Teratogens and drugs of abuse in pregnancy

Prof. Hanan Hagar

Dr. Ishfaq Bukhari

Pharmacology Unit

College of Medicine

Teratogenesis

Occurrence of congenital defects of the fetus.

What is a teratogen? is any agent *(medication, street drug, chemicals, disease, environmental agents)* that result in structural or functional abnormalities in the fetus or in the child after birth as a consequence of maternal exposure during pregnancy. Drug exposure could be more severe during critical periods of development e.g. **(organogenesis).**

Medications in pregnancy

- **Placental membrane is semi-permeable.**
- **Most drugs can cross placenta by passive diffusion.**

Factors controlling placental drug transfer

1. **Physiochemical properties of the drug**
   - **Lipid solubility or diffusion.**
   - **Molecular size.**
   - **Protein binding.**
2. **Duration of exposure to 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 & Tubocurarine.

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 especially . e.g Heparin, chloramphenicol and propythiouracil**

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 17 days).**
- **Organogenesis (17-60 days).**
- **maturation of function.**

Blastocyste formation (First 2 weeks)

- **Occurs from (1-16 days) in the first trimester.**
- **Period of dividing zygote, implantation**
- **Drugs have an all-or-nothing effect.**
- **Exposure to drugs during this period → death of the embryo → abortion**
- **Either the pregnancy will proceed, or abortion will occur.**

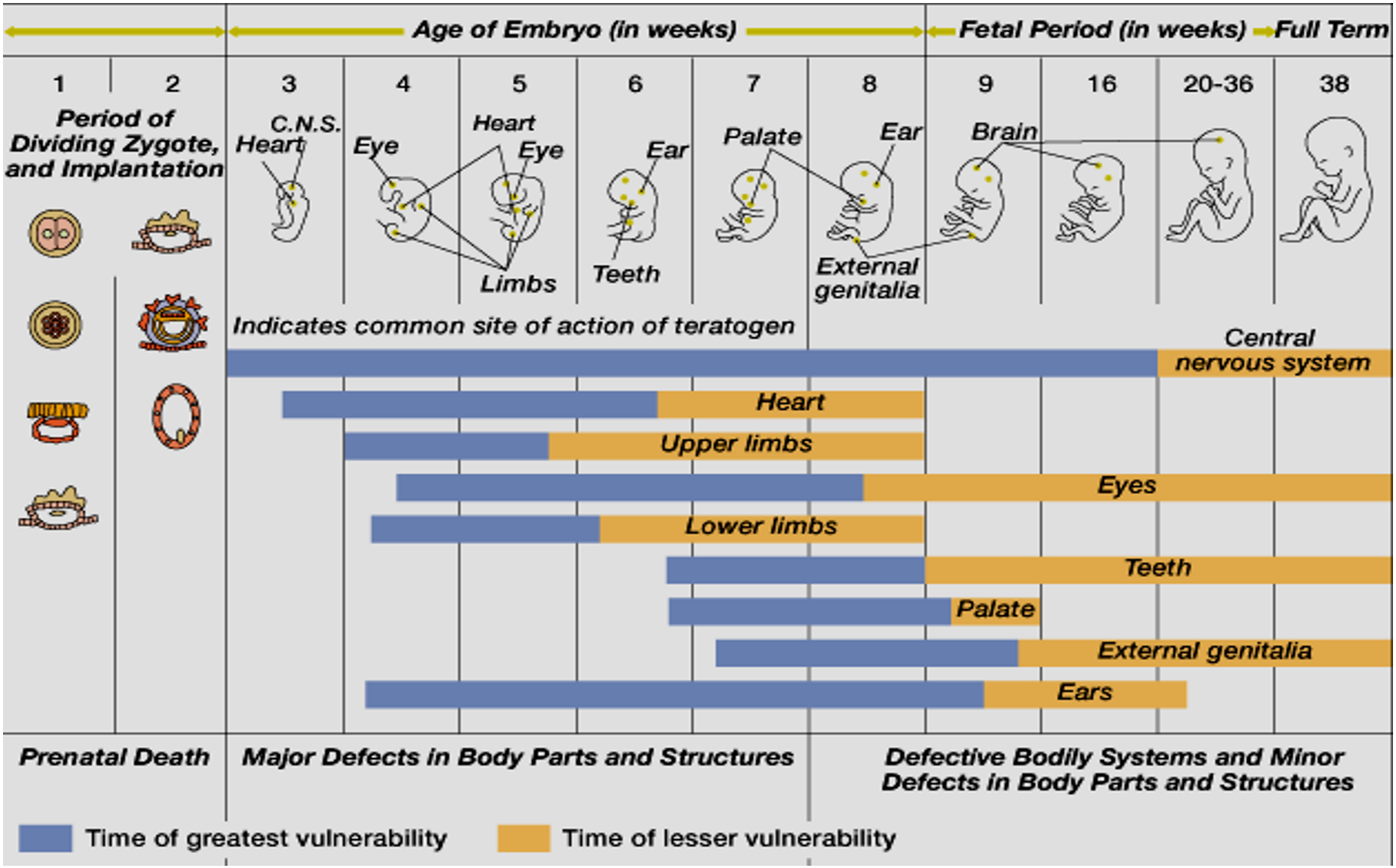
Organogenesis: (2-8 weeks)

- **Occurs in (17- 60 days) in the first trimester.**
- **The most sensitive period of pregnancy because major body organs and systems are formed.**
- **Exposure to harmful drugs during organogenesis → major birth defect or gross malformation (Teratogenesis)**

Histogenesis and functional maturation (8 weeks onwards)

- **Maturation occurs during this stage & fetus depends upon nutrients & hormonal supply.**
- **Exposure to drugs during (8 weeks onwards) will not induce major malformation but drugs can produce minor morphologic abnormalities, growth retardation and functional defect.**
- **However, CNS is sensitive to toxic effects throughout pregnancy.**

Critical Periods of Human Development



FDA Classification System

Category A

- Controlled human studies with no risk to fetus
- Drugs can be used

Category B

- Adverse effects on animal studies only
- Adequate Human studies lacking or not shown similar results. Drug can be used in pregnancy

Category C

- Adverse effects on animal studies only
- No human studies, human fetal risk is unknown. Drug may be used in serious situation despite its potential risk.

FDA Classification System

Category D

- **Evidence of human fetal risk**
- **May be used in serious diseases or life threatening situations e.g phenytoin**

Category X

- **Fetal abnormalities in animal and human studies**
- **Drugs are teratogens and contraindicated in pregnant women or planning to conceive.**

Proven teratogens

- **Thalidomide (sedative/ hypnotics).**
- **Cytotoxic drugs**
  - **Folate antagonists (methotrexate).**
  - **Alkylating agents (cyclophosphamide).**
- **Lithium (valvular heart abnormality)**
- **Alcohols (fetal alcohol syndrome).**
- **Anticonvulsant drugs (valproic acid, phenytoin).**
- **Anticoagulants (warfarin).**
- **Antibiotics (tetracyclines, quinolones)**

Proven teratogens

- **Retinoids e.g.**
  - **vitamin A**
  - **isotretinoin (used in treatment of Acne)**
- **Angiotensin converting enzyme inhibitors (ACEIs)**
- **Ionizing radiation (diagnostic X-ray or radiation therapy).**
- **Radioactive iodine (I^{131}).**
- **Corticosteroids.**
- **Hormones**

Teratogenesis of drugs

Thalidomide	Phocomelia
(TheThe most notorious human teratogen) it had no teratogenic effects in mice and rats but proved teratogenic when used in pregnant women.	➢ shortened or absent long bones of the limbs ➢ Absence of External Ears

Teratogenesis of drugs

Phenytoin	**Fetal Hydantoin Syndrome** **Nail & Digital hypoplasia** **Oral Clefts (cleft lip and palate)** **Cardiac Anomalies** **Mental & growth retardation**
Corticosteroids	**Cleft lip and Palate**
Tetracyclines	**Permanent teeth staining** **Enamel hypoplasia** **altered growth of teeth and bones.**
Warfarin	**Hypoplasia of nasal bridge** **CNS malformation**

Teratogenesis of drugs

Valproic acid	**Antiepileptic drug** **Neural tube defect (spina bifida)** **Impair folate absorption**
Hormones **Estrogens** **Androgens** **diethylstilbestrol**	**Serious genital malformation** **Testicular atrophy in male** **Fetal masculinization in female** **Vaginal carcinoma of female offspring**
Lithium	**Cardiovascular anomalies mainly valvular heart defect involving tricuspid valve** **Ebstein's anomaly**
ACE inhibitors **captopril,** **enalapril**	ACE inhibitors disrupt the fetal renin-angiotensin system, which is essential for normal renal development **Fetal & neonatal anurnia** **Renal damage** **Fetal hypotension, hypoperfusion - growth retardation**

Fetal hydantoin syndrome

Cleft lip and palate

Phenytoin cuases digital hypoplasia and cleft lip and palate.

Thalidomide

Phocomelia

Valproic acid

Spina bifida

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.

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 hypothyroidism and goitre**

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**
warfarin	**Risk of bleeding**

Adverse effects of drugs prior to labor

CNS depressants	**e.g. diazepam, morphine** **Interference with suckling** **Respiratory depression**
Sulfonamides	**Displacement of bilirubin from plasma protein (neonatal hyperbilirubinemia)**

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

2nd, 3rd : risk of bleeding

Probably safe

Heparin

Polar, does not cross placenta

Protamine sulphate as antidote for neutralization

Antithyroid drugs in pregnancy

Are used in thyrotoxicosis or Grave's disease

- **Propylthiouracil**
- **Methylthiouracil (Methimazole)**
- **Carbimazol**
- **Radioactive Iodine (I131)**

- **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 :

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

Probably safe

- **Penicillins (ampicillin, amoxicillin)**
- **Cephalosporins**
- **Erythromycin and azithromycin as alternative in penicillin-sensitive individuals BUT erythromycin estolate should be avoided *(risk of hepatic injury to mother).***

Summary of Drugs of choice in pregnancy

Antihypertensive	**α-methyl dopa** **Labetalol (α - β Blocker)** **Hydralazine (emergency only)**
Antibiotics	**penicillin, cephalosporins, erythromycin**
Antidiabetics	**Insulin is safe, avoids oral antidiabetics**
Anticoagulants	**Heparin**
Analgesics	**Acetaminophen**
Antithyroid drugs	**Propylthiouracil (protein-bound)**
Anticonvulsants	➢ **All antiepileptics have potential to cause malformations, carbamazepine may be choice.** ➢ **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; cocaine; nicotine; etc**

Alcohols

The use of alcohol is contraindicated during all trimesters of pregnancy

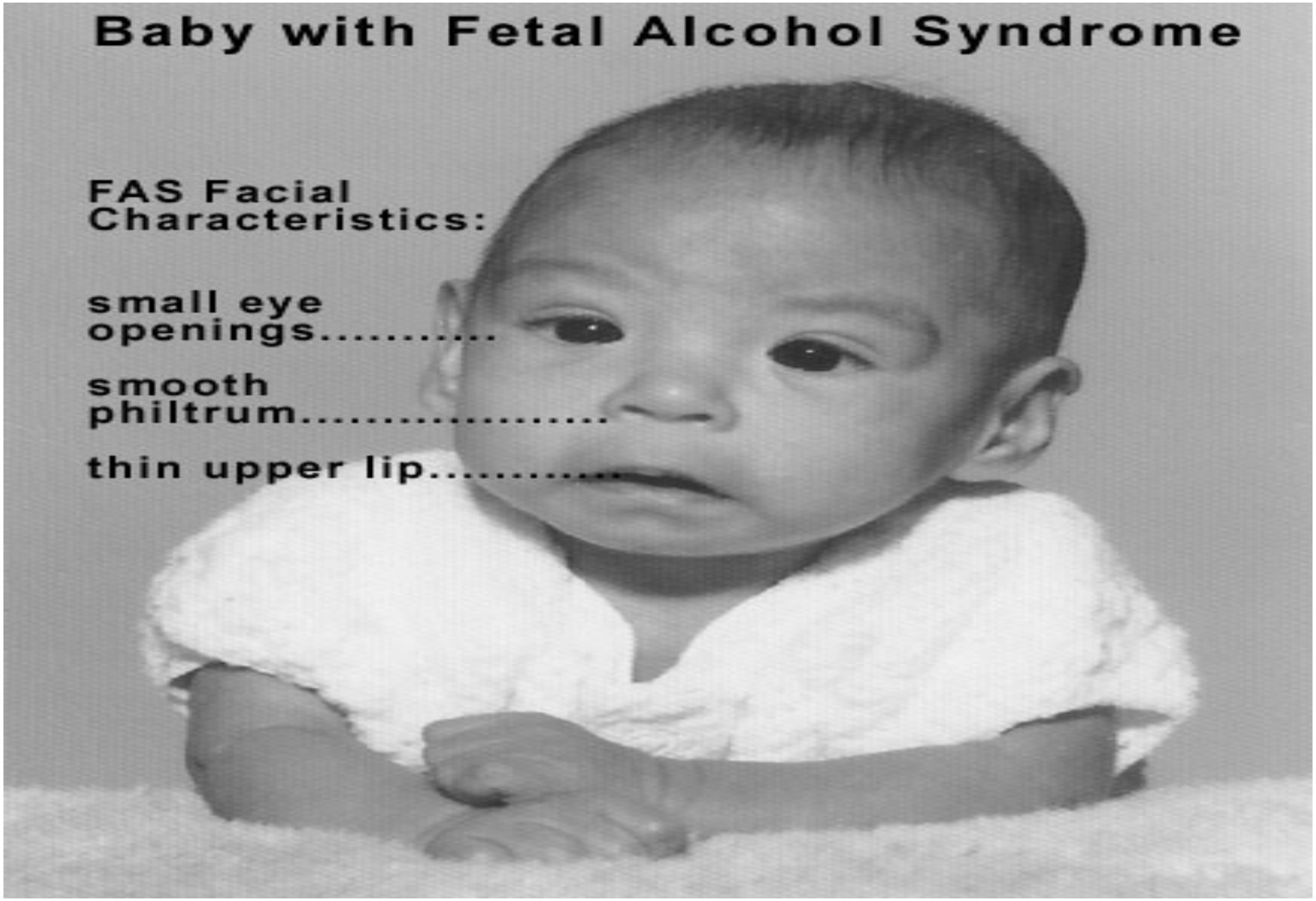
Fetal Alcohol Syndrome (FAS)

- **Caused by chronic maternal alcohol abuse during early weeks of first trimester of pregnancy.**

Characters

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

Fetal Alcohol Syndrome (FAS)



Cocaine

- Cocaine is low MW, water-soluble
- Cocaine 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, fetal oxygenation and intestinal blood flow.
- It increases uterine contractility

Cocaine

- **Microcephaly**
- **Prematurity**
- **Low birth weight.**
- **Abruptio placentae (separation of placenta from uterus wall before delivery)**
- **Growth retardation**
- **Mental retardation**
- **Withdrawal symptoms**

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.**

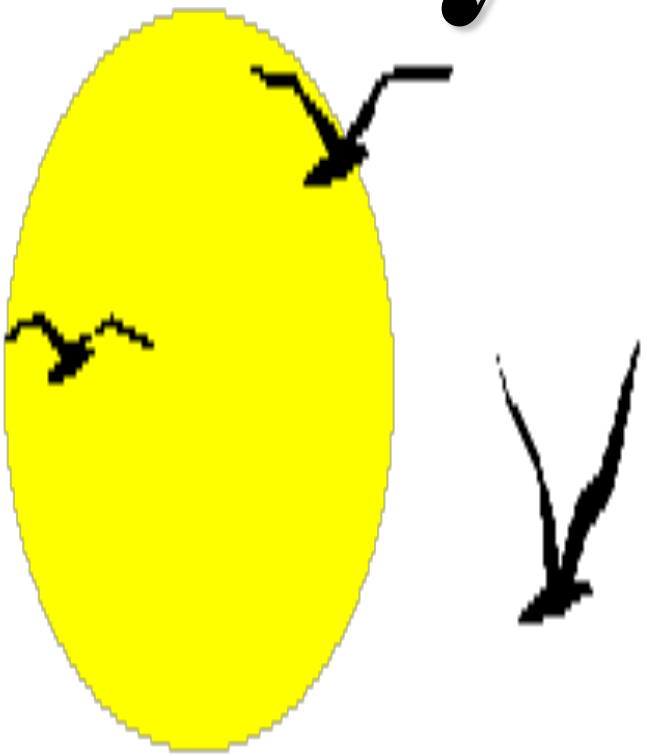
Tobacco can produce:

- **Decreased blood flow to placenta**
- **Fetal hypoxia**
- **Retarded fetal growth**
- **Low birth weight**
- **Increased spontaneous abortion**
- **Preterm labor and stillbirth**

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 (17 days – 8 weeks).**
- **Alcohol, nicotine and other addicting drugs should be avoided.**

Thank you



Questions ?