Pharmacology
Team 437

Teratogens & drugs of abuse

Objectives:

1. Factors affecting drug placental transfer.
2. Harmful effects of drugs during different stages of development.
3. FDA classifications of drugs.
4. Teratogenic drugs.
5. Adverse effects of drugs.
6. Drugs of abuse.

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Color index:
Important Note Extra Gold

MED437
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Introduction

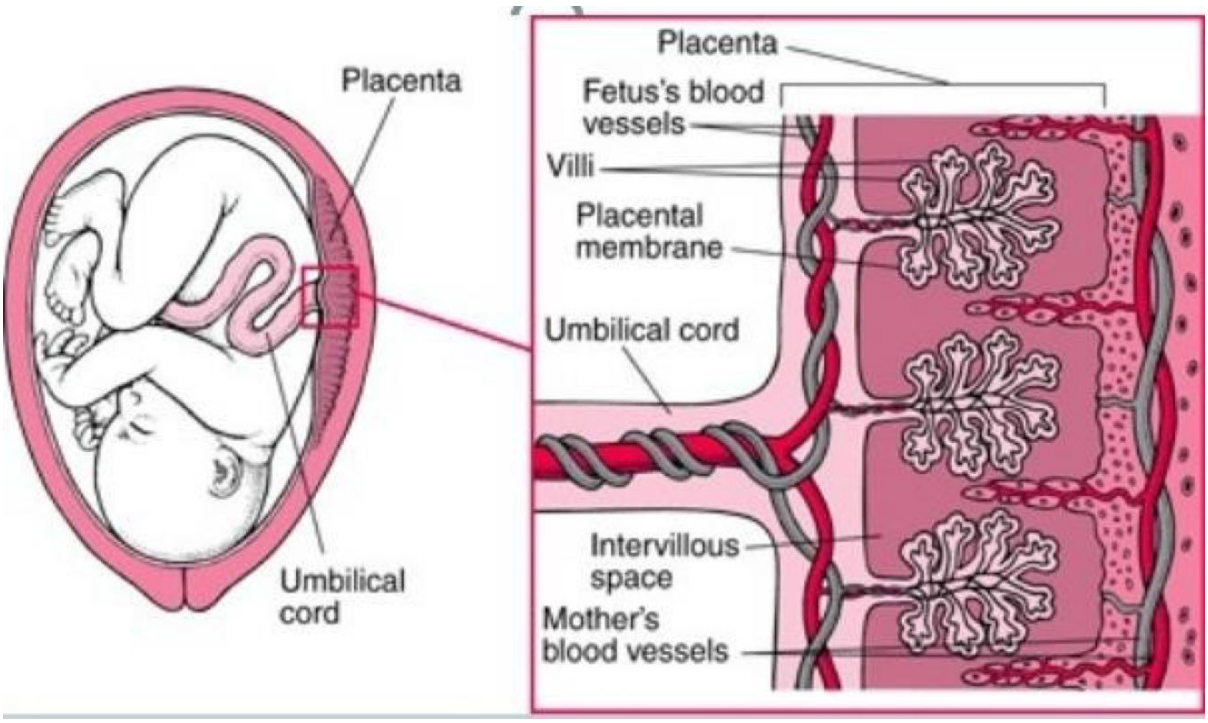
Medications in Pregnancy:

- Majority of 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.

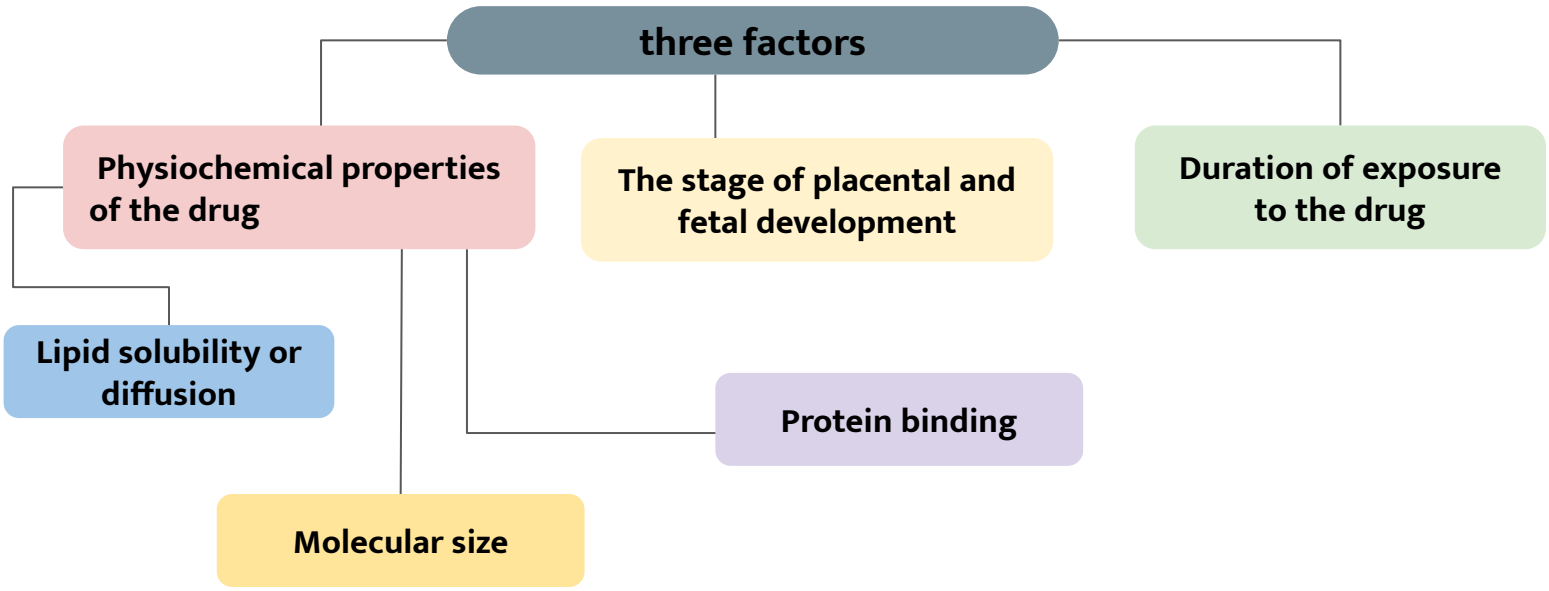
Could result in 3 types of side effects:
1- Abortion
2- Congenital anomalies
3- Mental retardation

How Drugs Can Cross Placenta?

- Most drugs can cross placenta through the placental membrane (semi-permeable).
- 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.



Factors controlling placental drug transfer



I. Physiochemical Properties of the Drug

Lipid soluble drugs should always be avoided (polar, ionized drugs are safer)

Lipid solubility or diffusion

Lipophilic drugs

diffuse readily across the placenta and enter fetal circulation. e.g. Thiopental → crosses placenta & causes sedation, apnea in newborn infants. (Thiopental is a barbiturate used for induction of anesthesia)

Ionized drugs

cross the placenta very slowly → very low conc. In the fetus e.g. Succinylcholine & pancuronium

Most CNS drugs are lipid soluble

Molecular Size

The larger the molecular size the safer the drug

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

Protein Binding

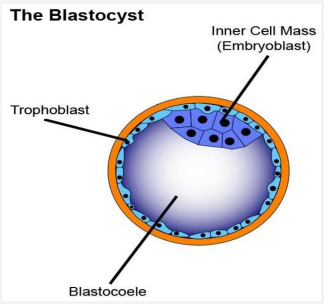
- **Protein binding in maternal circulation hinders passage of drugs**
- e.g propylthiouracil and chloramphenicol

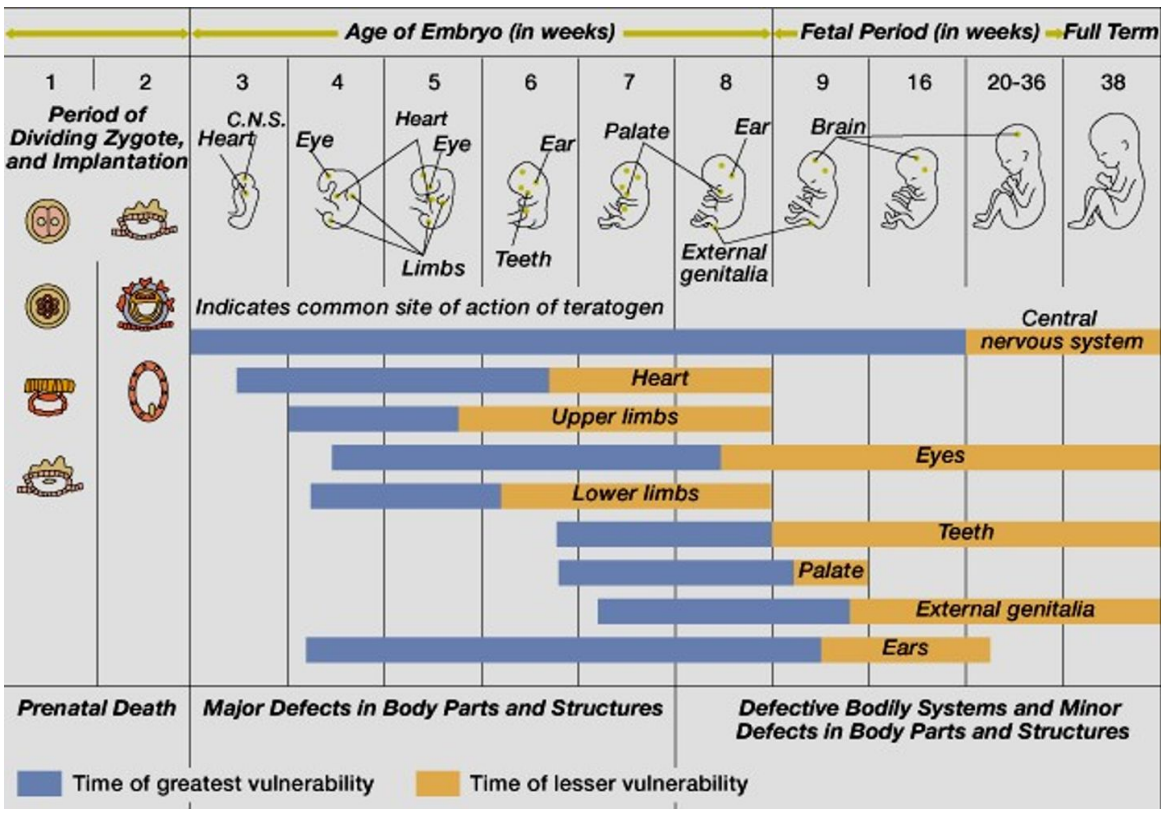
It's better to give highly protein bound drugs as they have a lower volume of distribution

II. The Stage of Placental and Fetal Development

First Trimester (week 1 - week 12)		Second & third Trimester (week 13 - week 28)	Near Term (week 29 - week 40)
Blastocyst formation (1st 2 weeks)	Organogenesis (week 3 week 8)	Histogenesis & maturation of function (8 weeks onwards)	
Occurs from (1-16 days) in the first trimester.	is the process by which cells specialize and organize to form the tissues and organs of an organism.	Growth and fetal development occur during this stage.	
Period of dividing zygote and implantation.	Occurs in (17- 60 days) in the first trimester.	Fetus depends upon nutrients & hormonal supply.	
Pre-differentiated period (conceptus).	The most sensitive period of pregnancy. Do NOT take drugs	Exposure to drugs can cause "Function problems" rather than "gross malformation" loss of organ function	
Drugs have an all-or-nothing effect.	Exposure to harmful drugs → major birth defect in body parts or major congenital Malformation (teratogenesis).	Exposure to drugs during 2nd and 3rd trimesters will not induce major malformation but drugs can produce minor morphologic abnormalities, growth retardation and functional defects. No major congenital malformations	

Exposure to drugs during this period leads to death of the embryo & abortion





Teratogenesis

What is Teratogenesis?

- Occurrence of congenital defects of the fetus.

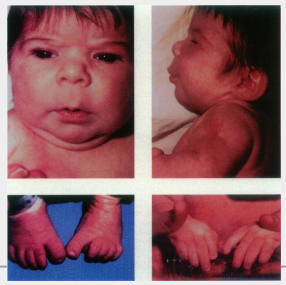
What are Teratogens?

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

FDA Classification System

Category	General information	Example/s
A	❖ Adequate and well-controlled human studies have failed to demonstrate a risk to fetus (show no risk). No risk in animals + humans ✓ **Drugs can be used**	Folic acid Folic acid is a pregnancy supplement Thyroxine
B	❖ No risk in animal studies (Animal studies ok) . ❖ No adequate and well-controlled human studies (No human data). ✓ **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. (No human data) ❖ Drug may be used in **serious situation** despite its potential risk. (Risk cannot be ruled out)	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** (Benefits outweigh risks)	Antiepileptic e.g. Phenytoin
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

Proven Teratogens (category X) In 1st trimester

Teratogen	Teratogenic effect
(Thalidomide) Sedative and Hypnotics	❖ **Phocomelia:** ○ shortened or absent long bones of the limbs ○ absence of external ears ❖ The most notorious human teratogen, but it had no teratogenic effects in mice and rats but proved teratogenic when used in pregnant women  
Anticonvulsant Phenytoin	❖ **Fetal Hydantoin Syndrome** ○ Nail & Digital hypoplasia ○ Oral Clefts (cleft lip and palate) ○ Cardiac Anomalies. 
Valproic acid Proven teratogen, NEVER give	❖ Neural tube defect (spina bifida) ❖ Impairs folate absorption. 
Antibiotics (Tetracycline)	❖ Altered growth of teeth and bones ❖ Permanent teeth staining ❖ Enamel hypoplasia 
Anticoagulants (Warfarin)	❖ Hypoplasia of nasal bridge ❖ CNS malformation
Corticosteroids	❖ Cleft lip and Palate  
Hormones: Estrogens Androgens Diethylstilbestrol	❖ Serious genital malformation ○ Testicular atrophy in male fetus (estrogen) ○ Fetal masculinization in female fetus (androgen) ○ Vaginal carcinoma of female offspring (diethylstilbestrol) ■ Single exposure of diethylstilbestrol is enough to cause vaginal carcinoma later in life
Lithium	❖ Ebstein's anomaly: **Cardiovascular anomalies** mainly valvular heart defect involving tricuspid valve
ACE inhibitor: Captopril Enalapril	❖ ACE inhibitors disrupt the fetal renin-angiotensin system, which is essential for normal renal development: ○ Renal damage ○ Fetal & neonatal anuria ❖ Fetal hypotension, Hypoperfusion → Growth retardation

Other drugs	❖ **Cytotoxic drugs:** ○ Folate antagonists (methotrexate) ○ Alkylating agents (cyclophosphamide) ❖ Alcohols (fetal alcohol syndrome) ❖ **Retinoids:** ○ Vitamin A (should be limited to 700 ug/day) ○ Isotretinoin (used in treatment of acne) ❖ **Ionizing radiation:** diagnostic X-ray or radiation therapy/radioactive iodine (I131) ❖ **Antibiotics**: quinolones.

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.
- ❖ Affect **growth and fetal development**.

Drug	Adverse effect
Tetracyclines	❖ Impaired teeth & bone development ❖ Yellow-brown discoloration of teeth
Aminoglycosides (streptomycin, kanamycin)	❖ Ototoxicity = 8th cranial nerve damage ❖ Nephrotoxicity
Chloramphenicol	❖ Gray baby syndrome
Corticosteroids	❖ Adrenal atrophy - growth retardation
Propranolol	❖ Bradycardia, neonatal hypoglycemia, placental insufficiency, reduced uterine blood flow ⟶ fetal distress
Antithyroid	❖ Iodide, methimazole, carbimazole, propylthiouracil ❖ Risk of neonatal hypothyroidism and goiter
NSAIDs e.g. aspirin-indomethacin	❖ Prostaglandin synthesis inhibitors: ❖ Constriction of ductus arteriosus (close prematurely) ❖ Pulmonary hypertension in newborns ❖ Increase in gestation time ❖ If taken near delivery: prolong labor, neonatal bleeding, risk of postpartum hemorrhage

Benzodiazepines as Diazepam hypnotics	❖ Chronic use → neonatal dependence and withdrawal symptoms
ACEIs	❖ Renal damage
Warfarin	❖ Risk of bleeding
CNS depressant e.g. diazepam, morphine	❖ Interference with suckling ❖ Respiratory depression ❖ Reduced blood flow → fetal distress
Sulfonamides	❖ Can displace bilirubin from albumin (neonatal hyperbilirubinemia, jaundice) → kernicterus

	Probably Safe	Contraindicated	Emergency
Hypertension in pregnancy	❖ Alpha-methyldopa ❖ Labetalol	❖ ACE inhibitors ❖ Angiotensin II receptor blockers ❖ Thiazide diuretics ❖ Propranolol (not selective) ❖ Calcium channel blockers in mild hypertension	Hydralazine Labetalol
Coagulation Disorders in pregnancy	❖ Heparin : Polar, doesn't cross placenta ❖ Protamine sulphate As antidote for neutralization	❖ Warfarin is contraindicated in ALL trimesters ❖ Cross placenta membrane ❖ 1st trimester: teratogenicity ❖ 2nd & 3rd: risk of bleeding	-
Antibiotics in pregnancy	❖ **Penicillins** (ampicillin, amoxicillin) ❖ **Cephalosporins** ❖ **Macrolides** (erythromycin, azithromycin) **as alternative in penicillin sensitivity,** Erythromycin estolate should be avoided (risk of hepatic injury to the mother)	❖ **Aminoglycosides**: ototoxicity ❖ **Tetracyclines**: teeth and bone deformity ❖ **Sulfonamides**: neonatal jaundice-kernicterus ❖ **Chloramphenicol**: gray baby syndrome ❖ **Quinolones as ciprofloxacin:** bone and cartilage damage (**arthropathy**)	-

Antithyroid drug in pregnancy

- ❖ Used in thyrotoxicosis or Grave's disease: **Propylthiouracil, Methylthiouracil (methimazole), Carbimazole, 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 the others (protein-bound)

Don't skip it, there's drugs were not mentioned before

Summary of drugs of choice in pregnancy	
Antihypertensive	❖ Alpha-methyldopa ❖ Labetalol (alpha - beta blocker) ❖ Hydralazine (EMERGENCY ONLY)
Antibiotics	❖ Penicillin ❖ Cephalosporins ❖ erythromycin
Antidiabetics	❖ Insulin, avoids oral antidiabetics
Anticoagulant	❖ Heparin
Analgesics	❖ Acetaminophen
Antithyroids	❖ 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

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

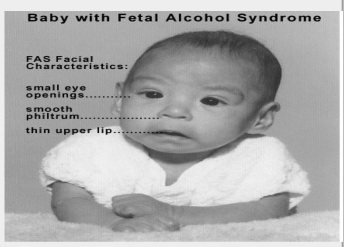
Drugs of Abuse in Pregnancy

Alcohol

it has a very low molecular weight and is very lipid soluble

- 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
  - Low birth weight
  - Craniofacial abnormalities
  - CVS abnormalities
  - CNS abnormalities (attention deficits, intellectual disability, mental retardation) even if consument in 3rd trimester

Cocaine

- Low MW → easily passes into fetus through placenta.
- Inhibits reuptake 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
- **Characters**:
  - Microcephaly
  - Prematurity
  - Intrauterine growth retardation
  - Abruptio placentae (separation of placenta from uterus wall before delivery)

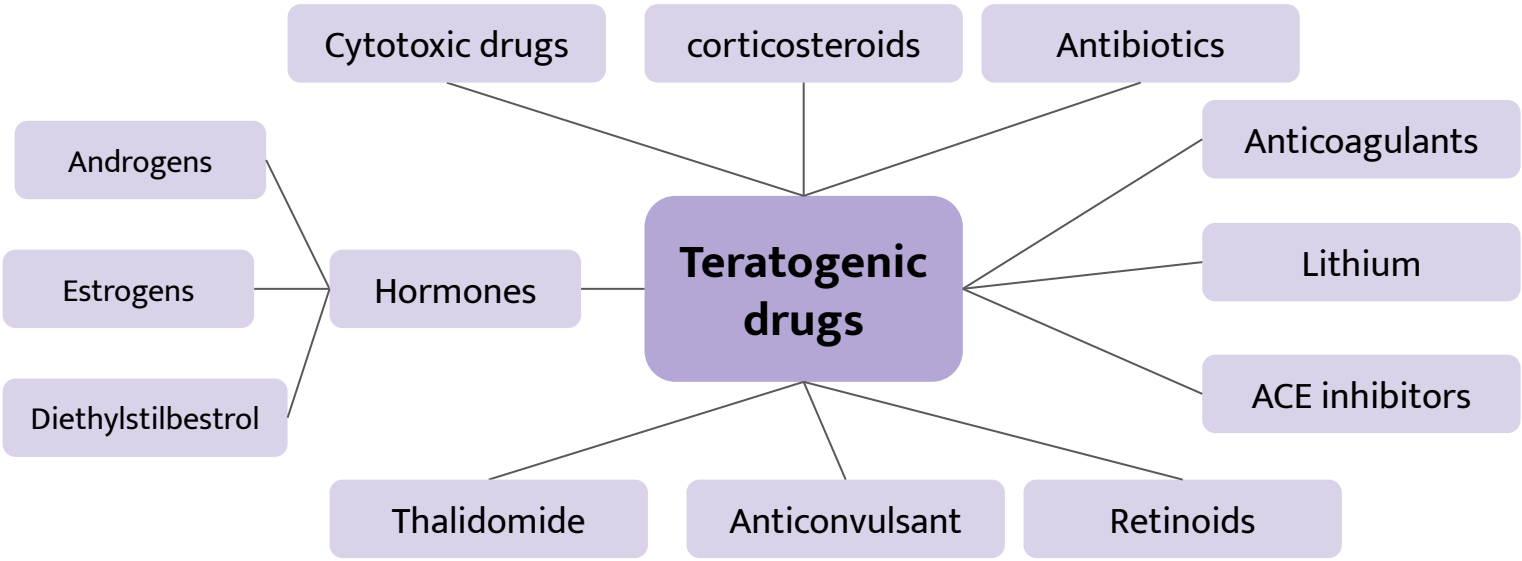
	○ Growth retardation ○ Mental retardation
Tobacco	❖ Tobacco contains nicotine and carbon monoxide that may harm fetus. ❖ **No evidence it causes birth defects BUT, Tobacco can increase risk of:** ○ Low blood flow to placenta ○ Fetal hypoxia ○ Retarded fetal growth ○ Low birth weight ○ Increased spontaneous abortion → preterm labor and stillbirth (perinatal mortality)

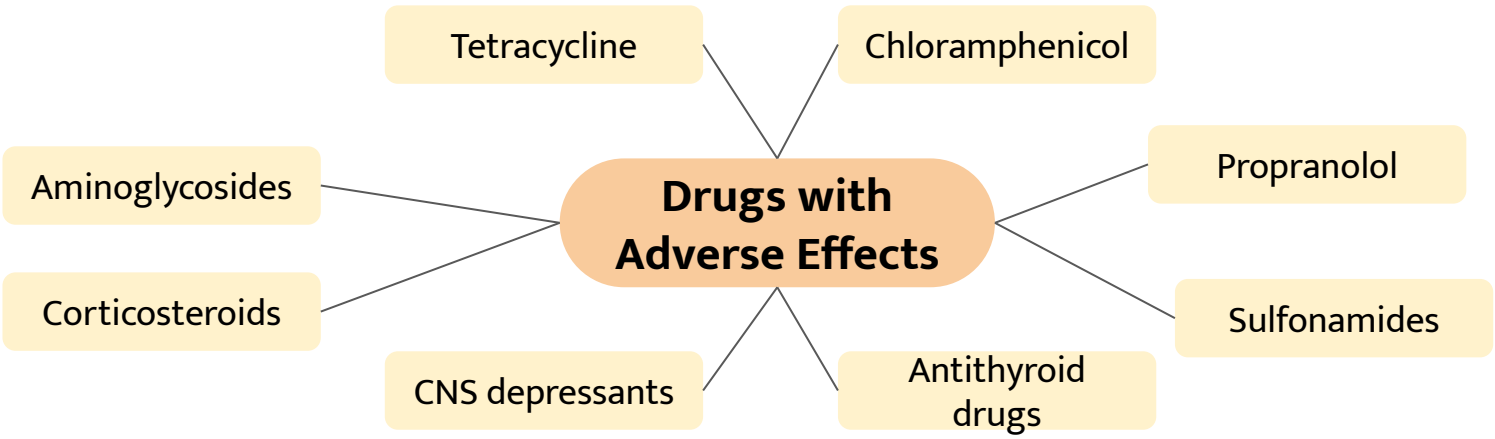
Conclusion

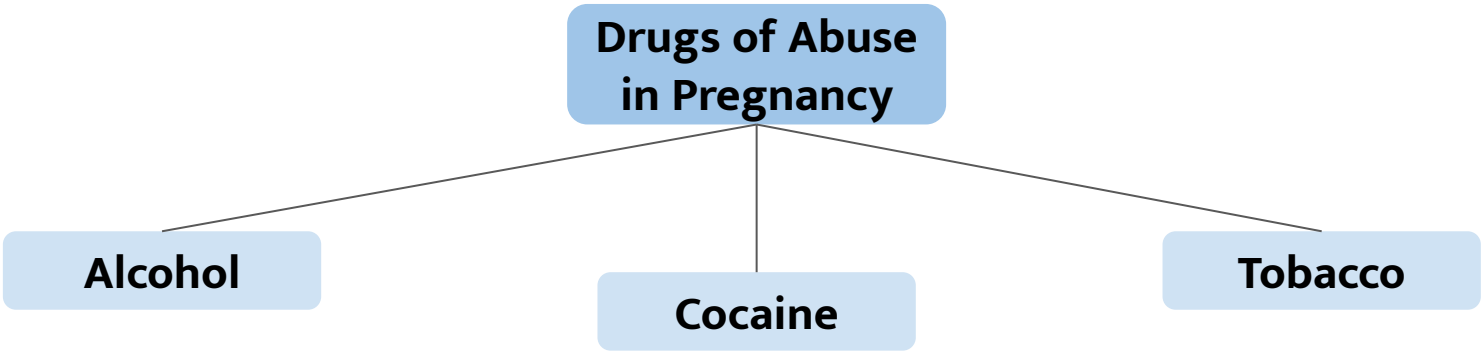
- ❖ The use of drugs should during pregnancy should be avoided unless absolutely necessary.
- ❖ Most drugs cross the placenta to some extent.
- ❖ Birth defects are of great concern.
- ❖ Drugs can harm the embryo or fetus depending upon the stage of fetal development.
- ❖ The most critical period of pregnancy is **organogenesis** (week 2 - week 8).
- ❖ Alcohol, nicotine and other addicting drugs should be avoided.

- ❖ **First trimester (week 1 - week 12):**
  - ○ Blastocyst formation (all or none).
  - ○ Organogenesis: major congenital malformations (teratogenesis).
- ❖ **Second & third trimesters: (week 13 - week 28)**
  - ○ Affect growth & fetal development.
- ❖ **Near term: (week 29 - week 40)**
  - ○ Adverse effects on neonates or labor after delivery.

Mindmap


Teratogenic drugs
Cytotoxic drugs
corticosteroids
Antibiotics
Androgens
Estrogens
Hormones
Diethylstilbestrol
Anticoagulants
Lithium
ACE inhibitors
Thalidomide
Anticonvulsant
Retinoids


Drugs with Adverse Effects
Tetracycline
Chloramphenicol
Aminoglycosides
Corticosteroids
Propranolol
Sulfonamides
CNS depressants
Antithyroid drugs


Drugs of Abuse in Pregnancy
Alcohol
Cocaine
Tobacco

Quiz

Q1: A baby was born with shortened long bones of the upper limbs. Which of the following drugs will you most likely find in the mother's drug history?

A. Warfarin
B. Tetracycline
C. Thalidomide
D. Valproic acid

Q2: Which of the following drugs impairs folate absorption?

A. Phenytoin
B. Valproic acid
C. Corticosteroids
D. ACE inhibitors

Q3: Administration of chloramphenicol during the second and third trimesters of pregnancy leads to which one of the following ?

A. Permanent staining of the teeth.
B. Gray baby syndrome
C. Ototoxicity
D. Neonatal hypoglycemia

Q4: Exposure to Diethylstilbestrol during pregnancy leads to :

A. Spina bifida
B. Vaginal carcinoma of female offspring
C. Cardiac anomalies
D. Renal damage.

Q5: A pregnant lady in her 37th week of gestation developed a urinary tract infection and was treated with sulfonamides. Which of the following will most likely occur in the newborn baby?

A. Neonatal jaundice
B. Respiratory depression
C. Neoonatal hypogylcemia
D. Gray baby syndrome

Q6: According to the FDA classification system , all of the following are in category X except for :

A. Retinoids
B. Alcohol
C. Corticosteroids
D. Morphine

Q7: A diabetic lady found out she was pregnant. Her doctor decided to change her Medication. What medication should he prescribe to her?

A. Metformin
B. Glyburide
C. Insulin
D. No drugs and only lifestyle modification.

Answers:
1) C
2) B
3) B
4) B
5) A
6) D
7) C

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Notes by

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References:

✓ Doctors' slides and notes
✓ Team 435

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