



Reproductive
System

PHARMACOLOGY
432 TEAM



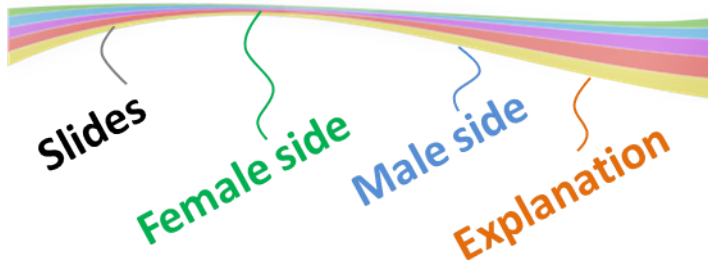
Teratogens and drugs of abuse in pregnancy

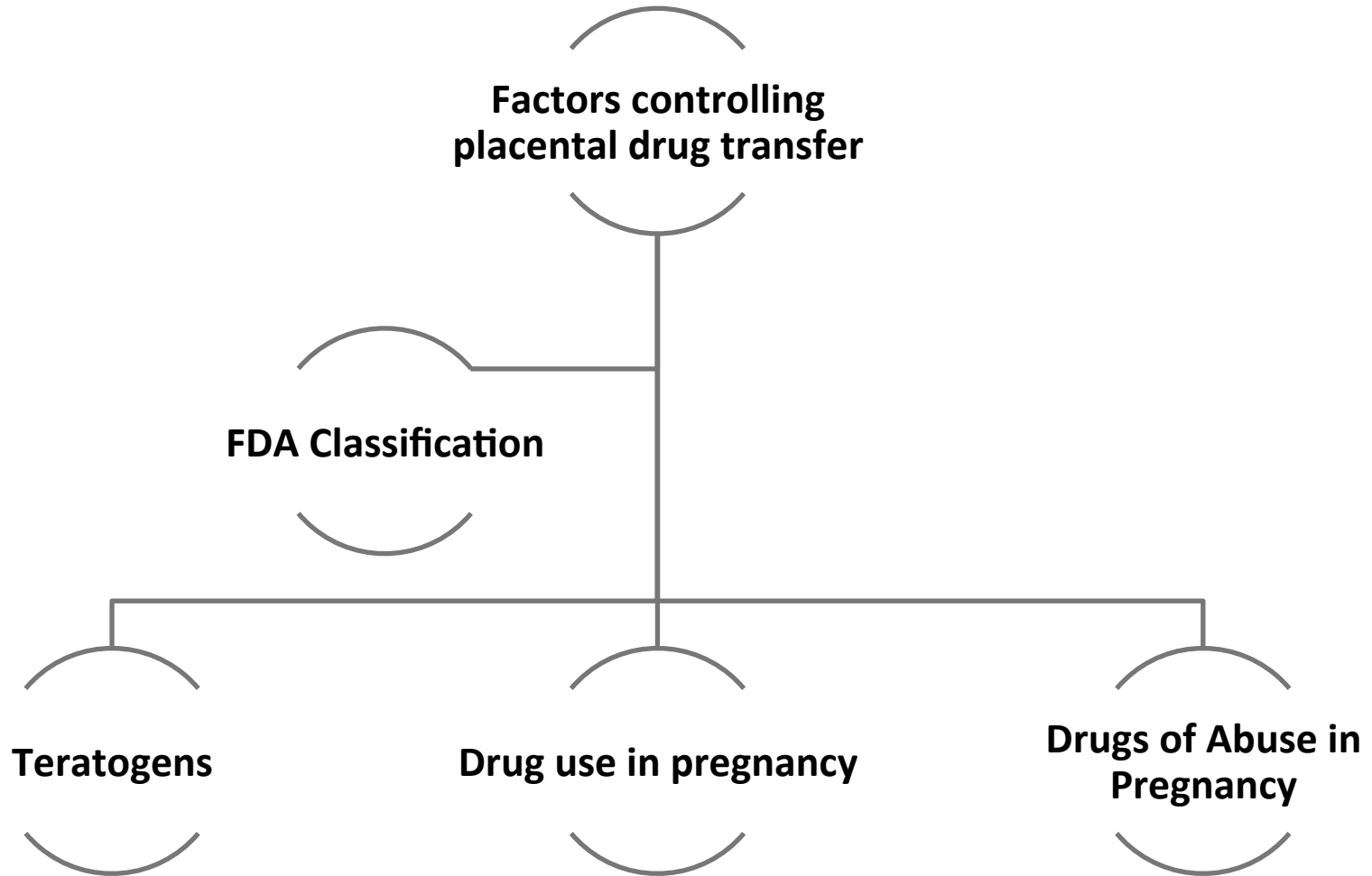
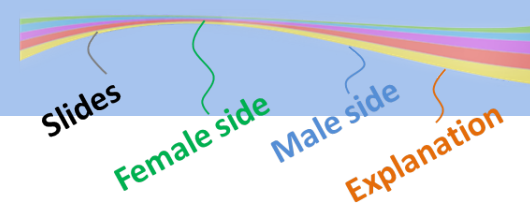
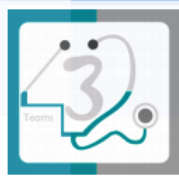
This lecture was done by:
Abdullah AlFaifi

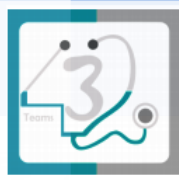
And reviewed by:
Sarah Alabdulqader

Learning Objectives:

Not Given







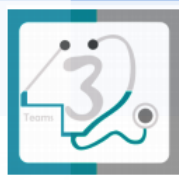
Placental membrane is semi-permeable.
Most drugs can cross placenta by passive diffusion.

Factors controlling placental drug transfer

1. Physiochemical properties of the drug

Lipid solubility or diffusion	Molecular size	Protein binding
<p>a) Lipophilic drugs diffuse readily across the placenta and enter fetal circulation e.g. Thiopental (anesthetic drug) crosses placenta & causes sedation, apnea in newborn infants</p> <p>b) Ionized drugs cross the placenta very slowly “very low conc. in the fetus.” (e.g. Succinylcholine & Tubocurarine)</p> <p>*Lipid soluble drugs can cross any membrane easily</p>	<p>“MW” affects the rate of transfer:</p> <p>250 - 500 cross placenta easily.</p> <p>500 - 1000 cross placenta with more difficulty.</p> <p>1000 or more can not cross placenta e.g. Heparin</p> <p>*high molecular weight → more difficult to cross placental membrane</p>	<p>Protein binding in maternal circulation hinders “Obstruct” passage of drugs especially .</p> <p>e.g Heparin, chloramphenicol and propythiouracil</p>

FYI \1-“Succinylcholine”\ used medically to produce brief but complete muscular relaxation.
2-“Tubocurarine” used as a muscle relaxant



Factors controlling placental drug transfer

2. The stage of Mammalian Fetal development

Blastocyste formation (up to 17 days).	Organogenesis (17-60days).	Histogenesis & maturation of function.
<p>Occurs in First 2 Weeks in the first trimester. Period of dividing zygote, implantation Pre-differentiated period (conceptus). Drugs have an all-or-nothing effect. Exposure to drugs during this period death of the embryo abortion</p>	<p>Occurs in (2- 8 weeks) in the first trimester. The most sensitive and critical period of pregnancy because major body organs and systems are formed. Exposure to harmful drugs during organogenesis lead to major birth defect or gross malformation (Teratogenesis)</p>	<p>Maturation occurs during this stage & fetus depends upon nutrients & hormonal supply. Exposure to drugs during (8 weeks onwards) 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.</p>

What is a teratogen?

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



FDA Classification System

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>Safe</p>	<p>Adverse effects on animal studies only</p> <p>Adequate Human studies lacking 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 <u>fetal risk is unknown.</u> 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>Fetal abnormalities in animal and human studies</p> <p>Drugs are teratogens and contraindicated in pregnant women or planning to conceive.</p>

Teratogens

Thalidomide	Phenytoin	Valproic acid	Warfarin	Lithium
<p>Phocomelia</p> <p>↓</p> <p>Shortened or absent long bones of the limbs</p> <p>↓</p> <p>Absence of External Ears</p>	<ul style="list-style-type: none"> - Fetal Hydantoin Syndrome - Nail & Digital hypoplasia - Oral Clefts (cleft lip and palate) <ul style="list-style-type: none"> - Cardiac Anomalies - Mental & growth retardation 	<ul style="list-style-type: none"> - Antiepileptic drug - Neural tube defect (spina bifida) - Impair folate absorption 	<ul style="list-style-type: none"> - Hypoplasia of - Nasal bridge <ul style="list-style-type: none"> - CNS malformation - Risk of bleeding (During second and third trimesters only) 	<p>Cardiovascular anomalies</p> <p>“mainly valvular heart defect involving tricuspid valve”</p> <p>its called: Ebstein's anomaly</p>

Hormones \ "Estrogens, Androgens, Diethylstilbestrol"	ACE inhibitors \ (captopril, enalapril)	Corticosteroids
<ul style="list-style-type: none"> - Serious genital malformation - Testicular atrophy in male - Fetal masculinization in female - Vaginal carcinoma of female offspring 	<ul style="list-style-type: none"> - Fetal & neonatal anuria - Renal damage <p>Fetal hypotension, hypoperfusion</p> <ul style="list-style-type: none"> - growth retardation <p>ACE inhibitors disrupt the fetal renin-angiotensin system, which is essential for normal renal development</p>	<ul style="list-style-type: none"> - Cleft lip and Palate - Adrenal atrophy - Growth Retardation <p>*We mean systemic corticosteroids not localized</p>



Tetracyclines	Aminoglycosides	Antithyroid drugs	Propranolol
<ul style="list-style-type: none"> - Permanent teeth staining "yellow - brown discoloration of teeth" - Enamel hypoplasia - Altered growth of teeth and bones. 	<p>e.g.(Streptomycin kanamycin)</p> <p style="text-align: center;">↓</p> <ul style="list-style-type: none"> - Ototoxicity & nephrotoxicity <hr/> <p>Cloramphenicol</p> <hr/> <p>Gray baby syndrome</p>	<p>e.g.\(Iodide, Methimazole, Carbimazole, propylthiouracil)</p> <ul style="list-style-type: none"> - Risk of hypothyroidism and goitre 	<ul style="list-style-type: none"> - Bradycardia - Neonatal hypoglycemia - Placental insufficiency - Reduced uterine blood flow - Fetal distress
<p>NSAIDs e.g. Aspirin-indomethacin</p>		<p>Benzodiazepines</p>	<p>CNS depressants</p>
<ul style="list-style-type: none"> - Prostaglandin synthesis inhibitors - Constriction of ductus arteriosus - Pulmonary hypertension in newborns - Increase in gestation time - prolong labor - neonatal bleeding - Risk of postpartum hemorrhage 		<p>e.g.\(Diazepam)</p> <ul style="list-style-type: none"> - Neonatal dependence and withdrawal symptoms <hr/> <p>Sulfonamides</p> <hr/> <ul style="list-style-type: none"> - Neonatal hyperbilirubinemia 	<p>e.g.\(diazepam, morphine)</p> <ul style="list-style-type: none"> - Interference with suckling - Respiratory depression - Reduced blood flow & fetal distress



situation	Contraindicated	Probably safe (Drug of choice)	Emergency
Hypertension in pregnancy	<p>- ACE inhibitors</p> <ul style="list-style-type: none"> - Angiotensin II receptor blockers - Thiazide diuretics - Propranolol <p>- Calcium channel blockers in mild hypertension</p>	<p>α- methyl dopa & Labetalol</p>	<p>Hydralazine & Labetalol By injection</p>
Coagulation disorders in pregnancy	<p>warfarin is contraindicated in all trimesters</p> <p>Its crosses placenta and causes\ 1st trimester :Teratogenicity</p> <p>2nd, 3rd : risk of bleeding</p>	<p>Heparin</p> <ul style="list-style-type: none"> - Polar, does not cross placenta+high molecular weight - Protamine sulphate as antidote for neutralization 	<p><u>FYI:</u> Protamine sulfate is a drug that reverses the anticoagulant effects of heparin by binding to it.</p>
Other Disorders	<p><u>Anticonvulsants:</u></p> <ul style="list-style-type: none"> - (avoid valproic acid) - folic acid supplementation to prevent neural tube defects 	<p><u>Antidiabetics:</u></p> <p>Insulin is safe, (avoids oral antidiabetics)</p>	<p><u>Analgesics:</u></p> <p>Acetaminophen</p>



situation	Contraindicated	Probably safe (Drug of choice)
<p>Antithyroid drugs in pregnancy (used in thyrotoxicosis or Grave's disease)</p>	<ul style="list-style-type: none"> - Propylthiouracil - Methylthiouracil (Methimazole) - Carbimazol - Radioactive Iodine (I131) - All can cross placenta - All have risk of congenital goiter and hypothyroidism 	<p>Propylthiouracil is preferable over others Because it's a protein bound The lowest dose of antithyroid drugs should be used.</p>
<p>Antibiotics in pregnancy</p>	<ul style="list-style-type: none"> - <u>Aminoglycosides</u>: ototoxicity - <u>Tetracyclines</u>: Teeth and bones deformity - <u>Sulfonamides</u>: neonatal jaundice-kernicterus - <u>Chloramphenicol</u>: Gray baby syndrome - <u>Quinolones</u> 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 - "erythromycin estolate" should be avoided (risk of hepatic injury to mother).

Drugs of Abuse in Pregnancy

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

- Microcephaly

- Intrauterine growth retardation

- Craniofacial abnormalities

- CVS abnormalities

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

2-Cocaine

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

- Cocaine **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**, fetal oxygenation and intestinal blood flow.

- It increases uterine contractility

- Microcephaly

- Prematurity

- Low birth weight.

- **Abruptio placentae** (separation of placenta from uterus wall before delivery)

- Growth retardation

- Mental retardation

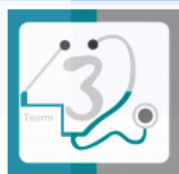
- Withdrawal symptoms

3-Tobacco

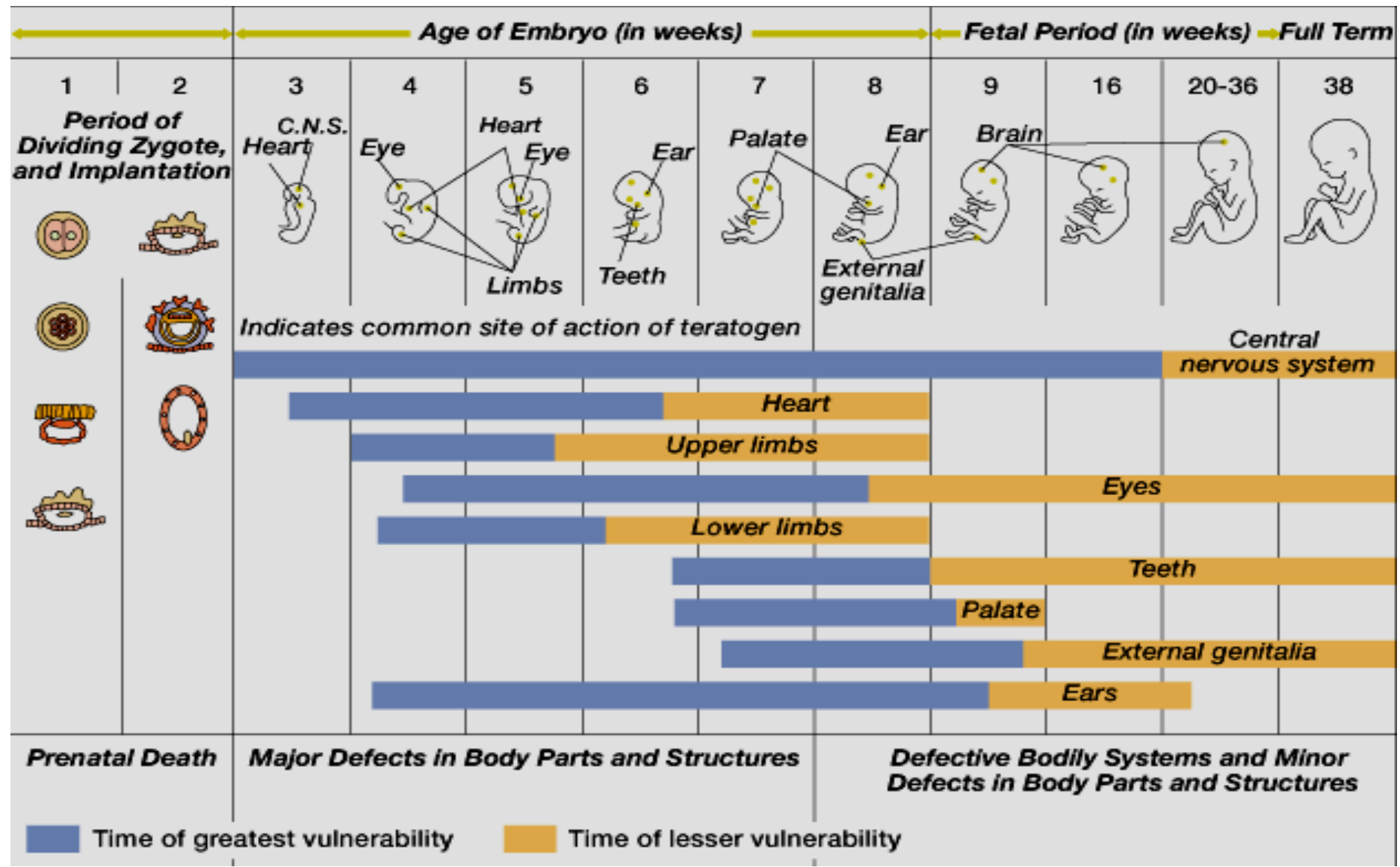
Tobacco contains nicotine and carbon monoxide that may harm the fetus.

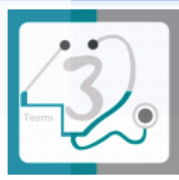
- **Decreased blood flow to placenta & Fetal hypoxia**

- Retarded fetal growth & Low birth weight
 Increased spontaneous abortion & Preterm labor and stillbirth

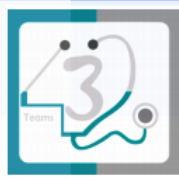


Summary



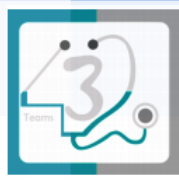


- The use of drugs during pregnancy should be avoided unless absolutely necessary.
- Most drugs cross the placenta to some extent.
- Birth defects are of great concern.
- Drugs can harm the embryo or foetus depending upon the stage of foetal development.
- The most critical period of pregnancy is organogenesis (17 days – 8 weeks).
- Alcohol, nicotine and other addicting drugs should be avoided.
- **Epileptics pregnant has to be treated by giving her monotherapy (low dose) and also should be giving folic acid.**
- **Systemic corticosteroids that are given by injection has a teratogenic effects but localized corticosteroids like inhalers won't cause a harm to the fetus.**



1. We always should be cautious when giving certain drugs to a pregnant women, which stage of pregnancy is most sensitive to drug effects on the fetus :
 - A. First 2 Weeks**
 - B. 8 weeks onwards**
 - C. First (2- 8) weeks**
 - D. 9th month of pregnancy**

2. Thalidomide was largely used in the mid nineties against nausea and to alleviate morning sickness in pregnant women, it was stopped afterwards due reported cases of malformation in newborns, what is the major malformation that was found :
 - A. Shortened or absent long bones of the limbs(Phocomelia)**
 - B. Neural tube defect (spina bifida)**
 - C. Gray baby syndrome**
 - D. Ototoxicity**



3. Ebstein's anomaly is caused by which one of the following:
 - A. Tetracyclines**
 - B. ACE inhibitors**
 - C. Phenytoin**
 - D. Lithium**

4. A pregnant woman comes to the Emergency department with severe hypertension, what is your best treatment option in this case :
 - A. α - methyl dopa**
 - B. Hydralazine**
 - C. Propranolol**
 - D. Thiazide diuretics**

5. A baby was born with Microcephaly, CVS abnormalities and Craniofacial abnormalities, what is possible abused drug in this case :
 - A. Cocaine**
 - B. Tobacco**
 - C. Alcohol**
 - D. nicotine**



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Pharmacology Leaders
Tuqa Al-Kaff & Abdullah Al-Anzi

Pharmacologyteam1@gmail.com