



# Teratogens and drugs of abuse in pregnancy

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Los



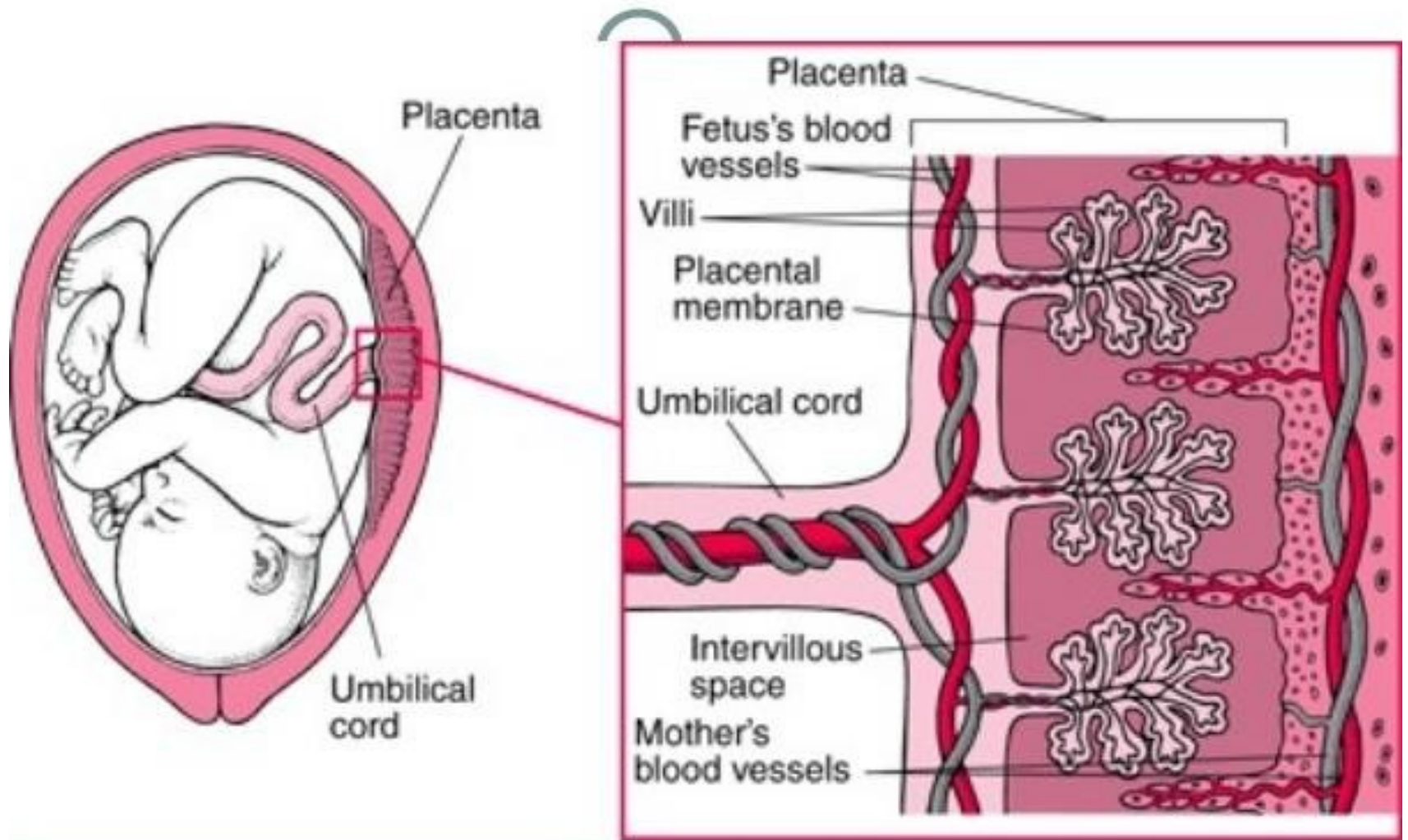
The students should be able to know:

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. Drugs of abuse

# **Medications in pregnancy**

- **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 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.**

# How drugs can cross placenta?



# 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 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.**

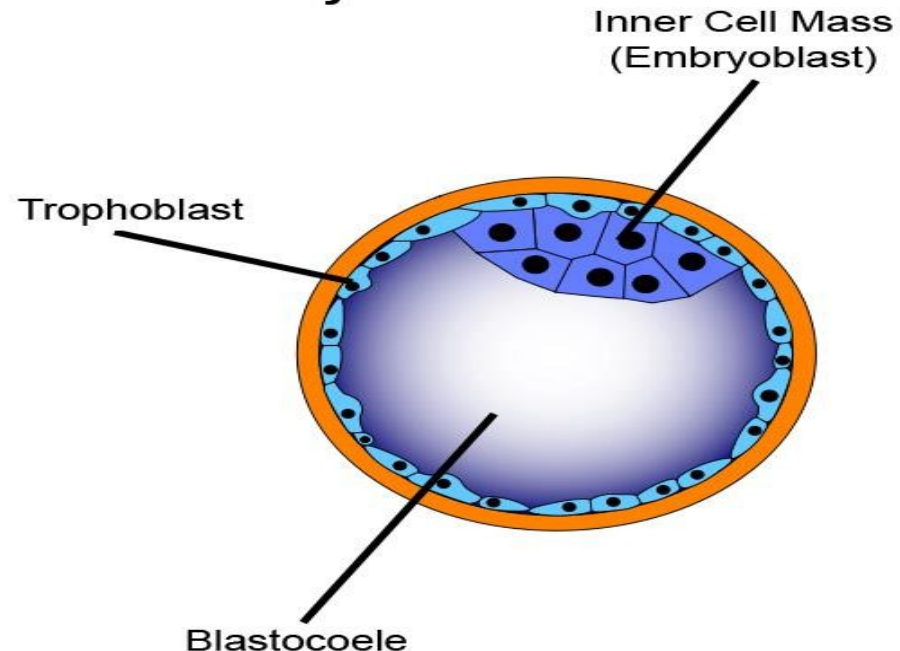
**Mammalian fetal development passes through three phases:**

- **Blastocyst formation (1 up to 16 days).**
- **Organogenesis (17-60 days).**
- **Histogenesis & maturation of function (8 weeks onwards).**

# 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 2<sup>nd</sup> and 3<sup>rd</sup> 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)**

**Blastocyst formation (all or none).**

**Organogenesis: major congenital malformations (teratogenesis).**

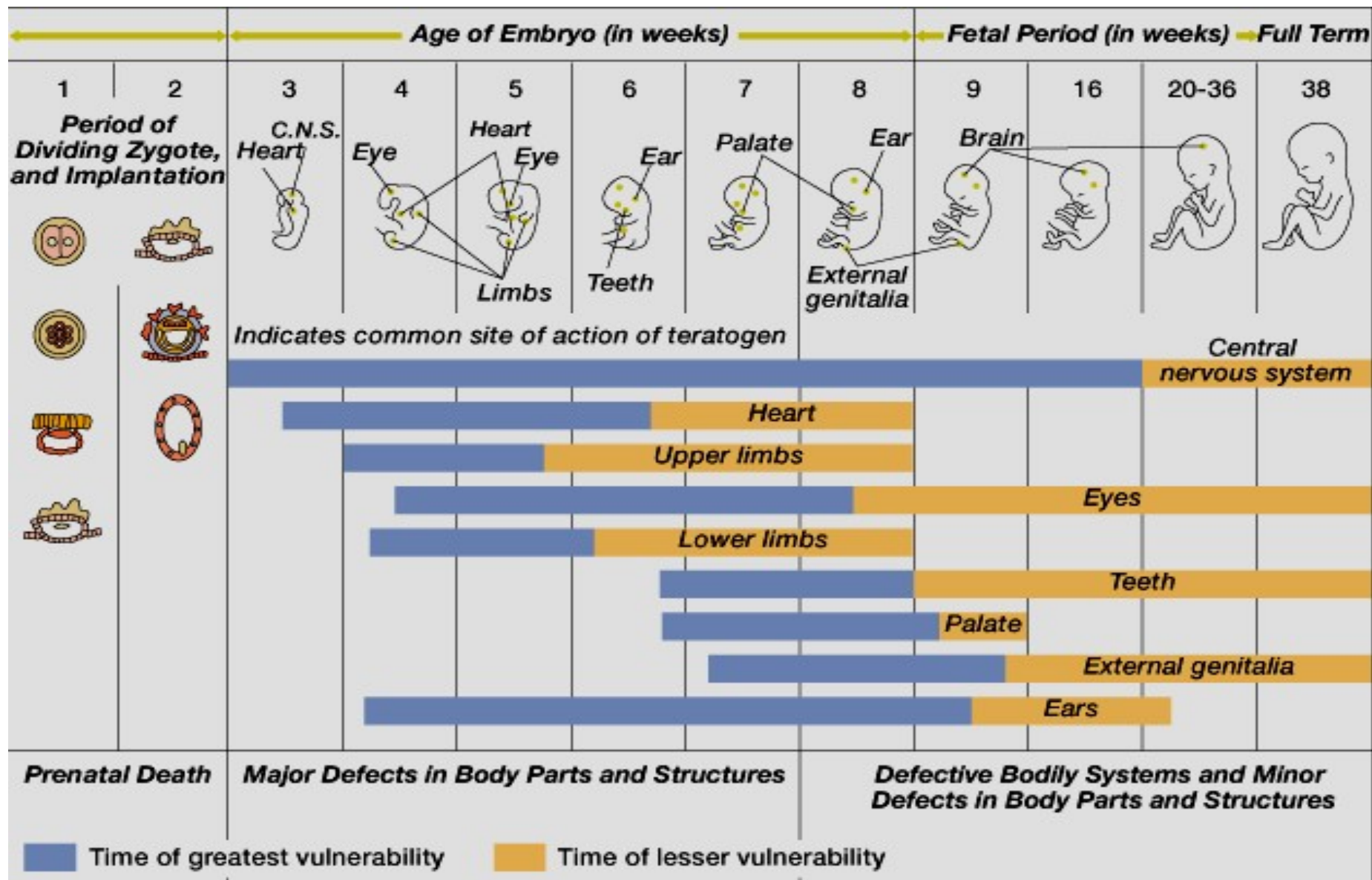
**Second & Third trimesters: (week 13-week 28)**

**affect growth & fetal development**

**Near Term: (week 29-week 40)**

**adverse effects on neonates or labor after delivery**

# Critical Periods of Human Development





# 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, environmental agents.
- This could be severe during critical periods of development e.g. **(organogenesis)**.

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

# Proven teratogens

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

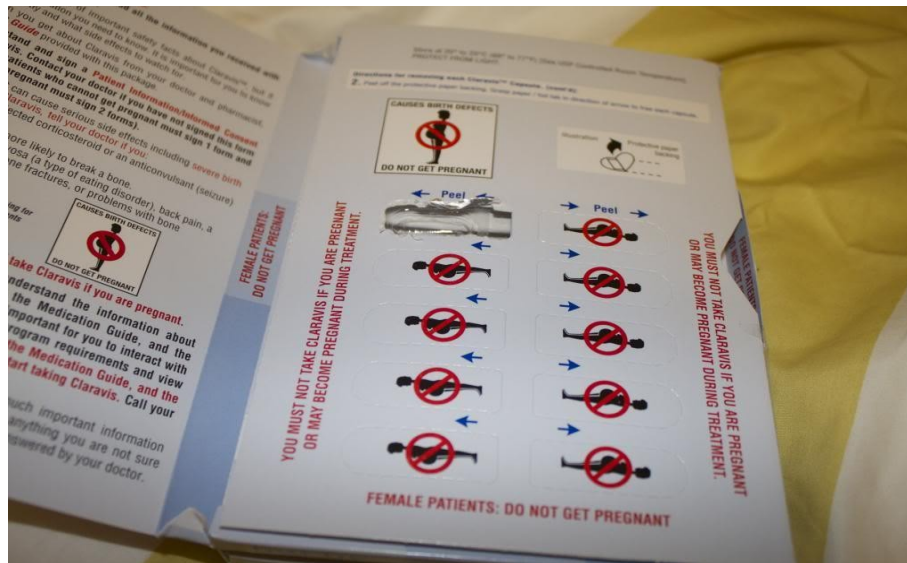
# Proven teratogens

- **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**

Serious genital malformation

Testicular atrophy in male fetus

- **Androgens**

Fetal masculinization in female fetus

- **Diethylstilbestrol**

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**

# Adverse effects of drugs

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

# Adverse effects of drugs

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

# 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**

**$\alpha$ -methyl dopa**

**Labetalol**

## **Emergency**

**Hydralazine**

**Labetalol**

# Coagulation disorders in pregnancy

## **Contraindicated**

**warfarin is contraindicated in all trimesters**

**Cross placenta**

**1<sup>st</sup> trimester : teratogenicity**

**2<sup>nd</sup>, 3<sup>rd</sup> : 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

<b>Antihypertensive</b>	<b><math>\alpha</math>-methyl dopa Labetalol (<math>\alpha</math> - <math>\beta</math> Blocker) Hydralazine (emergency only)</b>
<b>Antibiotics</b>	<b>penicillin, cephalosporins, erythromycin</b>
<b>Antidiabetics</b>	<b>Insulin, avoids oral antidiabetics</b>
<b>Anticoagulants</b>	<b>Heparin</b>
<b>Analgesics</b>	<b>Acetaminophen</b>
<b>Antithyroid drugs</b>	<b>Propylthiouracil (protein-bound)</b>
<b>Anticonvulsants</b>	<ul style="list-style-type: none"><li>➤ <b>All antiepileptics have potential to cause malformations</b></li><li>➤ <b>avoid valproic acid (highly teratogenic)</b></li><li>➤ <b>Folic acid supplementation prevents neural tube defects in women receiving AEDs</b></li></ul>

# **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 )

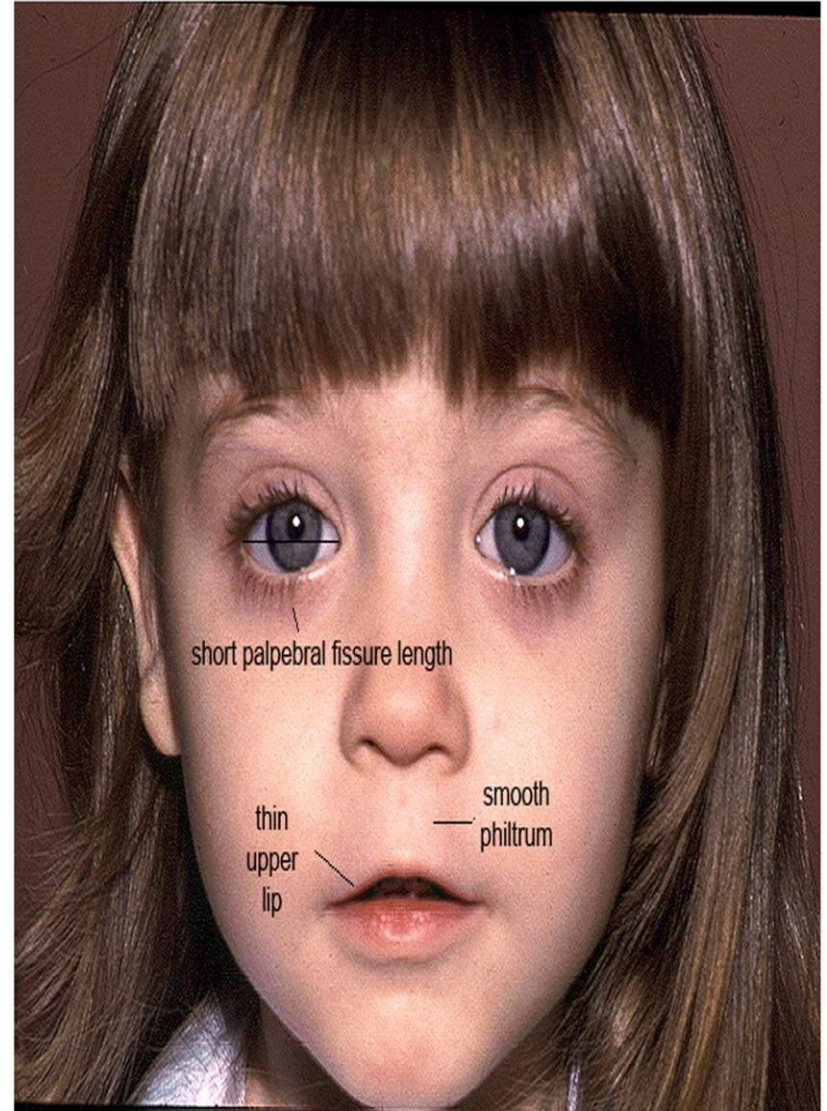
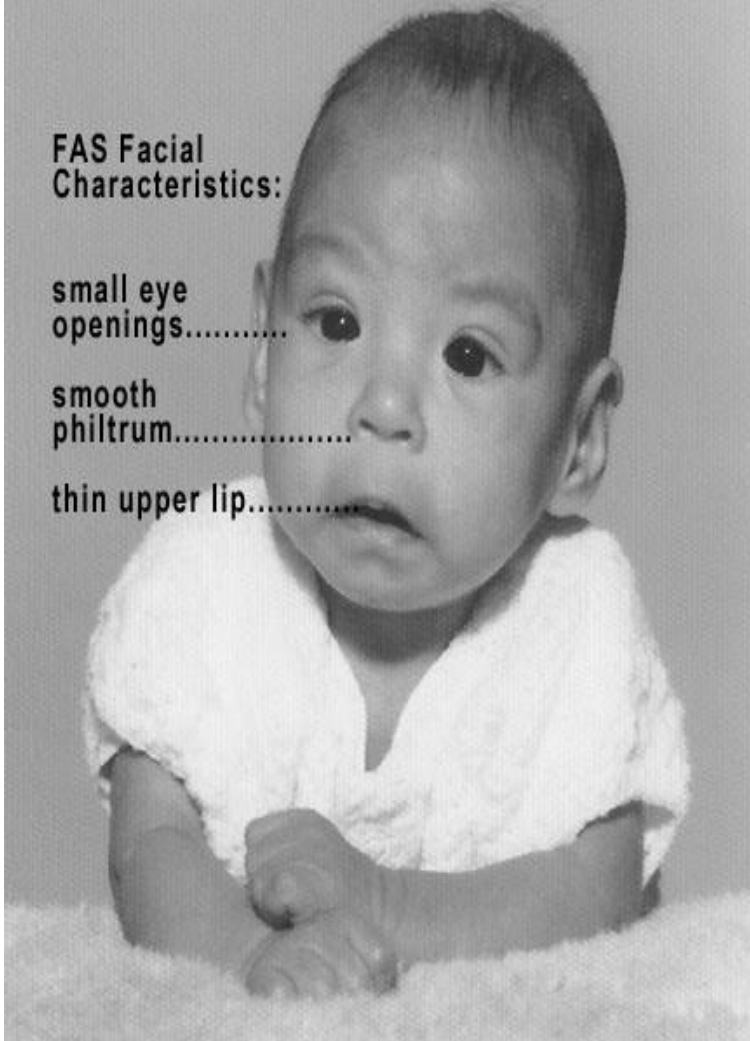
Baby with Fetal Alcohol Syndrome

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).

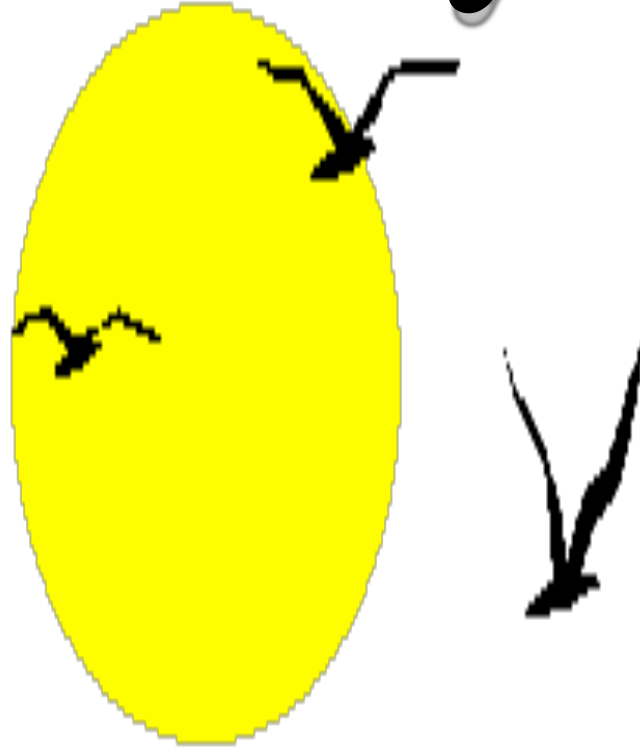
# Tobacco

- 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 ?