

Teratogens and drugs of abuse in pregnancy



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-Notes << purple

-Plz focus on the tables and alcohol in drug abuse

- @ = introduction (for reading to understand the lect.)

objectives:

1- Stages of mammalian fetal developments and the effect of drugs in each stage.

(teratogen + fetotoxic drugs) !!!

2- drugs of choice in pregnancy

3- Drugs of Abuse in Pregnancy:

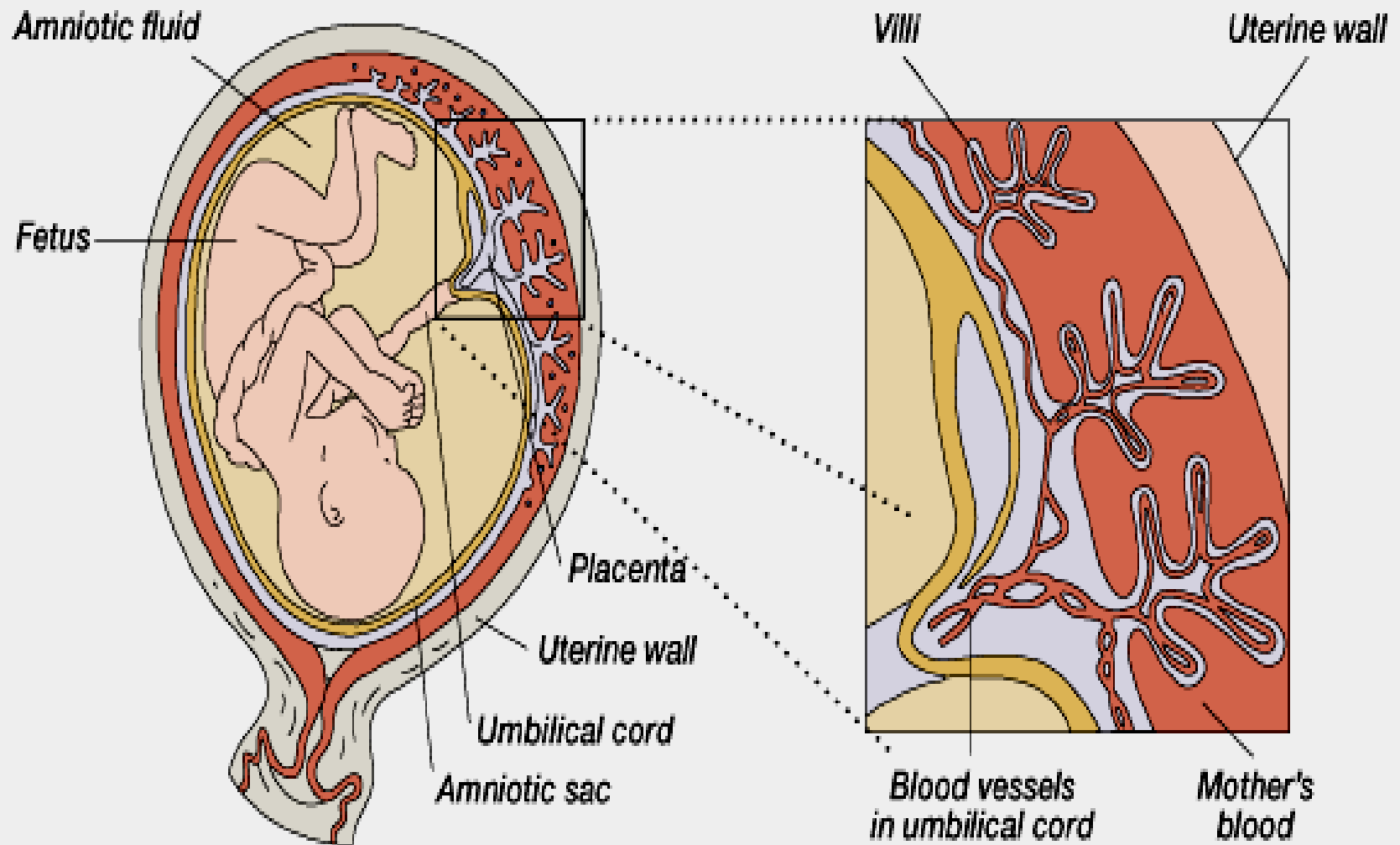
Alcohol , cocaine , nicotin

@ Medications in pregnancy

- Placental membrane is semi-permeable.
- Most drugs can cross placenta by passive diffusion.
- The movement of drugs across the placenta is limited by a single layer of cell called **trophoblasts**.(this cell separate the fetus circulation from mother circulation)



Prenatal Structures



@ Pharmacokinetic changes in pregnancy

- **↑ Plasma volume 50%**
- **↑ Cardiac output**
- **↑ GFR and renal elimination of drugs.**(when the Co increase → the blood flow to kidney increase → high GFR+ elimination of drugs)
- **↑ volume of distribution**
- **↑ Metabolic rate of some drugs.**(because the placenta is site for metabolism not just the liver)

@ Factors Controlling Rate of Placental Drug Transfer

1. **Physiochemical properties of the drug**
 - *Lipid solubility or diffusion.*
 - *Molecular size.*
 - *Protein binding.*
2. **The stage of placental and fetal development at the time of exposure to the drug.**
3. **Duration of exposure to the drug.**

@ Physiochemical properties of the drug

1. Lipid Solubility of drugs

Lipophilic drugs cross readily the placenta.

(more lipid solubility → more the chance to cross)

Ionized drugs cross the placenta very slowly.

(more ionized (water soluble) → less chance to cross)

2. Molecular Size of drugs

- MW affects the rate of transfer:
- 250 - 500 cross placenta easily.
- 500 - 1000 cross placenta with more difficulty.
- 1000 - ↑very poorly cross placenta. e.g. Heparin.

(so the drug of choice in case of pregnancy with need of anticoagulant drug is heparin because of having high molecular weight)

3. Protein binding of drugs

- Protein binding in maternal circulation hinder passage of drugs especially **poorly lipid soluble drugs**.

(more protein binding → less distribution in body so less chance to go to the fetus)



!! Imp



Stages of Mammalian Fetal Development

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

Stages of mammalian fetal developments:

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

Blastocyste formation

- Occurs from (1-16 days) in the first trimester.
- Cell division takes place.
- Period of dividing zygote, implantation
- Pre-differentiated period (conceptus).
- Drugs have an **all-or-nothing effect**.
- Exposure to drugs during this period → death of the embryo → **abortion**
- * in this period the cells are not differentiated, so the drug have two options either have no effect (not harmful) or be very harmful and leads to death of embryo (so no congenital defect in this period)

Organogenesis:

- 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 (**first trimester**) → major birth defect or gross malformation (**Teratogenesis**)

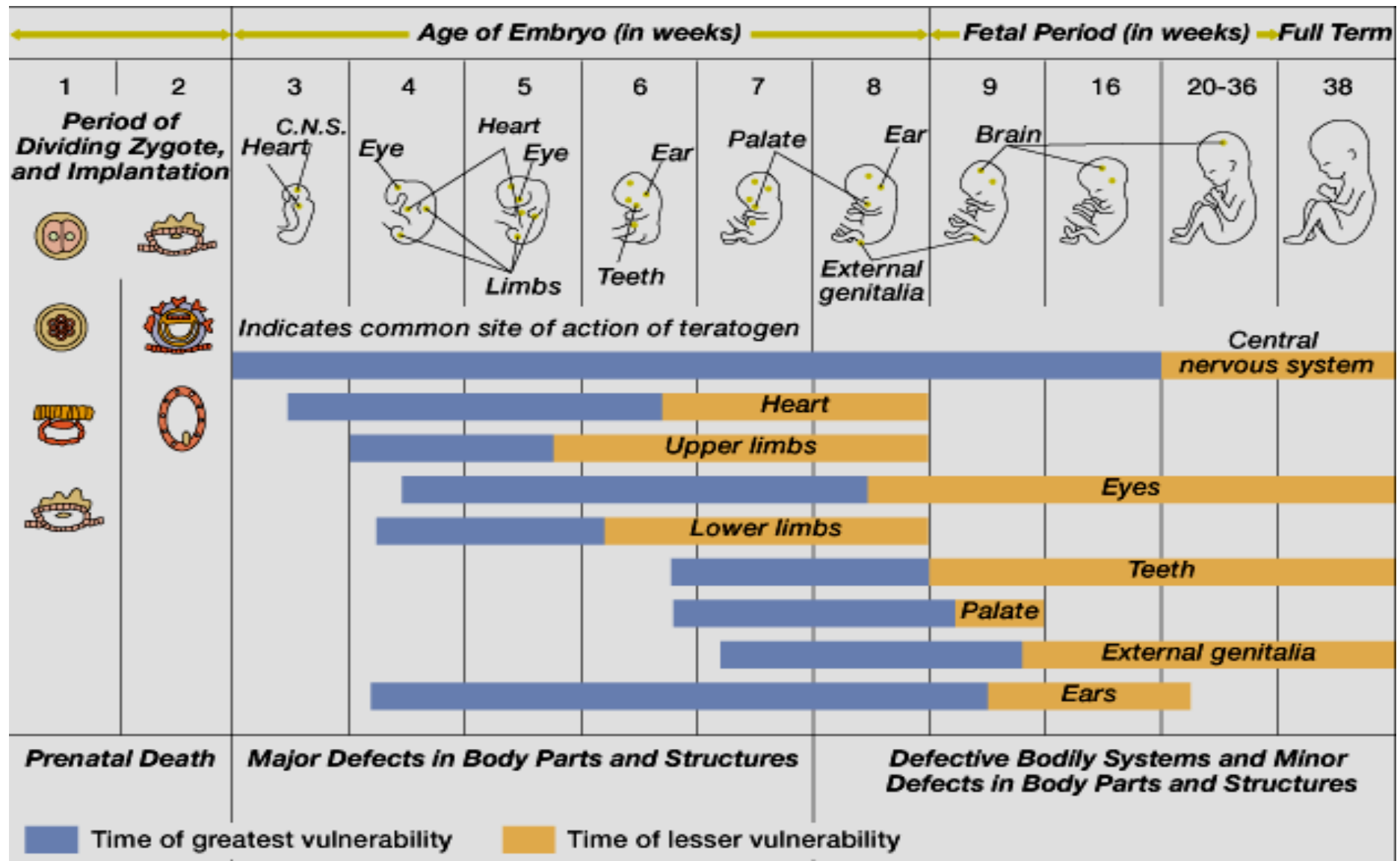
Histogenesis and functional maturation

- **During this stage maturation occurs & fetus depends upon nutrients & hormonal supply.**
- **Exposure to drugs during 2nd and 3rd trimester will not induce gross malformation but drugs can produce minor morphologic abnormalities, growth retardation and functional defect.**
- **The drug in this case called Fetotoxic drug**

summary

Stage	Blastocyste formation	Organogenesis	Histogenesis and functional maturation
period	1-16 days in the first trimester	17- 60 days in the first trimester	2 nd and 3 rd trimester
Effect of drugs	Exposure to drugs during this period → abortion Or may have no effect	Exposure to harmful drugs during organogenesis (first trimester) → major birth defect or gross malformation (major) (Teratogenesis)	Exposure to drugs during 2nd and 3rd trimester can produce : - minor morphologic abnormalities - growth retardation - functional defect.

Critical Periods of Human Development



Birth Defects

Incidence:

- Major birth defects (teratogenesis) in Organogenesis
- Minor birth defects. In Histogenesis

Causes:

- Unknown causes, genetics, maternal infection, drugs or chemicals.
- Between 2-10 % of all birth defects are the direct result of using OTC (Over The Counter drug, no need to have prescription) or prescription medications during pregnancy.

Mechanisms of birth defects

How do drugs cause birth defects?

- Direct damage to the fetus (**differentiation in developing tissues**) causing abnormal development.
- Interference with the supply of oxygen and nutrients through placenta.
- Direct effect on maternal tissues with secondary or indirect effects on fetal tissues.
- Stimulation of forceful uterine contractions, potentially injuring the fetus or prompting premature birth.

Teratogenesis

Production of gross malformation or congenital defects of the fetus.

What is teratogen?

is a drug or a chemical that is able to produce a congenital defects in the foetus when present during critical periods of development (organogenesis).

!!! FDA (*Food and Drug Administration*) PREGNANCY RISK CATEGORIES

تصنيف هيئة الغذاء والدواء
للأدوية أثناء الحمل

Category A	Category B	Category C	Category D	Category X
<div> <div>More risk</div> <div>→</div> </div>				
Controlled human studies with no risk to fetus	Adverse effects on animal studies only Human studies did not show similar results.	Adverse effects on animal studies only No human studies, human fetal risk is unknown.	Evidence of human fetal risk	Fetal abnormalities in animal and human studies -Drugs are teratogens and contraindicated
Drugs can be used	Drugs can be used	Drugs can be used but with precaution	May be used in serious diseases or life threatening situations (like anticonvulsant drug)	Should not be used in pregnant women or planning to conceive.

PROVEN TERATOGENS

- The following drugs are contraindicated during pregnancy (category X):
- **Retinoids** e.g.
 - *vitamin A* (in high dose)
 - *isotretinoin* (used in treatment of Acne حب الشباب)*
 - *etretinate* (treatment of psoriasis الصدفية)*

* : Even after not use the drug for months, it has potential to cause teratogenesis. (مثل حبوب الروكاتين للي قد عالج فيها عن حب الشباب)
- **Cytotoxic drugs**
 - (a) Folate antagonists (methotrexate).
 - (b) Alkylating agents (cyclophosphamide).
 - (c) All others : smaller risk.

PROVEN TERATOGENS

- **Anticonvulsant drugs** (valproic acid-phenytoin).
- **Anticoagulants** (Warfarin).
- **Antibiotics** (Tetracyclines).
- **Thalidomide** (Antihistamine, in the past it used in case of morning sickness of pregnancy)
- **Hormones**
- **Lithium** (Antimanic)
- **Corticosteroids.**
- **Alcohols**
- **Ionizing radiation** (diagnostic X-ray or radiation therapy).
- **Radioactive iodine** (I^{131}).
- **Angiotensin converting enzyme inhibitors (ACEIs)**

Imp !!! TERATOGENESIS OF DRUGS

Drug	Teratogenic actions (organogenesis in 1 st trimester)
Corticosteroids	<u>Cleft lip and Palate</u>
Tetracyclines *affect Teeth & bones*	<u>Permanent teeth staining</u> Enamel hypoplasia
Hormones Estrogens → Androgens → Diethylstilbestrol → (this drug used in women complains of repeated abortion)	Serious genital malformation Testicular atrophy in male Fetal masculinization in female Vaginal carcinoma of female offspring
Warfarin	<u>Hypoplasia of nasal bridge</u> CNS malformations

TERATOGENESIS OF DRUGS

Phenytoin	Fetal Hydantoin Syndrome Nail & Digital hypoplasia Oral Clefts (cleft lip and palate) Cardiac Anomalies Mental & growth retardation
Valproic acid	Neural tube defect (spina bifida)
Lithium	Cardiovascular anomalies mainly valvular heart defect involving tricuspid valve Ebstein's anomaly
ACE inhibitors (captopril, enalapril)	<u>Renal malformation</u> <u>Fetal & neonatal anuria</u> (no urine) fetal hypotension - growth retardation

TERATOGENESIS OF DRUGS

Thalidomide

Phocomelia:

- shortened or absent long bones of the limbs
- Anorectal stenosis
- Absence of External Ears

Iodide

Congenital goiter, hypothyroidism

Fetal hydantoin syndrome



Phenytoin

Cleft lip and palate



Corticosteroids

Thalidomide



Phocomelia

Valproic acid



Spina bifida

Cleft lip



Teeth staining



Tetracyclines

Fetal warfarin

_DDB patient 1. Note small nose, small mouth and flat nasal bridge.



Fetotoxic drug effects

- **Fetotoxic drug effects** : are the results of the pharmacological activity of drugs on fetus during second and third trimesters. (histogenesis stage)
- are more likely to occur than teratogenic effects.

Imp !!! Fetotoxic effects of drugs

Tetracycline	Impaired teeth & bone development
Aminoglycosides e.g , Streptomycin, Kanamycin	<u>Ototoxicity</u> = 8 th Cranial nerve damage *deafness*
Cloramphenicol	<u>Gray baby syndrome</u> *cyanosis of baby because it can't eliminate the drug *
Corticosteroids	Adrenal atrophy – growth retardation
Propranolol B-blocker	Bradycardia, neonatal hypoglycemia, placental insufficiency, <u>reduced uterine blood flow, fetal distress</u>
warfarin	Risk of bleeding
Antithyroid drugs Methimazole, Carbimazole, propylthiouracil	Risk of hypothyroidism

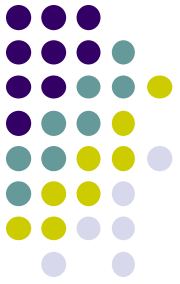
Imp !!! Drugs of choice in pregnancy

Antihypertensive	α-methyl dopa Hydralazine (emergency only)
Antibiotics	Penicillin cephalosporin Erythromycin * according to Preferences meaning the first choice is penicillin*
Antidiabetics	Insulin * it has high molecular weight can't cross placenta* So diabetic pregnant shouldn't use oral antidiabetic only insulin >> to prevent hypoglycemia of baby
Anticoagulants	Heparin
Analgesics	Acetaminophen
Antithyroid drugs	Propylthiouracil is preferable over Carbimazole & methimazole (Propylthiouracil drug of choice in case of hyperthyroidism in pregnancy)
Anticonvulsants (category D)	<ul style="list-style-type: none"> ➤ All antiepileptics have potential to cause malformations ➤ avoid valproic acid. *most harmful * ➤ Folic acid should be supplied.



Drugs of Abuse in Pregnancy

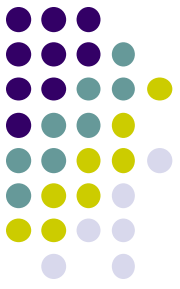
Drug abuse



Drug abuse:

is habitual use of drugs to alter mood, emotion, or state of consciousness (non therapeutic effect).

Drug abuse



- The most commonly abused drugs are alcohol; cocaine; nicotine; marijuana; amphetamines; barbiturates; opium alkaloids, benzodiazepines.

*_barbiturates & benzodiazepines are hypnotics drugs

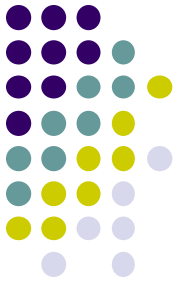
* amphetamines is like cocaine يعمل شائعة

Most of abuse drugs work on CNS and leads to addiction either by stimulation يشعشع ☺ or depression.

- Drug abuse may lead to organ damage, addiction, and disturbance of behavior.

All of the alcohol, cocaine ,smoking lead to mental , growth defect

1- Alcohols



The use of alcohol is contraindicated during all trimesters of pregnancy

Imp !! Fetal Alcohol Syndrome (FAS)



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

Characters

- **Microcephaly** (small head)
- **Intrauterine growth retardation**
- **Craniofacial abnormalities**
- **CVS abnormalities**
- **CNS abnormalities (*mental retardation*)**

Underlined the most important characteristics☺

Fetal Alcohol Syndrome (FAS)



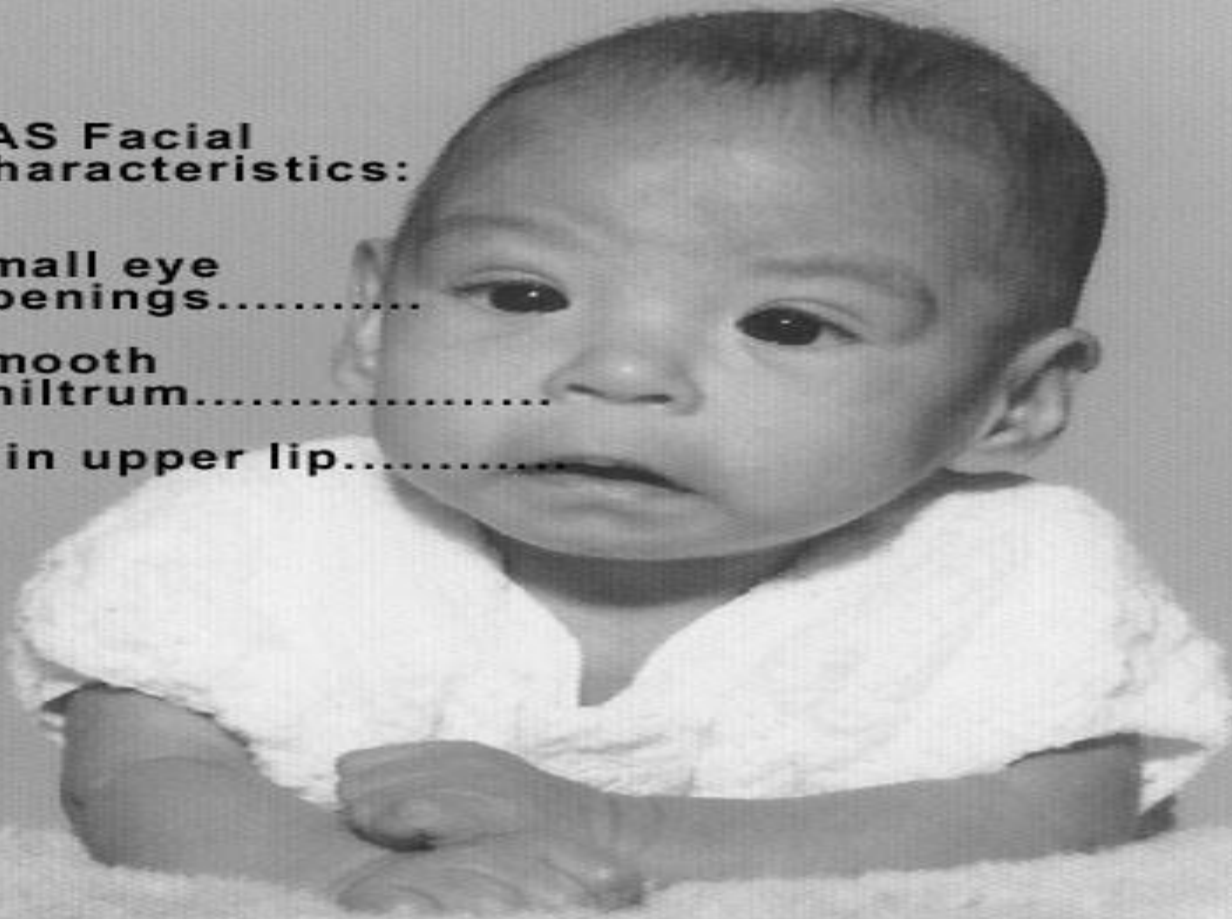
Baby with Fetal Alcohol Syndrome

FAS Facial Characteristics:

small eye openings.....

smooth philtrum.....

thin upper lip.....

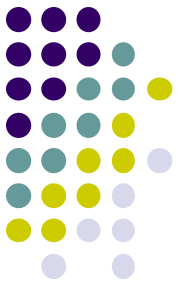


2- Cocaine



- **Cocaine is low MW, water-soluble**
- **Cocaine easily passes into fetus through placenta.**
- **cocaine base crosses even more efficiently.**

Cocaine



- **Inhibits re-uptake of sympathomimetics (Epinephrine, NE, dopamine), causing vasoconstriction, rapid heart rate, hypertension → Decreases blood flow to uterus, decreases fetal oxygenation and intestinal blood flow.(so the baby will be small size)**

Cocaine



- **Microcephaly**
- **Prematurity**
- **Low birth weight.**
- **Abruptio placentae** (separation of placentae from the uterine wall)
- **Growth retardation**
- **Mental retardation**

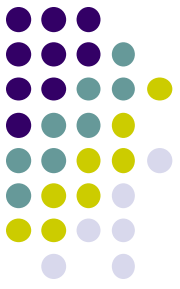
Fetal cocaine

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.



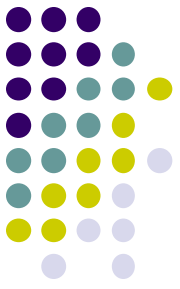
Robin NH, Zackai EH. Teratology, 50:160-164 (1994).

3- Tobacco



- Tobacco contains nicotine and carbon monoxide that may harm fetus.
- Nicotine can produce:
 - Decreased blood flow to placenta
 - Fetal hypoxia
 - Retarded fetal growth
 - Low birth weight
 - Increased spontaneous abortion
 - Preterm labor and stillbirth (stillbirth: fetus dead in uterus)

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 fetus 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.**