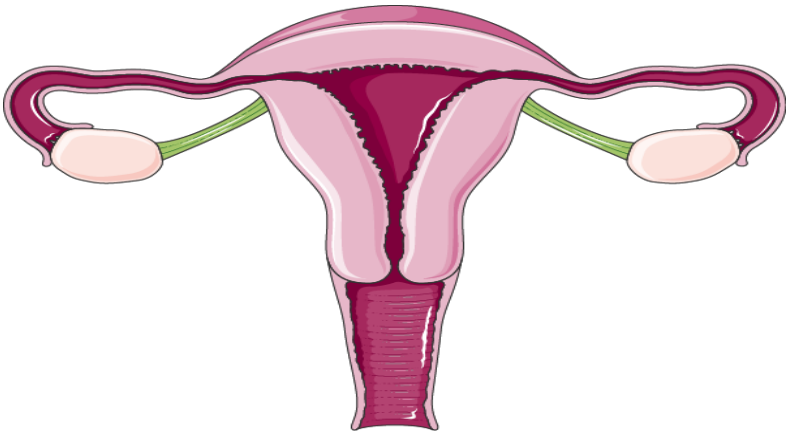
MEDICINE
KING SAUD UNIVERSITY

436 team
pharmacology



3: Teratogens and Drugs of Abuse in Pregnancy

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. Effects of drug abuse

Color index

- Doctors' notes
- Drugs names
- Extra information and further explanation
- Important
- Mnemonics

Kindly check the editing file before studying this document

Introduction

Medications in Pregnancy

- Majority of pregnant women are exposed to medications during pregnancy. (female slides)
- Unless absolutely necessary, drugs should not be used during pregnancy (especially during first trimesters) because many can harm the fetus. (only female slides)
- Fetal effects of most of the therapeutic agents are unknown for about one-half of medications. (only female slides)
- About 2 to 3 % of all birth defects result from the use of drugs. (only female slides)
- These 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. (only female slides)
- 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

Physiochemical properties of the drug. (can they across the placenta or not)

Lipophilic drugs:

- Diffuse readily across the placenta and enter fetal circulation.
- Thiopental: (as Hypnotics & induction of Anesthesia) crosses placenta & causes sedation, apnea in newborn infants

Ionized drugs:

- Cross the placenta very slowly → very low con. In newborn infants e.g. succinylcholine, Tubocurarine,

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 → can't cross the placenta → preferable
- e.g. propythiouracil, chloramphenicol, heparin

The stage of placental and fetal development

at the time of exposure to the drug

Next slide

Duration of exposure to the drug

Chronic use (daily) is different than acute use (once)

So the drug which given to pregnant should be :

- ✓ Lowest lipid solubility.
- ✓ Highest ionization= ionized= polar=water soluble
- ✓ Highest molecular weight.
- ✓ Highest protein binding.

The Stages of Mammalian Fetal Development

Harmful action of drugs depend upon stage of fetal development at time of drug exposure.

Blastocyst formation	Organogenesis	Histogenesis & maturation of function
• Occurs from (1-16 days) in the first trimester (First 2 weeks) • Period of dividing zygote and implantation • Pre-differentiated period (conceptus). • Drugs have an **all-or-nothing effect.** • Exposure to harmful drugs during this period → Prenatal death & **abortion**.	• It is the process by which cells specialize and organize to form the tissues and organs of an organism. (only female slides) • Occurs in (17- 60 days) in the first trimester (2-8 weeks) • The most sensitive period of pregnancy. • Exposure to harmful drugs → major birth defect in body parts or major congenital malformation (Teratogenesis) (Structural abnormality=major)	• 8 weeks onwards • Growth and fetal development occur during this stage. (female slides) • Fetus depends upon nutrients & hormonal supply. (female slides) • Exposure to drugs can cause "Function problems" rather than "gross malformation • 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 formation" (functional abnormality = minor) • However CNS is sensitive to toxic effects throughout pregnancy

Only female slides

- **First trimester (week 1- week 12):**
  - Blastocysts formation (all or none).
  - 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 neonate after delivery

Click here to see a very helpful illustration about Critical Periods of Human Development

Teratogenesis & FDA classification

Teratogenesis

- **What is teratogenesis?** Occurrence of congenital defects of the fetus.
- **What is teratogen?** are substances that may cause permanent birth defects via a toxic effect on an embryo or fetus. (functional or structural 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

Category	General information	Example/s
A **Safest**	1- Adequate and **well-controlled human studies** have failed to demonstrate a risk to fetus (**show no risk**) 2- Drugs can be used	Folic acid Thyroxine
B	1- No risk in animal studies (Animal studies ok) 2- No adequate and well-controlled human studies (No human data) 3- Drugs can be used in pregnancy	Paracetamol Erythromycin Most of the antibiotics
C	1- Adverse effects on the fetus in animals only 2- No adequate and well-controlled studies in humans. (No human data) According to the situation 3- Drug may be used in serious situation despite its potential risk. (Risk can not be ruled out)	Morphine Most of them are Drugs acting centrally
D	1- Positive evidence of human fetal risk based on adverse reaction data from studies in humans, investigational or marketing experience. 2- May be used in serious diseases or life threatening situations	Antiepileptic e.g. Phenytoin
X **C.I**	1- **Proven fetal abnormalities** in animal and **human** studies 2- The risks involved in the use of the drug in pregnant women clearly outweigh potential benefits. 3- Drugs are teratogens and contraindicated in pregnant women or planning to conceive.	Thalidomide Valproic acid

Proven Teratogens (category X)

Drug	Teratogenic effect
Retinoids: * Vitamin A[1] * Isotretinoin[2]	• women uses these drugs and planning for pregnancy should stop them 1 year before أنا في التحلية فتعالوا لي
Sedative and Hypnotics (Thalidomide)	• **Phocomelia:** shortened or absent long bones of the limbs and absence of external ears (click here) • The most notorious human teratogen, but it had no tetratogenic effects in mice and rats but proved tetratogenic when used in pregnant women
Ionizing radiation	• it is a diagnostic X-ray or radiation therapy
Phenytoin & Carbamazepine	• Fetal Hydantoin Syndrome Nail & Digital hypoplasia, Oral Clefts (cleft lip and palate), **Cardiac Anomalies**. (Click here) فينو هيدا اللي بيفهم بالديجتال؟
Valproic acid + Phynytoin[3]	• **Neural tube defect (spina bifida)** (click here) أشوفك قالب (فقلب) أسبانيا • Impairs folate absorption.
Antibiotics (Tetracycline, Quinolones)	• Altered growth of teeth and bones because they deposit with Ca • Permanent teeth staining (click here) • Enamel hypoplasia تري السيكل إذا ركبته ممكن تطيح وتتكسر أسنانك وعظامك
Anticoagulants (Warfarin)	• **Hypoplasia of nasal bridge** • CNS and CVS malformation راح حرب بعيدة ورجع وأنفه مكسور ومتشوه
Corticosteroids	• Cleft lip and Palate (during 1st trimesters) (click here)
Hormones: * Estrogens * Androgens * Diethylstilbestrol	• Serious genital malformation • Estrogen: Testicular atrophy in male fetus • Androgen: Fetal masculinization in female fetus • Vaginal carcinoma of female offspring (delayed effect of diethylstilbestrol after many years of exposure during childhood) طفلتها ماتت من السرطان
Lithium ليث عيب استني لا تدفع، معي الفيزا كارد	• Ebstein's anomaly: Cardiovascular anomalies mainly valvular heart defect involving tricuspid valve (click here)
ACE inhibitor: * Captopril * Enalapril	• ACE inhibitors disrupt the fetal renin-angiotensin system, which is essential for normal renal development • They cause renal damage, Fetal & neonatal anuria, **Fetal hypotension**, **Hypoperfusion**, Growth retardation
Cytotoxic drugs (only female slides)	• Folate antagonists (methorexate) • Alkylating agents (cyclophosphamide)

[1] Should be limited to 700 µg/day (only female slides)
[2] Used in treatment of acne
[3] Antiepileptic drug

ADRs of Drugs During 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 & fetal development or toxic effects on fetal tissues

Drug	Adverse effect
Tetracycline	• Impaired teeth & bone development • yellow-brown discoloration of teeth
Aminoglycosides	• Streptomycin, kanamycin • Ototoxicity = 8th Cranial nerve damage, nephrotoxicity
Chloramphenicol	• Gray baby syndrome which cyanosis due to hypoxia (because they do not yet have fully functional liver enzymes (UDP-glucuronic transferase)
Corticosteroids	• Adrenal atrophy, growth retardation
Propranolol	• Bradycardia, neonatal hypoglycemia, placental insufficiency, reduced uterine blood flow, fetal distress • Bradycardia → low blood flow to the placental insufficiency and the uterus → fetal distress
Antithyroid drugs[4]	• 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 (because Anti-prostaglandins cause uterine relaxation) → prolong labor • neonatal bleeding • Risk of postpartum hemorrhage
CNS depressants e.g. Diazepam, Morphine	• Interference with suckling • **Respiratory depression** • Reduced blood flow, fetal distress • **Chronic use (Diazepam):** neonatal dependence and **withdrawal symptom** (any drug affect CNS will cause addiction on chronic use)
ACEIs	• Renal damage
Warfarin	• Risk of bleeding
Sulfonamides	• can displace bilirubin from albumin (neonatal hyperbilirubinemia, Jaundice) because Bilirubin cross the placenta • It is oxidizing agents (may cause deficiency in GP6D)

[4] Iodide, methimazole, carbimazole, propylthiouracil

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 Can be given by injection

Coagulation Disorders in Pregnancy

Contraindicated

❖ **Warfarin**, because it leads to:

- Teratogenicity during 1st trimester (Hypoplasia of nasal bridge)
- Risk of bleeding during 2nd and 3rd trimester

Probably safe

❖ **Heparin**, because:

- It is polar
- It does not cross the placenta
- The antidote, **protamine sulphate** is available

Antithyroid Drugs in Pregnancy

Contraindicated[5]

- Drugs:
  - Methylthiouracil (Methimazole)
  - Carbimazol
  - Radioactive Iodine (I^{131})
- Effects[6]:
  - Cross placenta
  - Risk of congenital goiter and hypothyroidism

Probably safe

Is a **prop**er drug for pregnant

- Propylthiouracil

بصو كووول antithyroid عندهم

بس أقلهم هوا harmful effects

Propylthiouracil because of its

High Binding capacity

Antibiotics in Pregnancy

Contraindicated

- Tetracyclines: teeth and bones deformity
- Quinolones (ciprofloxacin): athropathy (bone and cartilage damage)
- Aminoglycosides: ototoxicity
- Sulfanamides: neonatal jaundice-kernicterus
- Chloramphenicol: gray baby syndrome

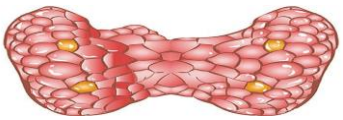
Probably safe

- Penicillin (ampicillin, amoxicillin)
- Cephalosporins
- Macrolides (erythromycin and azithromycin): as alternative in penicillin-sensitive individuals, BUT erythromycin estolate should be avoided, bc of the risk of hepatic injury to the mother

[5] If used during pregnancy, THE LOWEST DOSE of these drugs should be used

[6] Propylthiouracil has the same effect but in very less percentage

Drugs of Choice in Pregnancy

Category	Drugs
 Antihypertensive	▪ α methyl dope ▪ Lebatalol (α and β blocker) ▪ Hydralazine (emergency only)
 Anticoagulants	▪ Heparin
 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 antiepileptic drugs
 Antibiotics	▪ Penicillin ▪ Cephalosporins ▪ Erythromycin
 Antidiabetics	▪ Insulin ▪ Avoid oral antidiabetics
 Analgesics	▪ Acetaminophen

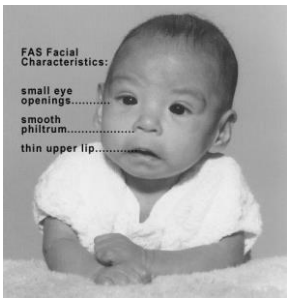
Drug Abuse

- **Definition:** Habitual use of drugs not for therapeutic purposes but for alteration of one's mood or state of consciousness.
- **The most common abuse drugs:** Benzodiazepines, Opium alkaloids amphetamines, barbiturates, Alcohol, Cocaine, Nicotine, Marijuana
- **Complications:** organ damage, dependence, addiction, and disturbance of behavior.

Alcohol

- The use of alcohol is contraindicated during all trimesters of pregnancy
- The chronic maternal alcohol abuse during early weeks of the 1st trimester of pregnancy cause Fetal Alcohol Syndrome (FAS), **which characterized by:**

1. Craniofacial abnormalities. (**thin upper lips**, small eye opening, smooth philtrum)
2. Microcephaly
3. Intrauterine growth retardation (only male slides)
4. Low weight birth (only female slides)
5. CVS abnormalities
6. CNS abnormalities (attention deficits, intellectual disability, mental retardation)



Cocaine

- Cocaine has low molecular weight → easily passes into fetus through placenta.
- Water soluble (only male slides)
- It decreases blood flow to uterus and fetal oxygenation **(Hypoxia).**
- Act as CNS stimulants Inhibits reuptake of sympathomimetic (epinephrine, NE, dopamine) , causing vasoconstriction, rapid heart rate, hypertension (Vascular disruption).
- It increases uterine contractility
- **It also cause:**

1. **Placental abruption (separation of placenta from uterus wall before delivery)**
2. Microcephaly
3. Prematurity
4. Intrauterine growth retardation
5. Growth retardation
6. Mental retardation

Drug Abuse

Tobacco

- Tobacco contains nicotine and carbon monoxide that may harm fetus. No evidence it causes birth defects
- **Tobacco can increase risk of:**
  1. Reduced blood flow to placenta → low amount of O_2 → Fetal hypoxia
  2. Retarded fetal growth
  3. **Low birth weight**
  4. Spontaneous abortion
  5. Prematurity (Preterm labor)
  6. **Perinatal mortality**

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

Summary

Proven Teratogens (category X)	
Drug	Teratogenic effect
Thalidomide	• Phocomelia
Phenytoin	• Fetal Hydantoin Syndrome
Valproic acid	• (spina bifida) • Impairs folate absorption
Tetracyclines	• Altered growth of teeth and bones • Permanent teeth staining • Enamel hypoplasia
Warfarin	• Hypoplasia of nasal bridge • CNS malformation
Corticosteroids	• Cleft lip and Palate
Hormones: * Estrogens * Androgens * Diethylstilbestrol	• Serious genital malformation
Lithium	• Ebstein's anomaly
ACE inhibitor	• ACE inhibitors disrupt RAAS.

ADRs of Drugs During 2nd and 3rd Trimesters	
Drug	Adverse effect
Tetracyclines	• Impaired teeth & bone development • yellow-brown discoloration
Aminoglycosides	• Streptomycin, kanamycin • Ototoxicity = 8th (Cranial nerve damage)
Cloramphenicol	• Gray baby syndrome
Corticosteroids	• Adrenal atrophy, growth retardation
Propranolol	• Bradycardia, neonatal hypoglycemia…
Antithyroid drugs	• Risk of neonatal hypothyroidism and goiter
NSAIDs	• Constriction of ductus arteriosus (close prematurely), pulmonary hypertension in newborns • Increase in gestation time • prolong labor, neonatal bleeding • Risk of postpartum hemorrhage
CNS depressants	• Respiratory depression • Chronic use (Diazepam): neonatal dependence and withdrawal symptom
ACEIs	• Renal damage
Warfarin	• Risk of bleeding
Sulfonamides	• neonatal hyperbilirubinemia, Jaundice

Alcohol

- contraindicated during all trimesters of pregnancy
- during early weeks of the 1st trimester of pregnancy cause Fetal Alcohol Syndrome (FAS)

Cocaine

- It decreases blood flow to uterus and fetal oxygenation (Hypoxia).
- It increases uterine contractility

Tobacco

- Tobacco can increase risk of:
  1. Reduced blood flow to placenta
  2. Fetal hypoxia
  3. Retarded fetal growth
  4. Low birth weight
  5. Spontaneous abortion
  6. Prematurity (Preterm labor)
  7. Perinatal mortality

MCQs

Q1: Which of the following is recommended and safe to be given to pregnant lady with diabetes ?

A. Glibenclamide.. B. Pioglitazone. C. Insulin. D. Metformin.

Q2: Lady visit clinic and she is Pregnant. She was on Warfarin for atrial fibrillation. The physician want to switch to safer drug. Which of the following is recommended to be given to her ?

A.Ibuprofen. B. Aspirin. C. Heparin. D. All of them.

Q3: Which of the following drugs may lead to Cardiovascular anomalies such as valvular heart defect ?

A. Propylthiouracil. B. Thalidomide. C. Lithium. D. Warfarin.

Q4: Which of the following is recommended and safe to be given to pregnant lady with Hypertension?

A. Captopril.. B. Hydrochlorothiazide. C. Losartan. D. α- methyl dopa.

Q5: Which of the following is recommended and safe to be given to pregnant lady with Hyperthyroidism ?

A. Methimazole. B. Carbimazol. C. Radioactive Iodine. D. Propylthiouracil

Q6: Pregnant lady came to ER with preeclampsia. She had severe elevated in blood pressure with edema. Which of the following antihypertensive agent is recommended to be used in her case ?

A. Labetalol. B. Hydralazine. C. α- methyl dopa. D. Both A & B.

Q7: Which of the following drugs may lead to Nail & Digital hypoplasia, cleft lip and palate and Cardiac Anomalies ?

A. Phenytoin. B. Thalidomide. C. Lithium. D. Warfarin.

Q8: Newborn baby have small head and special face features such as thin upper lips, small eye opening, smooth philtrum and mental retardation. What most likely cause of this abonormality ?

A.Clomiphene. B. Alcohol. C. Warfarin. D. Hydralazine.

Q9: Which of the following is incorrect regarding the valproic acid during pregnancy ?

A. It is under category X.
B. It cause Neural tube defect (spina bifida).
C. It safe to be used in 2nd & 3rd trimesters.
D. It Impairs folate absorption.

Q10: Which of the following can easily cross the placenta ?

A. Lowest lipid solubility. B. Lowest ionization/non ionized. C. Highest molecular weight. D. Highest protein binding.

Q11: All of the following is classified under category X EXCEPT :

A. Thalidomide. B. Isotretinoin. C. Warfarin. D. Methotrexate. E. Azithromycin. F. Valproic acid

Q12:Which of the following antibiotic have high risk to induce neonatal hyperbilirubinemia and brain damage (kernicterus) ?

A. Cefixime. B. Erythromycin. C. Chloramphenicol. D. Sulfonamide.

Q13: Which of the following drugs may lead to Hypoplasia of nasal bridge in baby, if her mother take it during pregnancy ?

A. Phenytoin. B. Thalidomide. C. Lithium. D. Warfarin.

Q14: Which of the following Vitamins should be restricted in pregnancy ?

A. Vit A. B. Vit C. C. Vit D. D. Vit B.

Q15: Newborn baby have small head with Low weight birth , what most likely cause of this abonormality ?

A. Alcohol. B. Cocaine. C. Tobacco. D. All of them.

Q16: Which of following may lead to mothers' complain that their newborn tend to be reluctant to to breastfeeding or suckling ?

A. Lithium. B. Aspirin. C. morphine. D. Diethylstilbestrol.

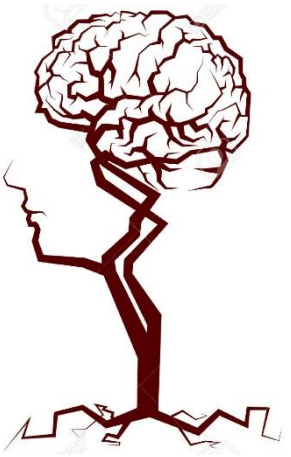
Q17:Which of the following pain killers is safe to be used in pregnant women ?

A. Ibuprofen. B. Aspirin. C. morphine. D. Paracetamol.

Q18: Which of following has delayed effect on female baby and may lead to vaginal carcinoma ?

A. Lithium. B. Aspirin. C. morphine. D. Diethylstilbestrol.

1) C.
2) C.
3) C.
4) D.
5) D.
6) D.
7) A.
8) B.
9) C.
10) B.
11) E.
12) D.
13) D.
14) A.
15) D.
16) C.
17) D.
18) D.



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