



Teratogens and drugs of abuse in pregnancy

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The students should be able to know:

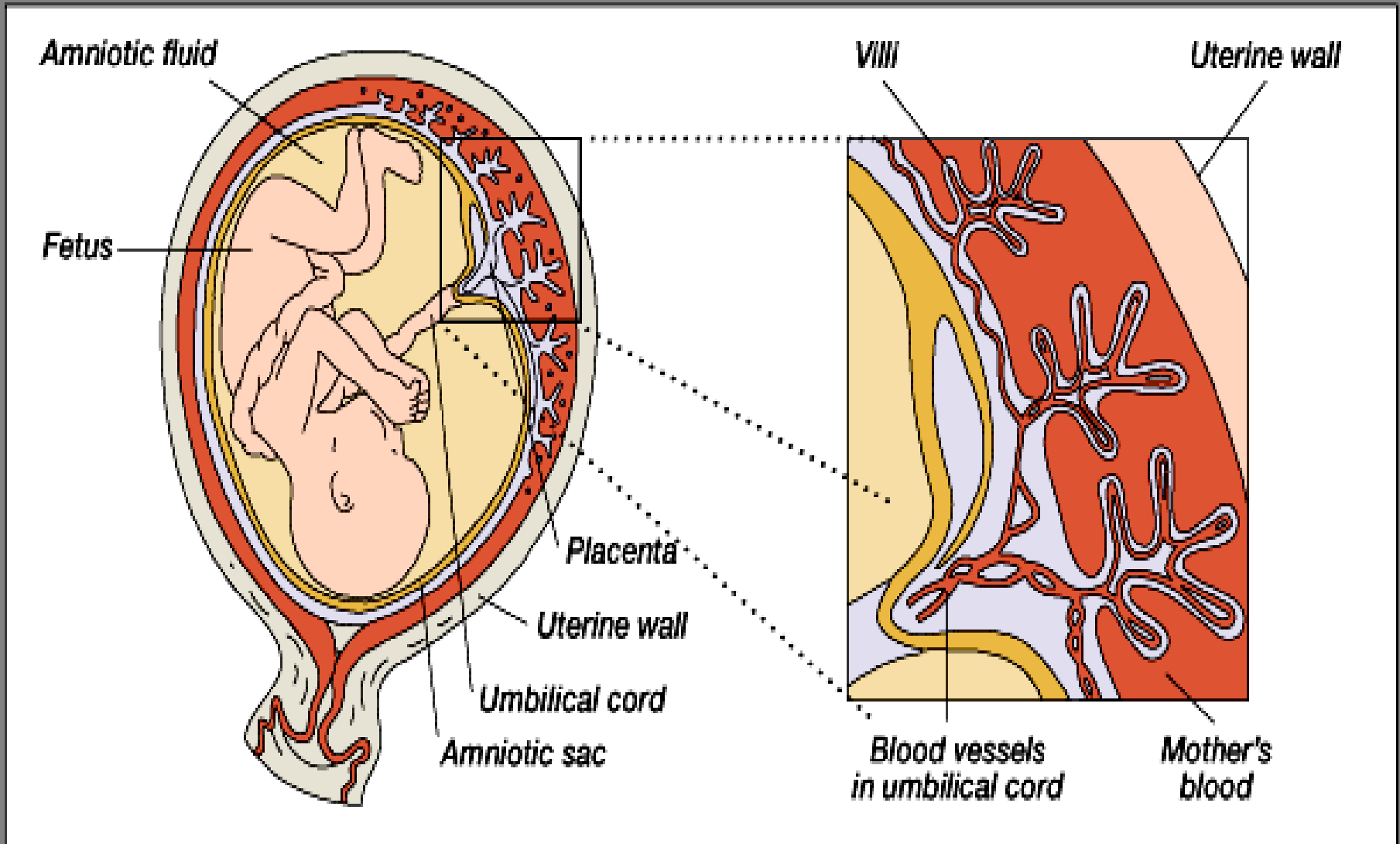
1. Factors affecting drug placental transfer
2. Harmful effects of drugs during different stages of development
3. FDA classifications of drugs.
4. Teratogenic drugs
5. Adverse effects of drugs
6. Effects of drug abuse

Medications in pregnancy

- 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.



Prenatal Structures



Factors controlling placental drug transfer

I. Physiochemical properties of the drug

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

II. The stage of placental and fetal development

at the time of exposure to the drug.

III. Duration of exposure to the drug.

I. Physiochemical properties of the drug

Lipid solubility of the drug:

Lipophilic drugs

diffuse readily across the placenta and enter fetal circulation. e.g. Thiopental → crosses placenta & causes **sedation, apnea** in newborn infants.

Ionized drugs

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

Molecular size of 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**

II. The stage of mammalian fetal development

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

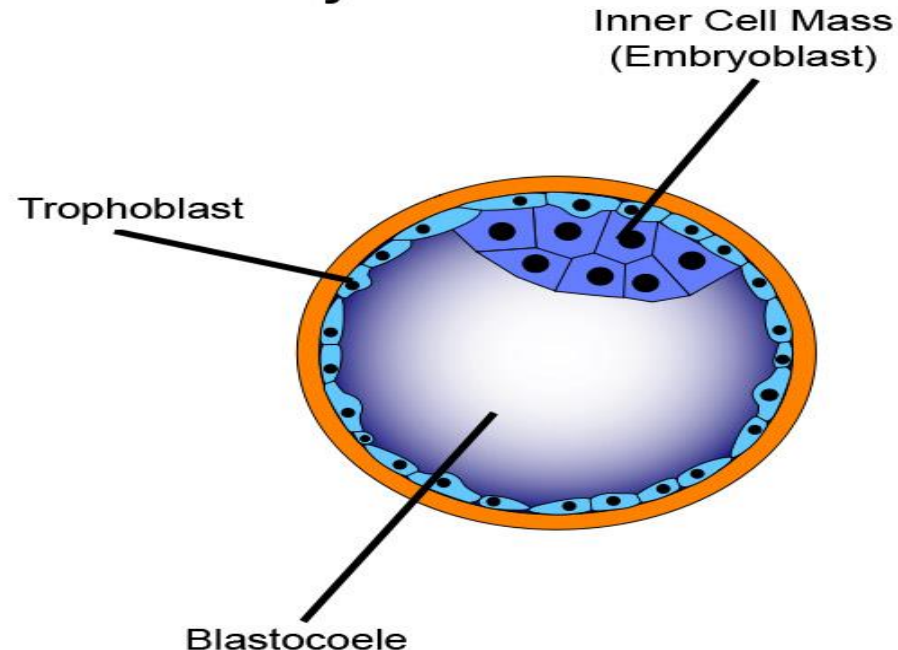
Mammalian fetal development passes through three phases:

- **Blastocyste formation (up to 16 days).**
- **Organogenesis (17-60 days).**
- **Histogenesis & maturation of function.**

Blastocyst formation (First 2 weeks)

- Occurs from (1-16 days) in the first trimester.
- Period of dividing zygote and implantation
- Pre-differentiated period (conceptus).
- Drugs have an **all-or-no**
- Exposure to harmful dr
period → **Prenatal death**

The Blastocyst



Organogenesis: (2-8 weeks)

- is the process by which cells specialize and organize to form the tissues and organs of an organism.
- Occurs in (17- 60 days) in the first trimester.
- The **most sensitive period** of pregnancy.
- Exposure to harmful drugs → **major birth defect in body parts or major congenital malformation.**

Histogenesis and functional maturation (8 weeks onwards)

- **Growth and fetal development occur during this stage.**
- **Fetus depends upon nutrients & hormonal supply.**
- **Exposure to drugs can cause “Function problems” rather than “gross malformation”**

Histogenesis and functional maturation

- **Exposure to drugs during 2nd and 3rd will not induce major malformation but drugs can produce **minor morphologic abnormalities, growth retardation and functional defects.****

II. The stages of mammalian fetal development

First trimester: week 1- week 12

Organogenesis week 2- week 8

major congenital malformations (teratogenesis).

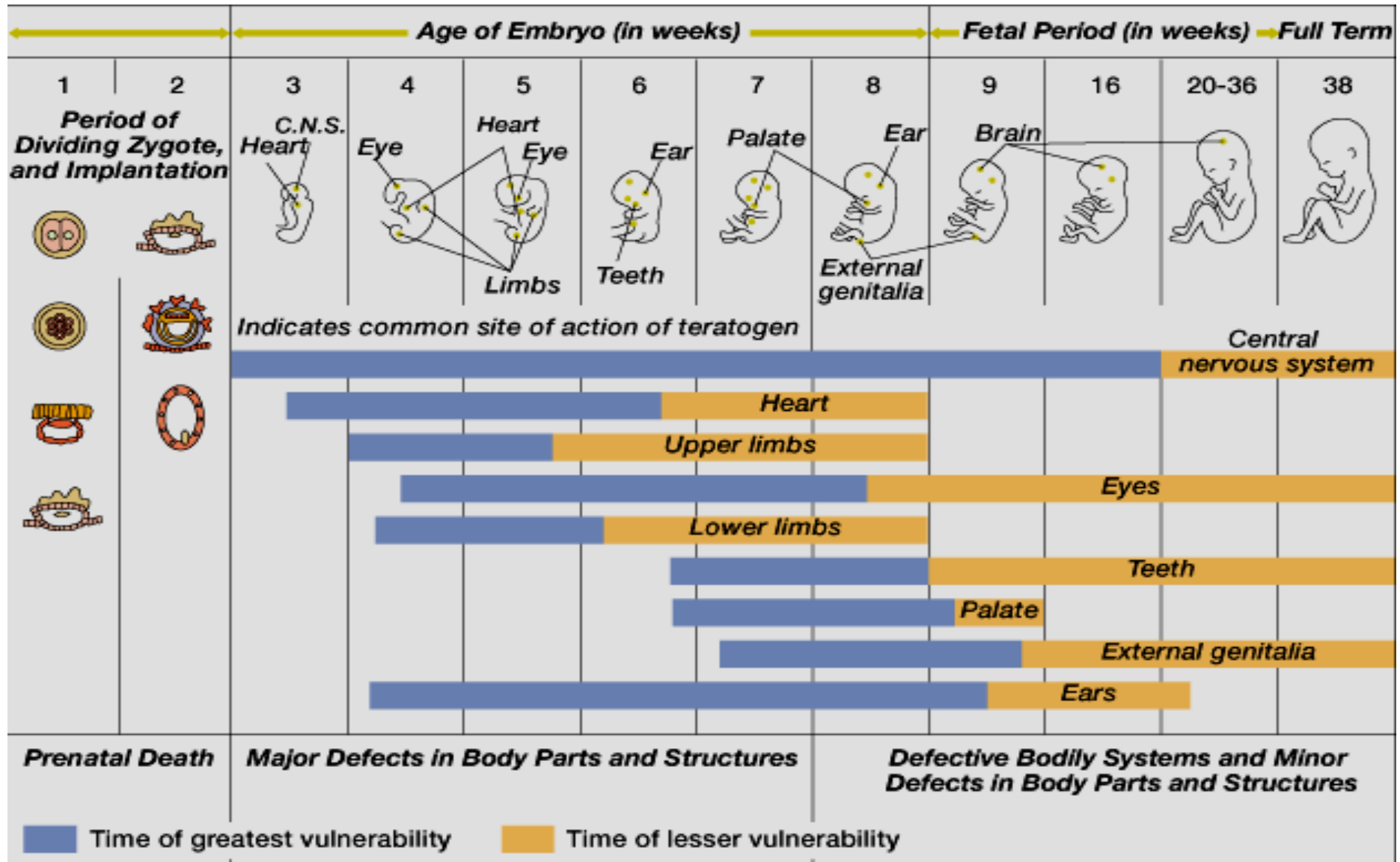
Second & Third trimesters: (week 13-week 28)

affect growth & fetal development

Near Term: (week 29-week 40)

adverse effects on labor or neonates after delivery.

Critical Periods of Human Development



Teratogenesis

Occurrence of congenital defects of the fetus.

What is a teratogen?

- is any agent that is able to interfere with fetal development and leads to **permanent birth 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 System

Category A

- Adequate and well-controlled human studies have failed to demonstrate a risk to fetus
- Drugs can be used

Category B

- No risk in animal studies
- No adequate and well-controlled human studies
- Drugs can be used in pregnancy

FDA Classification System

Category C

- **Adverse effects on the fetus in animals **only****
- **No adequate and well-controlled studies in humans.**
- **Drug may be used in serious situation despite its potential risk.**

FDA Classification System

Category 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**

FDA Classification System

Category 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.**

FDA Classification System

Category	Characteristics	Examples
A	Controlled human studies show no risk	Folic acid Thyroxine
B	Animal studies ok No human data	Paracetamol Erythromycin
C	Animal studies are not ok No human data Risk can not be ruled out	morphine
D	Positive evidence of risk Benefits outweigh risks	Antiepileptics
X	Contraindicated in pregnancy	Thalidomide

Proven teratogens

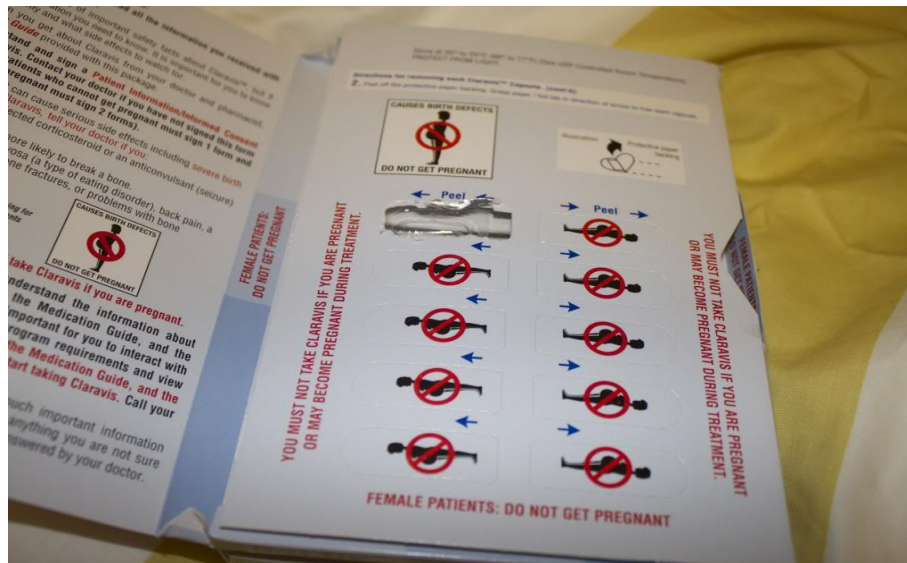
- **The following drugs are contraindicated during pregnancy (category X):**
- **Retinoids**
- **Thalidomide** (sedative/ hypnotics).
- **Lithium**
- **Alcohols**
- **Cytotoxic drugs**
 - Folate antagonists (methotrexate).
 - Alkylating agents (cyclophosphamide).
- **Anticonvulsant drugs** (valproic acid, phenytoin, carbamazepines).

Proven teratogens

- **Anticoagulants** (warfarin).
- **Antibiotics** (tetracyclines, quinolones)
- **ACEIs**
- **Ionizing radiation** (diagnostic X-ray or radiation therapy).
- **Radioactive iodine (I^{131})**.
- **Corticosteroids**.
- **Hormones**

Proven teratogens

- **Retinoids e.g.**
 - vitamin A (should be limited to 700 $\mu\text{g}/\text{day}$)
 - isotretinoin (used in treatment of acne)



Teratogenesis of drugs

Thalidomide

Phocomelia

shortened or absent long bones of the limbs

Alcohol

Fetal Alcohol Syndrome (FAS)

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

Teratogenesis of drugs

Phenytoin

Fetal Hydantoin Syndrome

Nail & Digital hypoplasia

Oral Clefts (cleft lip and palate)

Cardiac Anomalies

Valproic acid

Neural tube defect (spina bifida)

Antiepileptic drug

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

Testicular atrophy in male fetus

Fetal masculinization in female fetus

Vaginal carcinoma of female offspring

Lithium

Ebstein's anomaly

Cardiovascular anomalies mainly valvular heart defect involving tricuspid valve

ACE inhibitors

Captopril

Enalapril

Renal damage

Fetal & neonatal anuria

Fetal hypotension

Hypo- perfusion

Growth retardation

ACE inhibitors disrupt the fetal renin-angiotensin system, which is essential for normal renal development

Phocomelia



Thalidomide

Spina bifida



Valproic acid

Fetal hydantoin syndrome



Cleft lip and palate



Phenytoin causes digital hypoplasia and cleft lip and palate.

Cleft lip



**Corticosteroids and
phenytoin**

Teeth staining



Tetracycline

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 & fetal development or toxic effects on fetal tissues**

Adverse effects of drugs

Tetracyclines	Impaired teeth & bone development, yellow-brown discoloration of teeth
Aminoglycosides	Streptomycin, kanamycin Ototoxicity = 8th Cranial nerve damage
Cloramphenicol	Gray baby syndrome
Corticosteroids	Adrenal atrophy – growth retardation
Propranolol	Bradycardia, neonatal hypoglycemia, placental insufficiency, reduced uterine blood flow, fetal distress
Antithyroid drugs	Iodide, methimazole, carbimazole, propylthiouracil, risk of neonatal hypothyroidism and goiter

Adverse effects of drugs

NSAIDs	e.g. Aspirin-indomethacin Prostaglandin synthesis inhibitors Constriction of ductus arteriosus (close prematurely), pulmonary hypertension in newborns Increase in gestation time prolong labor, neonatal bleeding Risk of postpartum hemorrhage
Benzodiazepines as Diazepam	Chronic use → neonatal dependence and withdrawal symptoms
ACEIs	Renal damage
warfarin	Risk of bleeding

Adverse effects of drugs prior to labor or near term

CNS depressants	e.g. diazepam, morphine Interference with suckling Respiratory depression Reduced blood flow, fetal distress
Sulfonamides	can displace bilirubin from albumin (neonatal hyperbilirubinemia, Jaundice)

Hypertension in pregnancy

Contraindicated

- **ACE inhibitors**
- **Angiotensin II receptor blockers**
- **Thiazide diuretics**
- **Propranolol**
- **Calcium channel blockers in mild hypertension**

Probably safe

α -methyl dopa

Labetalol

Emergency

Hydralazine

Labetalol

Coagulation disorders in pregnancy

Contraindicated

warfarin is contraindicated in all trimesters

Cross placenta

1st trimester : teratogenicity (Chondroplasia)

2nd, 3rd : risk of bleeding

Probably safe

Heparin

Polar, does not cross placenta

The antidote, protamine sulphate is available

Antithyroid drugs in pregnancy

Are used in thyrotoxicosis or Grave's disease

- Propylthiouracil
- Methylthiouracil (Methimazole)
- Carbimazol
- Radioactive Iodine (I^{131})

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.

Antibiotics in pregnancy

Contraindicated :

- **Tetracyclines:** Teeth and bones deformity
- **Quinolones as ciprofloxacin:** arthropathy (bone and cartilage damage)
- **Aminoglycosides:** ototoxicity
- **Sulfonamides:** neonatal jaundice-kernicterus
- **Chloramphenicol:** Gray baby syndrome

Probably safe

- **Penicillins:** (ampicillin, amoxicillin)
- **Cephalosporins**
- **Macrolides (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	<ul style="list-style-type: none">➤ 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

Drug abuse:

Habitual use of drugs not for therapeutic purposes but for alteration of one's mood or state of consciousness.

Drug abuse

- 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.

Alcohols

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 weight birth**
- **Craniofacial abnormalities**
- **CVS abnormalities**
- **CNS abnormalities (*attention deficits, intellectual disability, mental retardation*)**

Fetal Alcohol Syndrome (FAS)

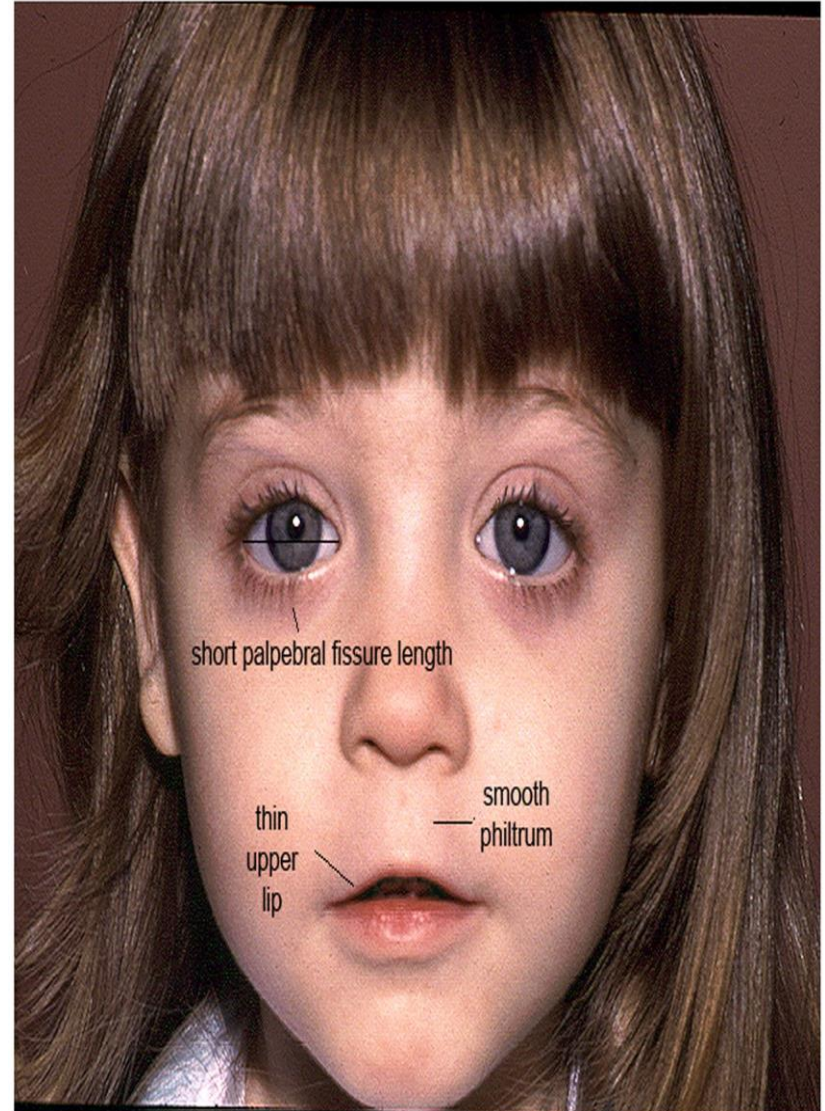
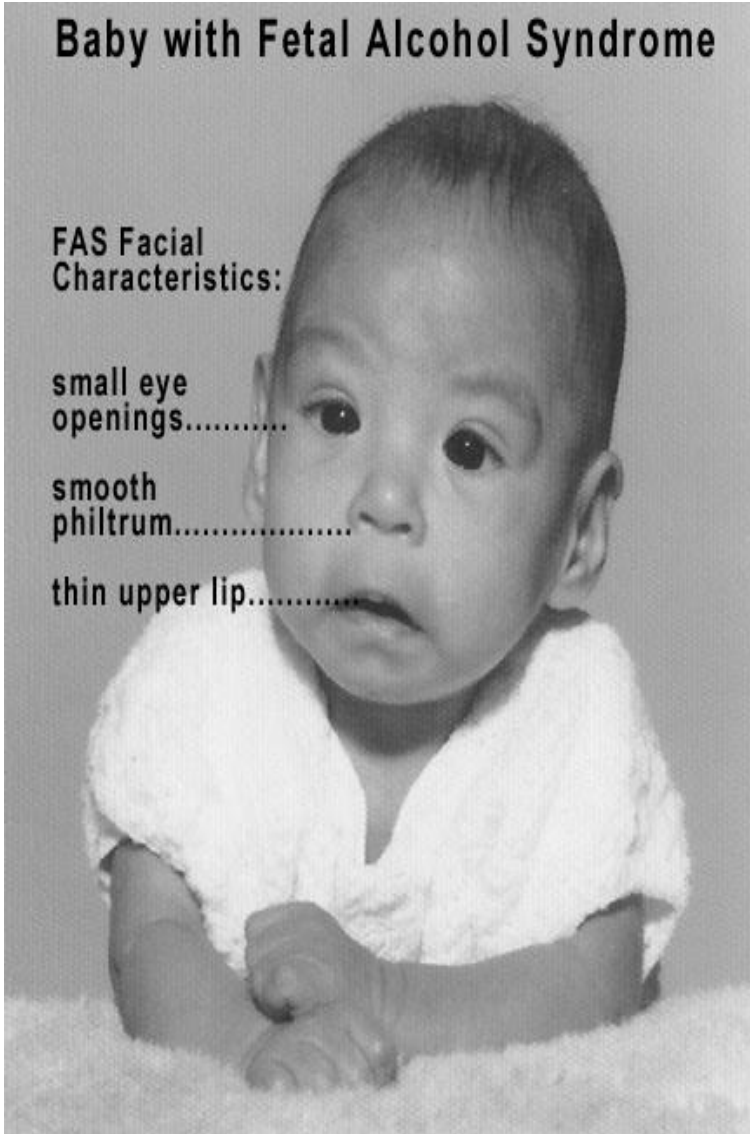
Baby with Fetal Alcohol Syndrome

FAS Facial Characteristics:

small eye openings.....

smooth philtrum.....

thin upper lip.....



Cocaine

- Cocaine has low molecular weight, easily passes into fetus through placenta.
- Inhibits re-uptake 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

Cocaine

- Microcephaly
- Prematurity
- Intrauterine growth retardation.
- Placental abruption (separation of placenta from uterus wall before delivery)
- Growth retardation
- Mental retardation

Fetal cocaine

Child with intra-uterine exposure to both cocaine and alcohol, at 4 months. Note the prominent glabellar region, bitemporal narrowing, proptotic eyes, puffy eyelids, short nose with a flat bridge and anteverted nares, and small chin. The philtrum is long and flat with a thin upper lip and the ears are bilaterally low-set, thick, inferiorly cupped and crumpled.



Robin NH, Zackai EH. *Teratology*, 50:160-164 (1994).

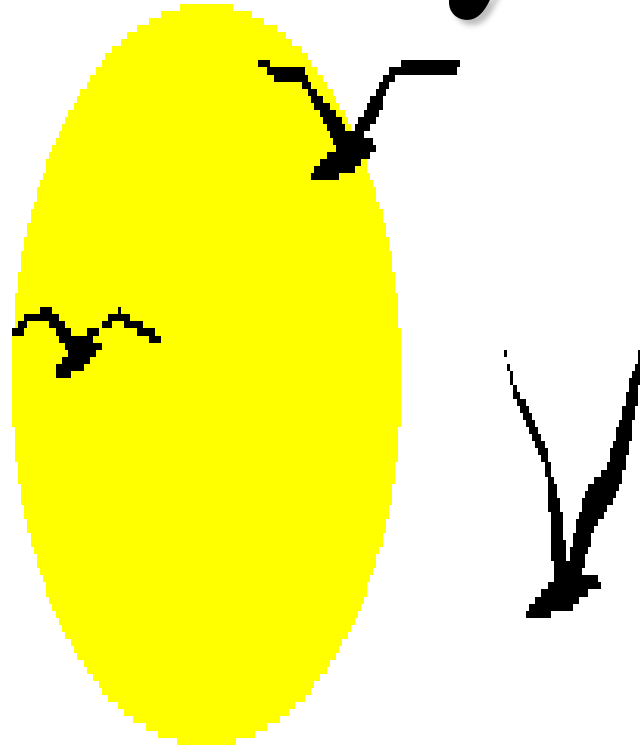
Tobacco

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

Conclusions

- 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.

Thank you



Questions ?