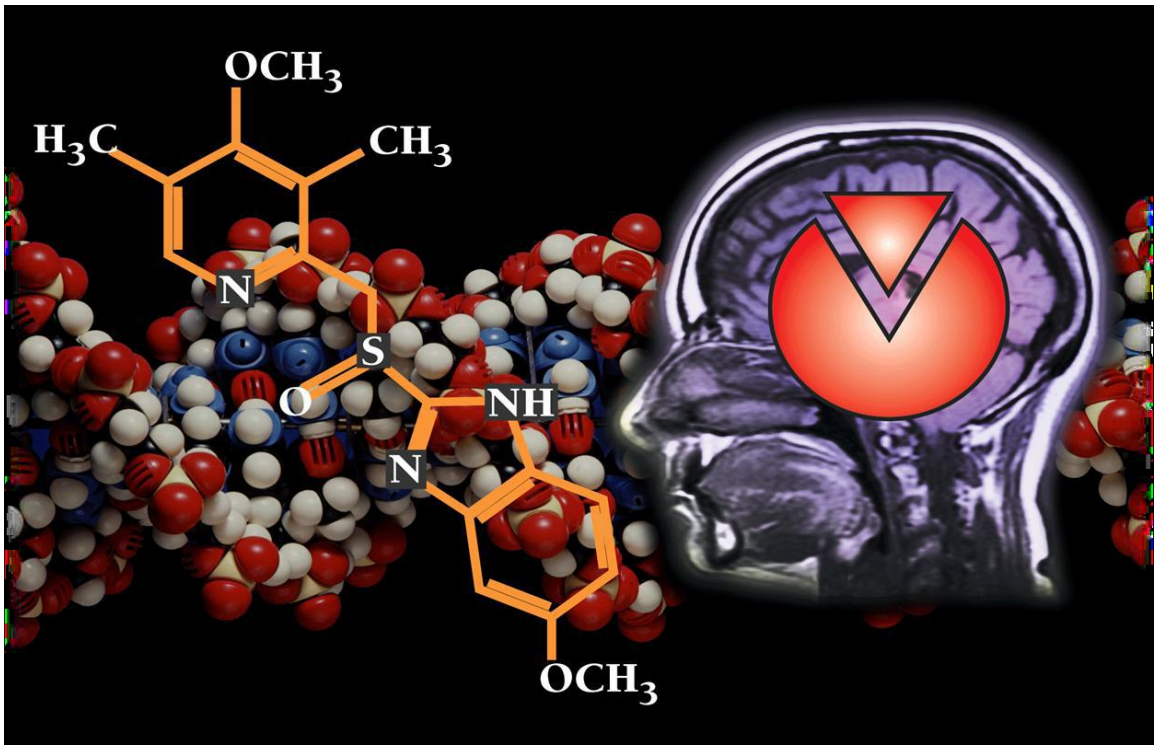
oKing Saud University
College Of Medicine
Pharmacology Team 430
Reproductive Block

03- Teratogens and drugs of abuse in pregnancy



Note text in blue and textboxes with thick light blue margins are additional info. Text in red is important.

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Introduction:

In pregnancy:

- Placental membrane is semi-permeable. (so diffusion will be affected by molecular weight)
- Most drugs can cross placenta by passive diffusion. (depending on the lipid solubility & the variation of concentration of the drug)
- The movement of drugs across the placenta is limited by a single layer of cells called trophoblasts.

Pharmacokinetic changes in pregnancy

- 1-↑ Cardiac output → 2-↑ Plasma Volume → 3-↑ volume of distribution → 5-↑ Metabolic rate of some drugs. → 4-↑ GFR and renal elimination of drugs.

Factors controlling placental drug transfer:

Physiochemical properties of the drug

- **Lipid solubility or diffusion.**
- **Molecular size.**
- **Protein binding.**

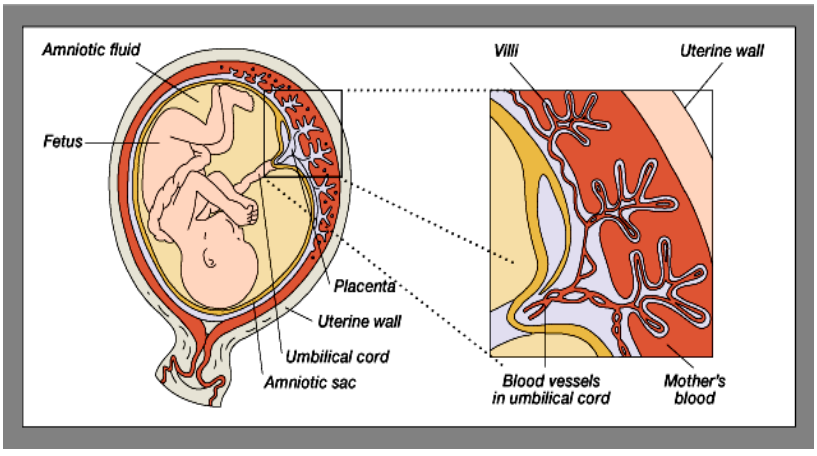
The stage of placental and fetal development "at the time of exposure to the drug"

Duration of exposure to the drug

"the longer duration of exposure the highr risk to affect the fetus"

1- Physiochemical properties of the drug

Lipid solubility of the drug	Molecular size of the drug	Protein binding.
Lipophilic drugs diffuse readily across the placenta and enter fetal circulation. **e.g.*Thiopental*** → crosses placenta & causes sedation (CNS depression), apnea(respiratory depression) in newborn infants. **Ionized drugs** cross the placenta very slowly → very low conc. in the fetus. ***e.g. Succinylcholine & Tubocurarine.*** **(safe to give a pregnant woman)**	**MW affects the rate of transfer:** • 250 – 500 (low MW) cross placenta easily. • 500 - 1000 (high MW) cross placenta with more difficulty. • ↑ 1000 cannot cross placenta e.g. ***Heparin*** (safe for pregnant)	Protein binding in maternal circulation hinders passage of drugs especially poorly lipid soluble drugs.
-More lipid soluble → cross placenta → affects fetus -Less lipid soluble → less crossing placenta → less effect on fetus.	-Low MW→ easy to diffuse placenta → affect fetus. -High MW → no diffusion in placenta → no affect on fetus.	-more protein binding → less diffusion in placenta. -less protein binding → more diffusion in placenta.



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:

- ➢ Blastocyste formation (up to 17 days).
- ➢ Organogenesis – stage in which organs are formed- (17-60 days). → **most sensitive stage**
- ➢ Histogenesis & maturation of function.

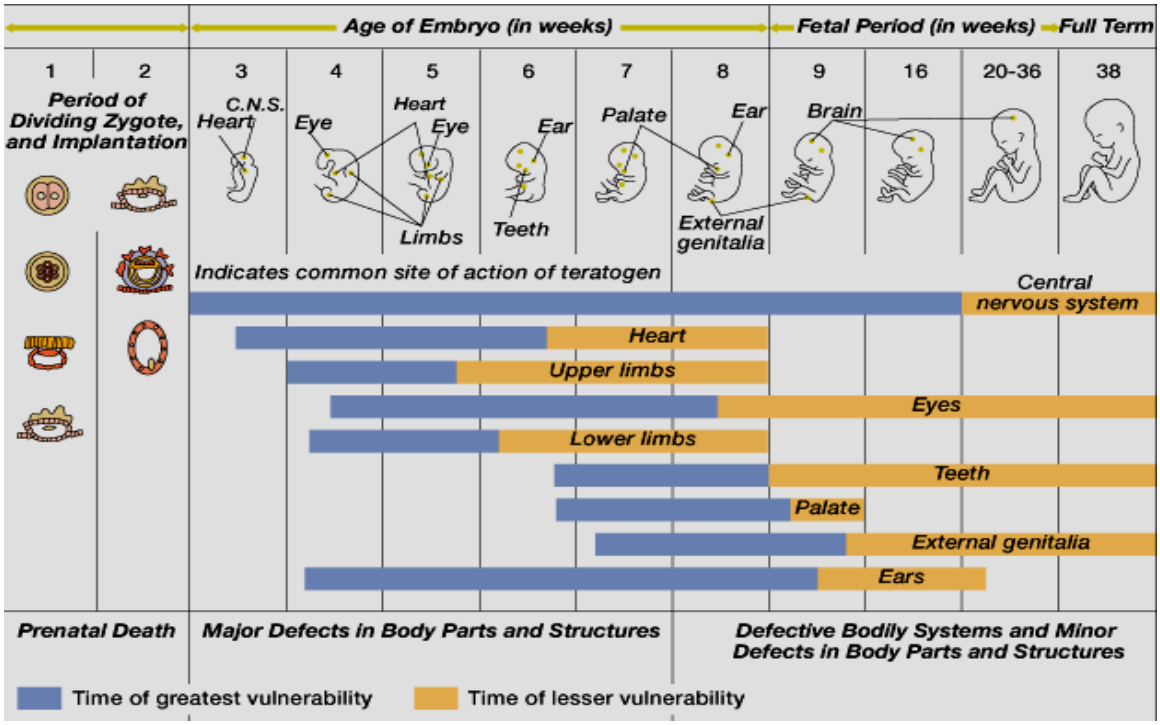
Three trimesters of pregnancy are:
First trimester: week 1- week 12
Second trimester: week 13-week 28
Third trimester: week 29-week 40

Blastocyste formation (First 2 weeks)	Organogenesis: (2-8 weeks)	Histogenesis and functional maturation (8 weeks onwards)
• Occurs from (1-16 days) in the first trimester. • Period of dividing zygote & implantation • Pre-differentiated period (conceptus – no organic differentiation). • Drugs have an all-or-nothing effect. • Exposure to drugs during this period → death of the embryo → abortion (all affect = abortion).	• Occurs in (17- 60 days) in the first trimester. • 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)	• Maturation occurs during this stage & fetus depends upon nutrients & hormonal supply. • Exposure to drugs during 2_{nd} and $3_{rd\ trimesters}$ (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. (last system that fully develops In the fetus is the CNS)

Teratogenesis :

Teratogenesis: Production of gross malformation or congenital defects of the fetus.
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).

Critical Periods of Human Development



FDA Classification System:

Category A:

- Controlled human studies with no risk to fetus.
- Drugs can be used (safe for pregnant).

Category B:

- Adverse effects on animal studies only.
- Human studies did not show similar results. (can be used for pregnant)

Category C:

- Adverse effects on animal studies only.
- No human studies, human fetal risk is unknown. (IMP to be careful when the drug is prescribed)

Category D:

- Evidence of human fetal risk.
- May be used in serious diseases or life threatening situations

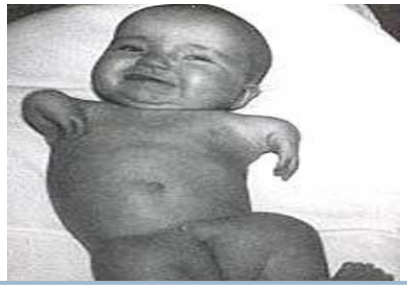
Category X:

- Fetal abnormalities in animal and human studies.
- Drugs are teratogens and contraindicated in pregnant women
- or planning to conceive.

Proven teratogens (category X):

- *Thalidomide* (sedative/ hypnotics) →result in *phocomelia*
- *Cytotoxic drugs (anticancer drugs)*
  - Folate antagonists *(methotrexate).*
  - Alkylating agents *(cyclophosphamide).*
  - All others: smaller risk.
- *Lithium* (antimanic).
- *Alcohols* (fetal alcohol syndrome- if used in the 1st trimester "especially")
- *Anticonvulsant drugs (e.g valproic acid, phenytoin).*
- *Anticoagulants (e.g warfarin- has low MW).*
- *Antibiotics (tetracyclines " the all group", quinolones)*
- *Drugs containing Retinoids e.g.*
  - *vitamin A (should be limited to 700 µg/day)*
  - *isotretinoin (used in treatment of Acne-)*
  - *etretinate (treatment of psoriasis)*
- *Angiotensin converting enzyme inhibitors (ACEIs)* (Anti hypertensive).
- *Ionizing radiation: either used as diagnostic X-ray Or radiation therapies like Radioactive iodine (I^{131})* (which is used in Hyperthyrodisim)
- *Corticosteroids.*
- *Hormones.*

- Anticancer drugs → inhibit cell proliferation → affect fetus growth
- Heparin is an Anticoagulant with high MW safe to be prescribed to a pregnant



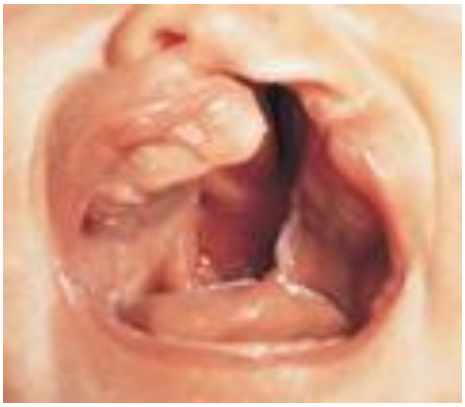
Phocomelia caused by Thalidomide

Spina bifida caused by valproic acid

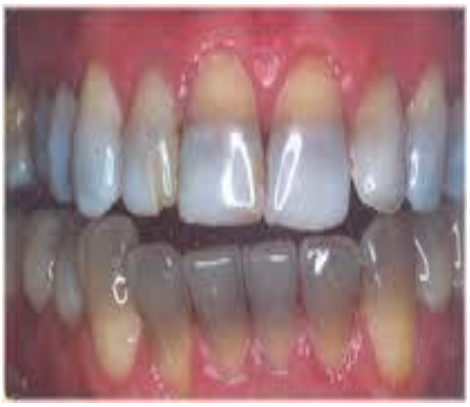
Teratogenesis of drugs:

Thalidomide	Alcohol	Phenytoin
Phocomelia : ➢ shortened or absent long bones of the limbs ➢ Anorectal stenosis ➢ Absence of External Ears	**Fetal Alcohol Syndrome (FAS)** ➢ Microcephaly ➢ Intrauterine growth retardation ➢ Craniofacial abnormalities ➢ CVS abnormalities ➢ CNS abnormalities *(attention deficits, intellectual disability, mental retardation)*	**Fetal Hydantoin Syndrome** Nail & Digital hypoplasia Oral Clefts (cleft lip and palate) Cardiac Anomalies Mental & growth retardation

Fetal hydantoin syndrome caused by Phenytoin



Cleft lip and Palate caused by corticosteroids



Teeth staining caused by Tetracyclines

Corticosteroids	Tetracyclines	Warfarin	Finasteride Used in prostatic hypertrophy
Cleft lip and Palate	Permanent teeth staining Enamel hypoplasia altered growth of teeth and bones.	-Hypoplasia of nasal bridge -CNS malformation.	-Abnormal development of genitalia of male fetuses

Valproic acid	Hormones: - Estrogens - Androgens - diethylstilbestrol	Lithium	ACE inhibitors: *captopril, enalapril*
Antiepileptic drug causing: -Neural tube defect (spina bifida) -Impair folate absorption	-Serious genital malformation -Testicular atrophy in male Fetal masculinization in female -Vaginal carcinoma of female offspring (later on could cause: vaginal adenocarcinoma)	Cardiovascular anomalies mainly valvular heart defect involving tricuspid valve Ebstein's anomaly	-Fetal & neonatal anurnia -Renal damage (by affecting RAAS in fetus) -Fetal hypotension -growth retardation

Adverse effects of drugs:

During second and third trimesters

Some drugs can produce adverse effects (minor defect) on the fetus more likely than major malformations due to their pharmacological actions.

Tetracyclines	Impaired teeth & bone development, yellow-brown discoloration of teeth
Aminoglycosides	e.g. *Streptomycin, kanamycin* causes: Ototoxicity = 8th Cranial nerve damage
Cloramphenicol	Gray baby syndrome (also contraindicated in children less than 4 yrs old)
Corticosteroids	Adrenal atrophy – growth retardation
Propranolol *(beta blocker)*	Bradycardia, neonatal hypoglycemia, placental insufficiency, reduced uterine blood flow, fetal distress
Antithyroid drugs	Iodide, Methimazole, Carbimazole, propylthiouracil Risk of hypothyroidism and goitre
NSAIDs	e.g. Aspirin-indomethacin - Prostaglandin synthesis inhibitors - Constriction of ductus arteriosus (close prematurely), pulmonary hypertension in newborns.

Benzodiazepines as Diazepam	Chronic use → neonatal dependence and withdrawal symptoms
ACEIs	Renal damage
warfarin	Risk of bleeding
Adverse effects of drugs prior to labor	
NSAIDs	**e.g. Aspirin-indomethacin** Prostaglandin synthesis inhibitors Increase in gestation time prolong labor, neonatal bleeding Risk of postpartum hemorrhage
CNS depressants	**e.g. diazepam, morphine** Interference with suckling Respiratory depression Reduced blood flow, fetal distress
Sulfonamides	Displacement of bilirubin from plasma protein (neonatal hyperbilirubinemia)

Hypertension in pregnancy:

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

Coagulation disorders in pregnancy:

Contraindicated	Probably safe
warfarin is contraindicated in all trimesters 1st trimester : Teratogenicity (Chondroplasia) 2nd, 3rd : risk of bleeding	*Heparin:* Polar, does not cross placenta. Protamine sulphate as antidote for neutralization

Antithyroid drugs in pregnancy:

Are used in thyrotoxicosis or Grave's disease

- *Propylthiouracil*
- *Methylthiouracil (Methimazole)*
- *Carbimazol*
- *Radioactive Iodine (I131)*

- 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 it binds to protein in the maternal circulation)

Antibiotics in pregnancy:

Contraindicated :	Probably safe:
• *Aminoglycosides:* ototoxicity • *Tetracyclines:* Teeth and bones deformity • *Sulfonamides:* neonatal jaundice-kernicterus • *Chloramphenicol:* Gray baby syndrome • *Quinolones as ciprofloxacin:* bone and cartilage damage (arthropathy)	• 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 anti-epileptics have potential to cause malformations ➢ If must be used avoid using 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.**

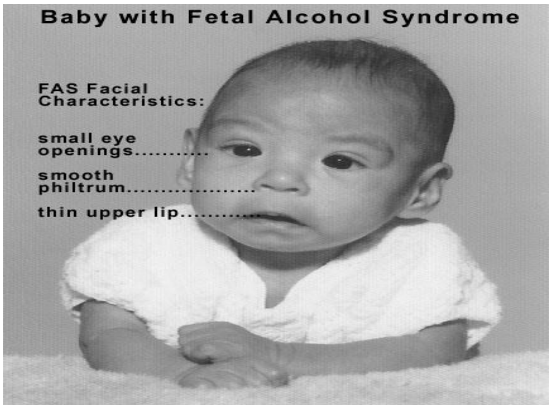
Alcohols

The use of alcohol is contraindicated during all trimesters of pregnancy **causing : 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)*



Cocaine

- Cocaine has a 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).**
- **Abruptio placentae (separation of placenta from uterus wall before delivery)**
- **It decreases blood flow to uterus, fetal oxygenation and intestinal blood flow.**
- It increases uterine contractility
- Microcephaly
- Prematurity
- Low birth weight.
- Growth retardation
- Mental retardation
- Withdrawal symptoms

Tobacco

- Tobacco 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

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 three points:
  - **Physiochemical properties of the drug:**

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

  - **The stage of mammalian fetal development:** The most critical period of pregnancy is organogenesis (17 days – 8 weeks).
  - **Duration of exposure to the drug.**
- Alcohol, nicotine and other addicting drugs should be avoided.
- **Teratogenesis of drugs:**

Major Teratogenesis (during the first trimester)	
Thalidomide	Phocomelia.
Alcohol	Foetal Alcohol Syndrome (FAS).
Phenytoin	Foetal Hydantoin Syndrome.
Corticosteroids	Cleft lip & palate.
Tetracyclines	Permanent Teeth staining enamel hypoplasia Altered growth of teeth & bone.
Warfarin	Hypoplasia of nasal bridge and CNS malformation.
Finasteride	Abnormal development of genitalia of male foetuses.
Valproic acid	Spina bifida and Impaired folate absorption
Hormones	Serious genital malformation -Testicular atrophy in male Fetal masculinization in female -Vaginal carcinoma of female offspring
Lithium	Cardiovascular anomalies mainly valvular heart defect involving tricuspid valve Ebstein's anomaly
ACE inhibitors: captopril, enalapril	Fetal & neonatal anurnia -Renal damage -Fetal hypotension -growth retardation
Major Teratogenesis (during the second & third trimesters)	
Tetracyclines	Impaired teeth & bone development, yellow-brown discoloration of teeth
Aminoglycosides	e.g. *Streptomycin, kanamycin* causes: Ototoxicity = 8th Cranial nerve damage
Cloramphenicol	Gray baby syndrome (also contraindicated in children less than 4 yrs old)

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