

03- Teratogens and drugs of abuse in pregnancy

Major Teratogenesis (during the first trimester)

<i>Thalidomide</i>	Phocomelia.
<i>Alcohol</i>	Foetal Alcohol Syndrome (FAS).
<i>Phenytoin</i>	Foetal Hydantoin Syndrome.
<i>Corticosteroids</i>	Cleft lip & palate.
<i>Tetracyclines</i>	Permanent Teeth staining, enamel hypoplasia Altered growth of teeth & bone.
<i>Warfarin</i>	Hypoplasia of nasal bridge and CNS malformation.
<i>Finasteride</i>	Abnormal development of genitalia of male foetuses.
<i>Valproic acid</i>	Spina bifida and Impaired folate absorption
<i>Hormones</i>	Serious genital malformation, testicular atrophy in male -Fetal masculinization in female -Vaginal carcinoma of female offspring
<i>Lithium</i>	Cardiovascular anomalies mainly valvular heart defect involving tricuspid valve Ebstein's anomaly
<i>ACE inhibitors: captopril, enalapril</i>	Fetal & neonatal anuria, Renal damage, Fetal hypotension, growth retardation

Major Teratogenesis (during the second & third trimesters)

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

ADRs During second and third trimesters

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Adverse effects of drugs prior to labor

<i>NSAIDs</i>	e.g. Aspirin-indomethacin Prostaglandin synthesis inhibitors Increase in gestation time prolong labor, neonatal bleeding Risk of postpartum hemorrhage
<i>CNS depressants</i>	e.g. diazepam, morphine Interference with suckling Respiratory depression Reduced blood flow, fetal distress
<i>Sulfonamides</i>	Displacement of bilirubin from plasma protein (neonatal hyperbilirubinemia)

Drugs of Abuse in Pregnancy

Alcohol	Fetal Alcohol Syndrome (FAS)
Cocaine	<ul style="list-style-type: none"> • 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)
Tobacco	<ul style="list-style-type: none"> • Decreased blood flow to placenta • Fetal hypoxia • Retarded fetal growth • Low birth weight • Increased spontaneous abortion • Preterm labor and stillbirth

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 (warfarin is contraindicated)
Analgesics	Acetaminophen
Antithyroid drugs	Propylthiouracil (protein-bound)
Anticonvulsants	<ul style="list-style-type: none"> ➤ All antiepileptics have potential to cause malformations ➤ avoid valproic acid. ➤ Folic acid should be supplied.

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.