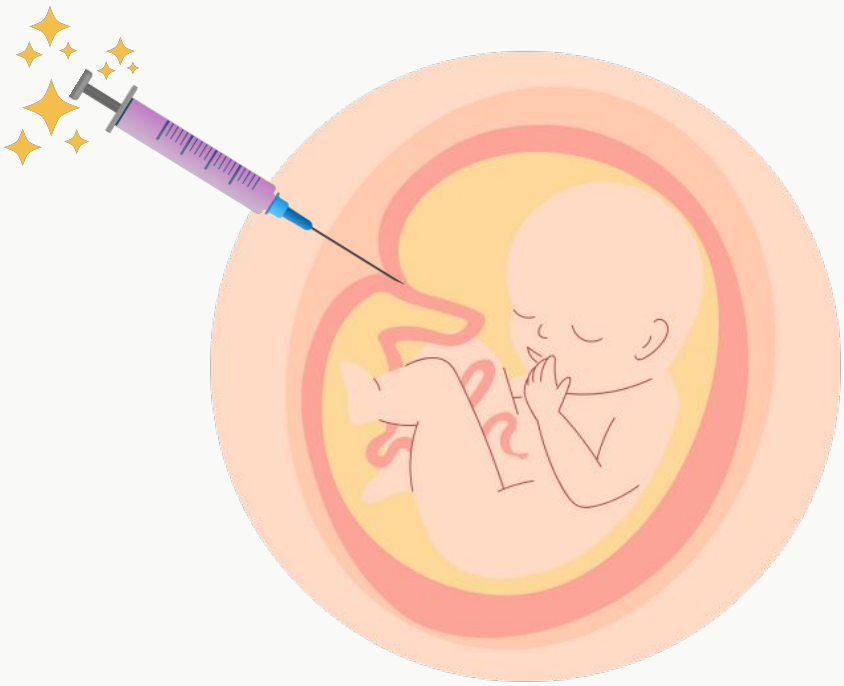
Teratogens and drugs of abuse in pregnancy

Dr. Alaa Alanteet | Dr. Abdullah Alhamed



- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

Objective

- Factors affecting drug placental transfer
- Harmful effects of drugs during different stages of development
- FDA classifications of drugs
- Teratogenic drugs, Adverse effects of drugs, Drugs of abuse

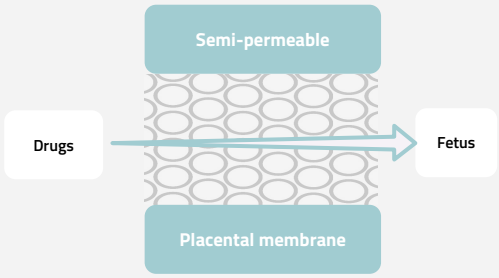
Medication in pregnancy

Intro

- Majority of pregnant 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 for about one-half of medication are unknown.
- About 2 to 3 % of all birth defects result from the use of drugs.

How Do Drugs Cross the Placenta?

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

Physicochemical Properties

Physiological aspect of drug eg: Lipid Solubility or diffusion ,Molecular Size, protein binding

Stage of Development

The time of exposure to the drug.

Duration of Exposure

Once or for chronic use ? Some drugs ADRs won't appear immediately, but will appear after puberty.

The Alien from the Pathology took a trip to Pharmacology just to ask you this :
During the first six weeks of the embryonic phase, what developments could not be affected if the fetus is exposed to teratogens?

A. Heart
B. Central nervous system
C. Upper and lower limbs
D. External genitalia
E. Palate

Answer: E

The Alien from the Pathology took a trip to Pharmacology just to ask you this :
What is not an examples of gross malformation birth defects?

A. Split in the roof of the mouth
B. Increased cerebral spinal fluid in the ventricles of the brain
C. Foot that is twisted out of shape or position
D. Yellowish discoloration of skin and eyes

Answer: D

Physicochemical Properties

Lipid Solubility and Ionization

(Safe in pregnancy: ↓lipid solubility and ↑Polarity (ionized))

- **Lipophilic drugs** diffuse readily across the placenta and **enter fetal circulation**
  - Ex: **Thiopental** (CNS depressant, used in general anesthesia)→ crosses placenta and causes **sedation and apnea** in newborn infants.
- **Ionized drugs** (Polar=safe) cross the placenta very slowly → very **low concentration in fetus.**
  - Ex: **Succinylcholine, & Pancuronium** (muscle relaxants)

Molecular Size

(Safe in pregnancy: ↑MW)

MW affects the rate of transfer:

- MW of 250-500 → cross the placenta easily.
- MW of 500-1000 → crosses the placenta with more difficulty.
- MW ↑ 1000 → can NOT cross the placenta. Ex: **Heparin**

Protein Binding

(Safe in pregnancy: ↑Plasma protein binding)

- Protein binding in the maternal circulation hinders the passage of drugs.
  Ex: **Propylthiouracil, chloramphenicol**

The Alien from the Pathology took a trip to Pharmacology just to ask you this :
Why is thalidomide considered a teratogen?

A. Thalidomide causes babies to have malformed limbs
B. Thalidomide causes early contractions and neonatal distress
C. Thalidomide causes a mother to have insomnia
D. Thalidomide causes a mother to have nausea

Answer: A

The Alien from the Pathology took a trip to Pharmacology just to ask you this :
Which medication is the safest in treating epilepsy during pregnancy?

A. Valproate
B. Carbamazepine
C. Levetiracetam
D. Lamotrigine
E. Phenytoin

Answer: D

The Stage of Mammalian Fetal Development

harmful actions of the drug depend upon stage of fetal development at time of drug exposure

First Trimester (Weeks 1-12)

Blastocyst Formation First 2 weeks- (pre-differentiated period, conceptus)	Organogenesis (2-8 weeks)
• Occurs from 1-16 days in the first trimester • Period of dividing zygote and implantation • Drugs have **all-or-nothing effect** (None: no ADRs, All: abortion) • Exposure to harmful drugs during this period → prenatal death → abortion	• The process by which cells specialize & organize to form tissues and organs of an organism. • Occurs in 17-60 days in the first trimester • The most sensitive period of pregnancy because major body organs & systems are formed. • **Exposure to harmful drugs → major birth defects or major congenital malformation (teratogenesis)**

2nd & 3rd Trimester (Weeks 13-28)

Affect growth & fetal development.

Histogenesis and Functional Maturation (8 weeks onward)

- Growth & fetal development occur at this stage.
- Fetus depends on nutrients and hormonal supply.
- **Exposure to drugs → functional problems** rather than **gross malformations**,
- Exposure to drugs during 2nd and 3rd will not induce major structural malformation.
- Drugs during this period can produce minor morphological abnormalities, growth retardation, and functional defects. However, CNS is sensitive to toxic effects throughout pregnancy.

Near Term (Weeks 29-40)

ADRs on neonates after delivery

Adverse effects on neonate after delivery. some drugs are safe during pregnancy but shouldn't be taken nearterm to avoid labor complications. (e.g. NSAID)

Click here for picture from slide

Teratogenesis

What is a teratogen?

Teratogenesis: Occurrence of congenital defects of fetus.

- Substances that may cause permanent birth defects via a toxic effect on an embryo or fetus
- This could be severe during critical periods of development e.g. **organogenesis.**
- **Examples**: medication, street drug, chemicals, diseases, environmental agents.

FDA Classification System

Category	Characteristics	Examples
A 	• Adequate and well-controlled human studies have failed to demonstrate a risk to fetus **(controlled human studies with no risk)** • **Drugs can be used** in pregnancy.	**Folic acid** **Thyroxine**
B 	• No risk in animal studies • No adequate and well-controlled human studies. • (Animal studies ok, No human data) • **Drugs can be used** in pregnancy	**Paracetamol** **Erythromycin**
C 	• Adverse effects on **animal fetus only** • No adequate & well-controlled studies in humans. • **Risk cannot be ruled out.** • (Animal studies are not ok, No human data) • **Drug may be used in serious situation despite its potential risk.**	**Morphine**
D 	• Positive evidence of human fetal risk based on adverse reaction data **from studies in humans**, investigational or marketing experience. (Benefits outweigh risks) • **May be used in serious diseases or life threatening situations**	**Antiepileptics:** 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** (sedative)

Proven Teratogens (category X)

Retinoids	A. Vitamin A (limited to 700 ug/day) B. Isotretinoin : used in treatment of acne
Thalidomide	sedative/hypnotic
Ionizing radiation	diagnostic x-ray or radiation therapy
Radioactive Iodine (I131)	Hyperthyroidism Treatment
Cytotoxic drugs	A. Folate antagonists (Methotrexate) B. Alkylating agents (Cyclophosphamide)
Anticoagulants	Warfarin
Antibiotics	Tetracyclines, Quinolone
ACEIs	renin-angiotensin-aldosterone inhibitor
Hormones	Hormonal supplement over all tend to manipulate the normal hormonal level during pregnancy

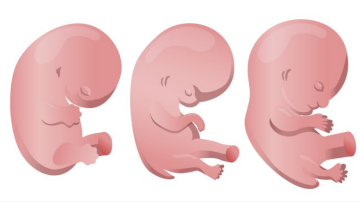
Teratogenesis of Drugs

Thalidomide

CATEGORY X

Phocomelia:

- Shortened or absent long bones of the limbs.

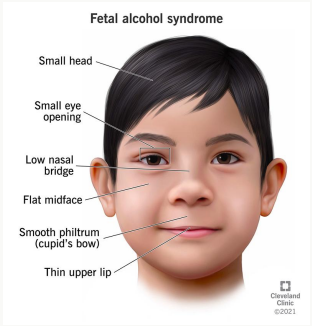


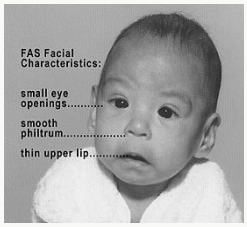
Alcohol

CATEGORY X

Fetal Alcohol Syndrome

- Microcephaly.
- Craniofacial abnormalities.
- Intrauterine growth retardation.
- CVS abnormalities.
- CNS abnormalities (attention deficits, intellectual disability, mental retardation).



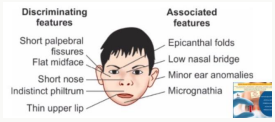


Anticonvulsants

CATEGORY D

Phenytoin

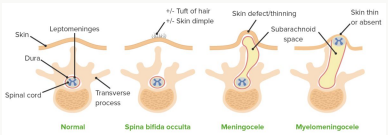
- Fetal Hydantoin Syndrome:
  - Nail and digital hypoplasia
  - Oral cleft (cleft lip and palate)
  - Cardiac anomalies



Valproic acid

antiepileptic drug

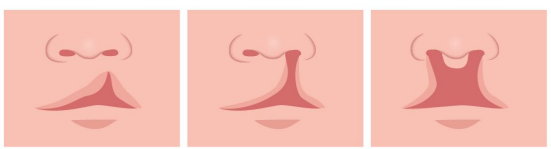
- Neural tube defect (spina bifida)
- impaired folate absorption
- Folic acid supplement will decrease ADRs.



Corticosteroids

CATEGORY C

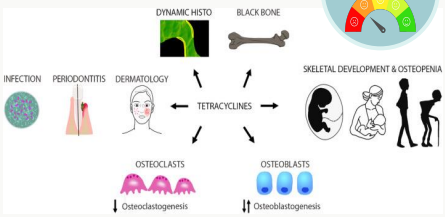
Cleft lip and palate



Tetracyclines

CATEGORY D

- Altered growth of teeth and bones.
- Permanent teeth staining (yellow-brown discoloration of teeth).
- Enamel hypoplasia.



Teratogenesis of Drugs

Warfarin

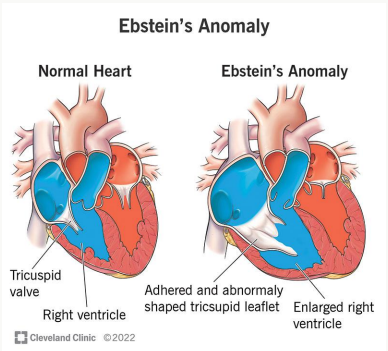
- **Hypoplasia of nasal bridge.** (1st trimester)
- **CNS malformation.** (1st trimester)
- **Near term:** neonatal hemorrhage.

CATEGORY D

Lithium

Ebstein's anomaly:

- CVS anomalies mainly **valvular heart defect involving tricuspid valve.**
- If we need to give it, fetal echocardiography should be considered for women.



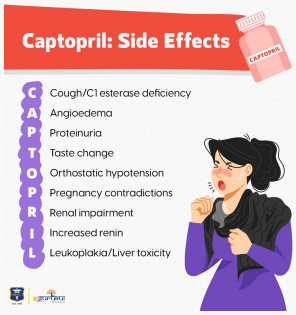
"Wall to wall " heart is one of the most common complications

CATEGORY D

ACE inhibitors

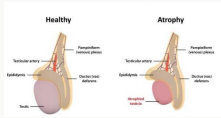
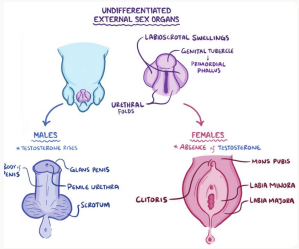
Captopril, Enalapril

- Renal damage: **ACEIs** disrupt fetal RAAS system which is essential for normal renal development.
- Neonatal anuria.
- Fetal **hypotension & Hypoperfusion.**
- Growth retardation.



CATEGORY D

Hormones

(cause serious genital malformation)		
Estrogens	Testicular atrophy in **male** fetus	
Androgens	Fetal masculinization in **female** fetus	
Diethylstilbestrol	Vaginal carcinoma of **female** offspring (Extended Teratogenic effect)	

Adverse Effects of Drugs
(2nd & 3rd trimesters)

During the 2nd and 3rd 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

Antibiotics	• **Tetracyclines** Class D
	  ○ Impaired teeth and bone development
	  ○ Yellow-brown discoloration of teeth

	• **Aminoglycosides ex: Streptomycin and Kanamycin** Class C, D
	  ○ Ototoxicity (8th cranial nerve damage)
	  ○ Nephrotoxicity.

	• **Chloramphenicol** ○ **Gray baby syndrome**
	• **Sulfonamides** ○ Displace bilirubin from albumin → neonatal hyperbilirubinemia, jaundice)
CNS depressants	• After delivery: causes sedation, hence interference with suckling. • Respiratory depression • Reduced blood flow → Fetal distress ○ **Ex: Diazepam and Morphine**
	• **Benzodiazepines :** CNS depressant/Sedative hypnotic • Chronic use → neonatal dependence and withdrawal symptoms ○ **Ex: Diazepam**
Corticosteroids	• Adrenal atrophy • Growth retardation • N.B: Cleft palate only in first trimester
Propranolol Non-selective B-blocker	• Bradycardia | Neonatal hypoglycemia • Placental insufficiency → reduced uterine blood flow → **fetal distress**
ACEIs	• Renal damage

Antithyroids
Class D
	• Risk for neonatal hypothyroidism and goiter
	  ○ **Ex: Methimazole, Carbimazole, Iodide & Propylthiouracil**
	  ○ Propylthiouracil less ADRs because have high capacity of plasma protein binding → less free.

NSAIDs	• **Prostaglandin synthesis inhibitors**
	  ○ Constriction of ductus arteriosus (close prematurely) → Pulmonary Hypertension in newborns
	  ○ Increase in gestation time
	  ○ Prolong labor, PGF2 alpha induces labor, so the inhibitor will prolong labor.
	  ○ Have effect on platelet action → neonatal bleeding and Increase risk for postpartum hemorrhage. (same as Warfarin) don't give in near term.
	• **Ex: Aspirin-indomethacin**
	• Effect mainly in near term and 3th trimester, because inhibit prostaglandin synthesis → increase risk of constriction ductus arteriosus → pulmonary Hypertension in newborns.

Warfarin	• Risk of bleeding • N.B: hypoplasia of nasal bridge only in first trimester

Drugs of Choice During Pregnancy

Hypertension in Pregnancy

Probably safe	Contraindicated
• **α -Methyl dopa** • Labetalol (alpha- and beta blocker) • **Emergency: Labetalol** or Hydralazine	• ACE inhibitors • Angiotensin II receptor blockers • Thiazide diuretics and loop diuretics→ cause electrolyte imbalance. • Propranolol (beta blocker) • Ca2+ channel blockers in mild HTN *Propranolol and calcium channel blockers can reach the fetus and cause hypertension, which can lead to fetal distress.

Coagulation Disorders in Pregnancy

Probably safe	Contraindicated
• **Heparin** (high molecular weight and polar) - It is polar → doesn't cross the placenta - There's an antidote **protamine sulphate.**	• **Warfarin in all trimesters** N.B: can be taken in breastfeeding - Cross the placenta - **1st trimester:** teratogenicity. - **2nd/3rd trimesters:** risk of bleeding.

Antibiotics in Pregnancy

Probably safe	Contraindicated
• **Penicillins** (ampicillin, amoxicillin)First line • **Cephalosporins:** Ceftriaxone • **Macrolides (erythromycin, azithromycin):** **As an alternative in penicillin-sensitive patients** but **erythromycin estolate** should be avoided (risk of hepatic injury to mother). • Drug of choice: **Penicillins, Cephalosporins, erythromycin**	• **Tetracyclines → teeth and bones deformities** • **Quinolones (ciprofloxacin)**→ arthropathy: bone and cartilage damage. • **Aminoglycosides** → ototoxicity. • **Sulfonamides → neonatal jaundice and kernicterus.** • **Chloramphenicol → Gray baby syndrome.**

Antithyroid Drugs in Pregnancy

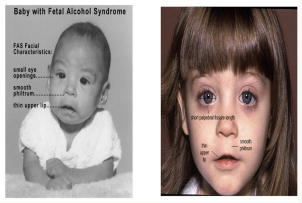
- **Are used in thyrotoxicosis or Grave's disease**
  - **Propylthiouracil:** preferable over others highly protein bound (class D) First line
  - Methylthiouracil (methimazole) (class D)
  - Carbimazole (class D)
  - Radioactive iodine (class X)
- All can cross the placenta, all have risk for congenital hypothyroidism and goiter.
- The **lowest dose** of antithyroid drugs should be used.

Other Drugs

Antidiabetics	Analgesics	Anticonvulsants
• **Insulin** is the best choice • Avoid oral antidiabetics	• **Acetaminophen / Paracetamol**	• All antiepileptics have potential to cause malformations. • **Avoid valproic acid - highly teratogenic.** • **Folic acid supplementations** can prevent neural tube defects in women receiving antiepileptics. • Phenytoin, valproic acid and carbamazepine are category D. • Depending on the type of epilepsy. If we need to use valproic acid, start with the lowest dose and gradually increase it until the symptoms are controlled. Folic acid supplementation is also recommended (very important).

Drugs of Abuse During Pregnancy

What is 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, and marijuana. • Drug abuse may lead to organ damage, dependence, addiction and behavioral disturbance.

Drug Abused	Description
Alcohol	• The use of alcohol is contraindicated in all trimesters of pregnancy. • ***Chronic use of alcohol during early weeks*** of the 1st trimester leads to **Fetal Alcohol Syndrome (FAS)** which is characterized by: 1. **Microcephaly** 2. **Low birth weight** 3. **Craniofacial abnormalities** 4. CVS abnormalities 5. CNS abnormalities: - Attention deficits - Intellectual disability - Mental retardation 
Cocaine	• Cocaine has ***low MW***, so it can easily pass into fetus through the placenta. • Inhibits reuptake of sympathomimetics (***epinephrine, norepinephrine and dopamine)*** causing: 1. Vasoconstriction 2. Rapid heart rate 3. Hypertension -vascular disruption- • **Hypoxia**: It decreases blood flow to uterus and fetal oxygenation. • It increases uterine contractility. • *Fetal gross malformations include:* 1. **Microcephaly** 2. Prematurity 3. Growth retardation 4. Intrauterine growth retardation 5. Mental retardation 6. **Placental abruption** (*early separation of the placenta from the uterus before delivery)* 7. Withdrawal symptoms 
Tobacco	• Tobacco contains ***nicotine & carbon monoxide*** that harm the fetus. No evidence that it causes birth defects but Tobacco increases the risk of: 1. Decreased blood flow to the placenta | Fetal hypoxia 2. Retarded fetal growth | **Low birth weight** 3. Spontaneous abortion 4. **Prematurity -preterm labor-** 5. Perinatal mortality -stillbirth-

Conclusion

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 foetal development.
- The most critical period of pregnancy is **organogenesis** (2– 8 weeks).
- Alcohol, nicotine and other addicting drugs should be avoided.

Team leaders

Sarah Alajaji **Maryam Alghannam**

Team members

Sarah Aldossary

Lama Hazzaa

Aroub Almahmoud

Layan Al-Ruwaili

Mohammed Alhudaithi

Mansour Alotaibi

 Lama Alotaibi

Ghaida Aldossary

Zeyad Alotaibi

Sultan Almishrafi

Omar Banjar

Fatimah Alghamdi

Naif Alateeq

Rahaf Alslimah

Wasan Alanazi

 Sultan Albaqami

Fahad Aldhafian

Alanoud Alolaywah

Special thanks to Norah Almania for the amazing logo