17-60 days) in the first trimester. ▪ The most sensitive period of pregnancy. ▪ Exposure to harmful drugs→ Major birth defect in body parts or major congenital malformation.
Histogenesis and functional maturation (8 weeks onwards)	▪ Maturation occurs during this stage & fetus depends upon nutrients & hormonal supply. ▪ Exposure to drugs during 2nd & 3rd will not induce major malformation but drugs can produce minor morphologic abnormalities, growth retardation and functional defects. Functional problems rather than gross malformation

Teratogenesis

- Occurrence of congenital defects of the fetus.
- What is a teratogen? is any agent that is able to interferes 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 (Food and Drug Administration)

Category	Explanation
Category A	❑ Adequate and well-controlled human studies have failed to demonstrate a risk to fetus. ❑ Drugs can be used. e.g. Folic acid
Category B	❑ No risk in animal studies. ❑ No adequate and well-controlled human studies. ❑ Drugs can be used in pregnancy. e.g. Antibiotic
Category C	❑ Adverse effects on the fetus on animals only. ❑ No adequate and well-controlled studies in humans. ❑ Drug may be used in serious situation despite its potential risk. e.g. Tramadol
Category 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 e.g. Anticonvulsants
Category 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.

should not prescribed under any Circumstances

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Proven teratogens

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

- Thalidomide (sedative/ hypnotics) → Antiemetic
- Cytotoxic drugs e.g :

1)Folate antagonists (methotrexate)

2)Alkylating agents (cyclophosphamide).

- Lithium
- Alcohols
- Anticonvulsant drugs (valproic acid, phenytoin).
- Anticoagulants (warfarin).
- Antibiotics (tetracyclines, quinolones)
- ACEIs
- Retinoids e.g :

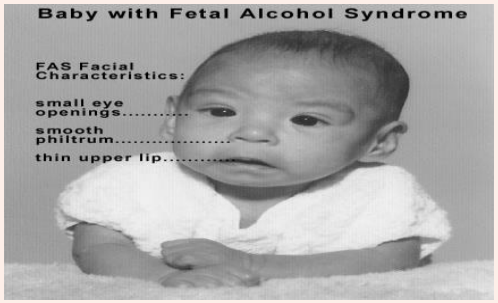
1)vitamin A (should be limited to 700 µg/day)

1)isotretinoin (used in treatment of acne)

- Ionizing radiation (diagnostic X-ray or radiation therapy).
- Radioactive iodine (I131).
- Corticosteroids.
- Hormones

ACEIs=angiotensin converting enzyme inhibitor

Teratogenesis of drugs

Drugs	Effects
Thalidomide Sedative & hypnotic drug	• 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 Antiepileptic drug	• Fetal Hydantoin Syndrome • Nail & Digital hypoplasia • Oral Clefts (cleft lip and palate) • Cardiac Anomalies  
Valproic acid Antiepileptic drug	• Neural tube defect (spina bifida) • Impairs folate absorption 
Tetracyclines Antibiotic	• Altered growth of teeth and bones • Permanent teeth staining • Enamel hypoplasia effect on calcium 

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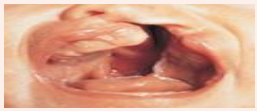
Teratogenesis of drugs

Drugs	Effects
Warfarin Anticoagulant	• Fetal warfarin syndrome • Hypoplasia of nasal bridge(flat nose) • CNS malformation 
Corticosteroids	• Cleft lip and Palate 
Hormones I. Estrogens II. Androgens III. Diethylstilbestrol	• Serious genital malformation • Testicular atrophy in male fetus • Fetal masculinization in female fetus • Vaginal carcinoma of female offspring
Lithium Antimanic	• Ebstein's anomaly • Cardiovascular anomalies mainly valvular heart defect involving tricuspid valve.
ACE inhibitors captopril, enalapril	• Renal damage • Fetal & neonatal anurnia • 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**

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

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.
Benzodiazepines as Diazepam	Chronic use → neonatal dependence and withdrawal symptoms
ACEIs	Renal damage
warfarin	Risk of bleeding

Adverse effects of drugs prior to labor or near term

CNS depressants	e.g. diazepam, morphine Interference with suckling - Respiratory depression - Reduced blood flow- fetal distress .
Sulfonamides	can displace bilirubin from albumin (neonatal hyperbilirubinemia) hyperbilirubinemia=jaundice

Hypertension in pregnancy

Contraindicated	• ACE inhibitors • Angiotensin II receptor blockers • Thiazide diuretics • Propranolol • Calcium channel blockers in mild hypertension
Probably safe	α- methyl dopa Labetalol
Emergency	Hydralazine Labetalol

Antithyroid drugs in pregnancy

Are used in thyrotoxicosis or Grave's disease

Propylthiouracil

Methylthiouracil (Methimazole)

Carbimazol

Radioactive Iodine (I^{131})

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

Coagulation disorders in pregnancy

Contraindicated	warfarin is contraindicated in all trimesters Cross placenta 1st trimester : teratogenicity (Chondroplasia) 2nd, 3rd : risk of bleeding.
Probably safe	Heparin Polar, does not cross placenta The antidote, protamine sulphate is available

Antibiotics in pregnancy

Contraindicated	**Tetracyclines:** Teeth and bones deformity **Quinolones as ciprofloxacin:** arthropathy (bone and cartilage damage) **Aminoglycosides:** ototoxicity **Sulfonamides:** neonatal jaundice-kernicterus **Chloramphenicol:** Gray baby syndrome
Probably safe	**Penicillins:** (ampicillin, amoxicillin) **Cephalosporins** **Erythromycin and azithromycin** as alternative in penicillin -sensitive individuals **BUT** erythromycin estolate should be avoided (risk of hepatic injury to mother).

Drugs of choice in pregnancy

Antihypertensive	**α-methyl dopa** **Labetalol (α - β Blocker)** **Hydralazine (emergency only)**
Antibiotics	**penicillin, cephalosporins, erythromycin**
Antidiabetics	**Insulin, avoids oral antidiabetics**
Anticoagulants	**Heparin**
Analgesics	**Acetaminophen**
Antithyroid drugs	**Propylthiouracil (protein-bound)**
Anticonvulsants	**-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 (Alcohols)

1-Alcohols : 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.

Characters :

1- Microcephaly

2-Intrauterine growth retardation

3-Craniofacial abnormalities

4- CVS abnormalities

5- CNS abnormalities (attention deficits, intellectual disability, mental retardation).

Drugs of Abuse in Pregnancy (Tobacco)

2- Tobacco contains nicotine and carbon monoxide that may harm fetus

- **Tobacco can increase risk of :**
- **Spontaneous abortion**
- **Prematurity (Preterm labor)**
- **Reduced blood flow to placenta**
- **Fetal hypoxia**
- **Retarded fetal growth**
- **Low birth weight**
- **Perinatal mortality**

Drugs of Abuse in Pregnancy (Cocaine)

3-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

-Microcephaly

- Prematurity

-Intrauterine growth retardation.

-Placental abruption (separation of placenta from uterus wall before delivery)

-Growth retardation

- Mental retardation

SUMMARY

Drugs of choice in pregnancy	
Antihypertensive	α-methyl dopa Labetalol (α - β Blocker) Hydralazine (emergency only)
Antibiotics	penicillin, cephalosporins, erythromycin
Antidiabetics	Insulin, avoids oral antidiabetics
Anticoagulants	Heparin
Analgesics	Acetaminophen
Antithyroid drugs	Propylthiouracil (protein-bound)
Anticonvulsants	All antiepileptics have potential to cause malformations avoid valproic acid (highly teratogenic) Folic acid supplementation prevents neural tube defects in women receiving AEDs
Antibiotics in pregnancy	
Tetracyclines	Teeth and bones deformity
Aminoglycosides:	ototoxicity
Sulfonamides:	neonatal jaundice-kernicterus
Chloramphenicol:	Gray baby syndrome

Quiz yourself

Q1/ Which of the following drugs is more lipid soluble and cross the placenta very rapidly :

A. Succinylcholine
B. Thiopental
C. Pancuronium
D. Heparin

Q2 / In what period of pregnancy taking drugs would cause congenital anomalies to the baby :

A. The first 2 weeks
B. From the 4^{th} – 6^{th} week
C. From the 2^{nd} - 6^{th} week
D. From the 2^{nd} – 8^{th} week

Q3/ which of the following drugs can be used in life threatening situations despite the harmful tratogenic effect it will cause to the baby :

A. Anticonvulsant
B. Antibiotic
C. Folic asid
D. B-blockers

Q4/ Which of the following tratogenic affect is caused by valproic acid :

A. Permenent teeth staining
B. Spina bifida
C. Oral defect
D. Tricuspid valve

Q5/ which of the following drugs can cause hyperbilirubinemia to the baby:

A. Warfarin
B. Aminoglycosides
C. Sulfonamides
D. cephalosporines

Q6/ which of the following is the drug of choice in pregnancy for a hypertensive woman :

A. Labetalol
B. Hydralazine
C. Thiazid diuritics
D. Ca++ channel blocker

Q7/ which of the following is the safest drug for hyperthyroid pregnant woman :

A. Methimazol
B. Radioactive iodine
C. Propylthiouracil
D. carbimazol

Q8/A mothe came to the pediatric clinic with her 2 years old baby who suffer bone deformities . Which antibiotic is the most likely to cause this abnormality :

A. Quinolones
B. Aminoglycosides
C. Chloramphenicol
D. tetracycline

Answers 1.B 2.D 3.A 4.B 5.C 6.A 7.C 8.D

Done by

PHARMACOLOGY 433

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