He is the One who shapes you in the wombs as He wills.' (Qur'an 3:6)

BIRTH DEFECTS

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BIRTH DEFECTS/CONGENITAL MALFORMATIONS/ CONGENITAL ANAMOLIES

- Structural, behavioural, functional and metabolic disorders present at birth

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RELATED TERMS

- **Teratology/Dysmorphology**
  - Branch of science which studies causes, mechanisms & patterns of abnormal development
- **Teratogen**
  - A teratogen is an agent that can produce a permanent alteration of structure or function in an organism exposed during embryonic or fetal life.

OR

  - A factor that causes birth defects

- Until 1940, it was assumed that congenital defects were caused primarily by hereditary factors.
- In 1941, the first well-documented cases were reported that an environmental agent (rubella virus) could produce severe anatomic anomalies
- In 1961 Lenz linked limb defects with thalidomide and proposed that drugs can cross placenta & produce birth defects

STATISTICS

- Birth defects are the leading cause of infant mortality - 21% of infant deaths
- Major structural anomalies (4-6%):
  - 2% - 3% of live born infants & additional
  - 2% – 3% recognized in children by age 5 years
- Minor anomalies ---- (15%)

CAUSES

a. In 40% to 60% of persons with birth defects, the cause is unknown

b. Genetic factors : 15%

c. Environmental factors: 10%

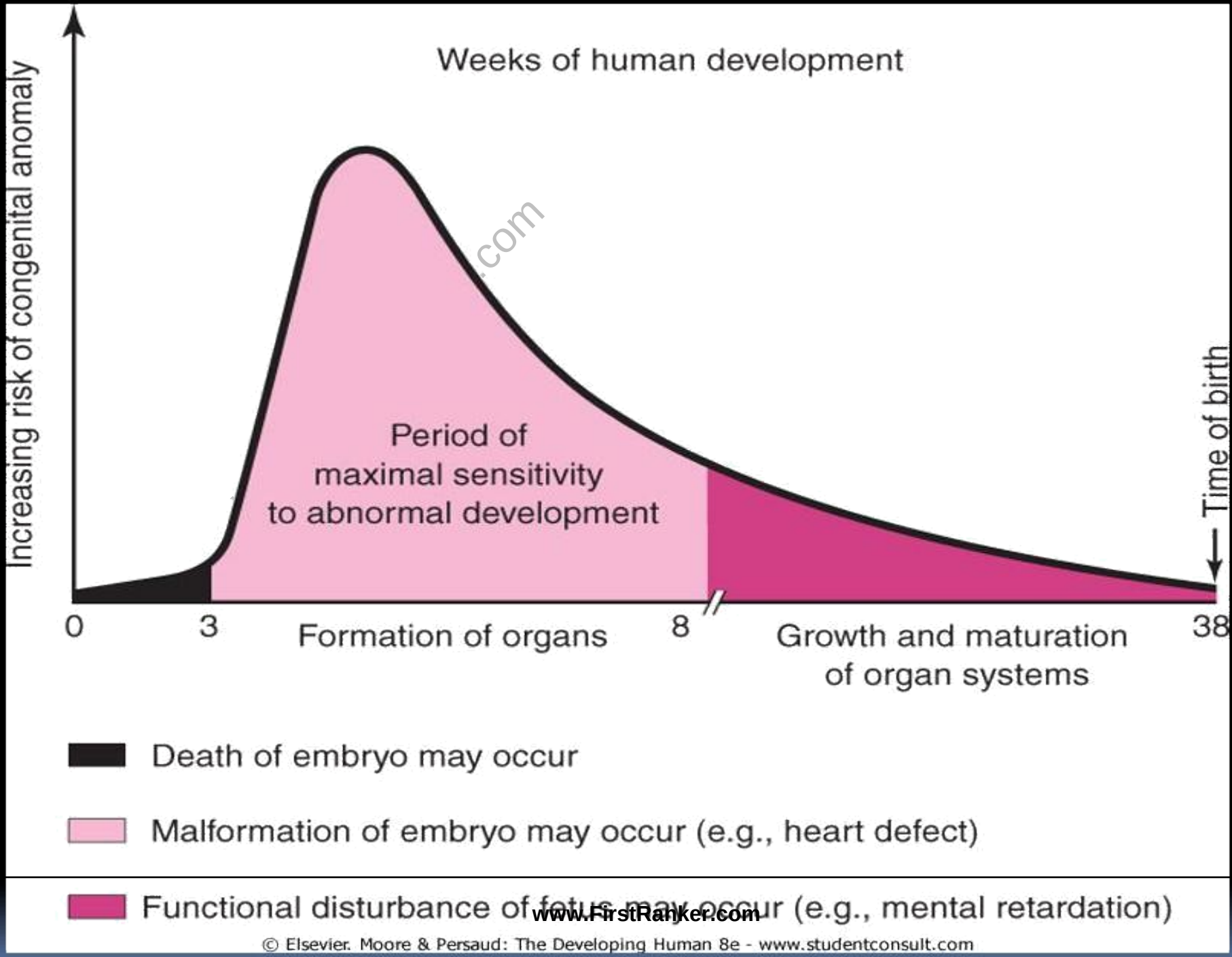
d. Combination of above :20% to 25%

e. Twinning : 0.5 % to 1%

MINOR VERSES MAJOR ANOMALY

- Minor anomalies such as microtia, pigmented spots and short palpebral fissures alone are not detrimental to health.

1 minor anomaly	----	3% chance of major anomaly
2 minor anomalies	----	10% chance of major anomaly
3 or more minor anomalies		20% chance of major anomaly



TYPES OF ABNORMALITIES

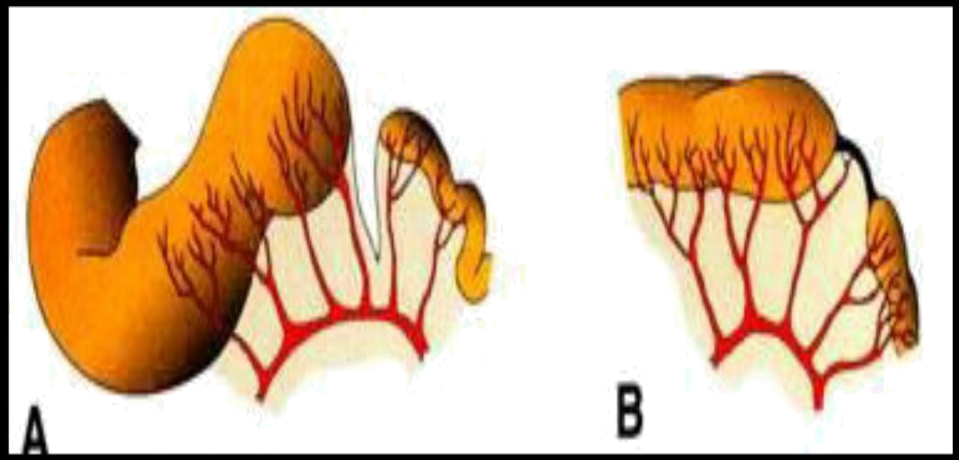
- Malformations
- Disruptions
- Deformations
- Syndrome
- Association

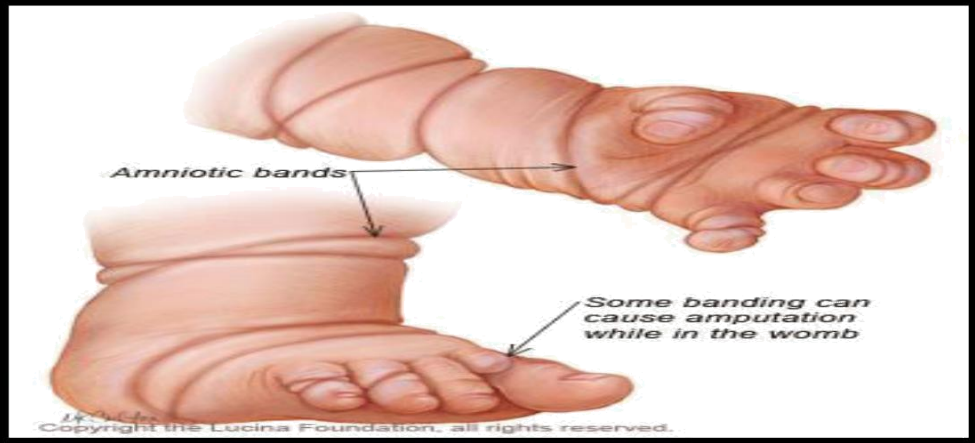
MALFORMATIONS

- Occurs during formation of structures - Organogenesis
- Result in complete or partial absence of a structure or in alterations of its normal configuration

Disruptions

- Disruptions result in morphological alterations of already formed structures
- They are due to destructive processes
- Examples:
  - Vascular accidents leading to bowel atresias
  - Defects produced by amniotic bands





Deformations

- Are due to mechanical forces that mold a part of the fetus over a prolonged period
- Often involve musculoskeletal system
- They may be reversible postnatally

- Examples:
  - Club feet ---- due to compression in the amniotic cavity

Syndrome

Is a group of anomalies occurring together that have a specific common cause.

- In syndrome, the cause is known.
- Diagnosis is made.
- The risk of recurrence is known.

Examples:

- **Down's syndrome**
- Fetal alcoholic syndrome

Association

- Is the non random appearance of two or more anomalies that occur together more frequently than by chance alone.
- Cause is not known.
- They do not constitute a diagnosis
- Example:
  - VACTERL
- Recognition of one component promotes search for others in the group.

PRINCIPLES OF TERATOLOGY

Factors determining the capacity of an agent to produce birth defects have been defined and set forth as Principles of teratology

Susceptibility to teratogenesis depends upon:

- Genotype of the conceptus & maternal genome
- Developmental stage / Time of exposure
- Dose & duration of exposure to a teratogen.
- Specific ways (mechanisms) in which a teratogen acts on the developing cells.
- Manifestations of abnormal development are :

Death, malformation, growth retardation & functional disorders.

TERATOGENIC AGENTS

1. Infectious agents
2. Physical agents: Radiation, hyperthermia
3. Drugs and chemical agents
4. Hormones
5. Maternal metabolic imbalances
   Diabetes/Alcoholism/Phenylketonuria
6. Nutritional deficiencies: iodine deficiency- cretinism
7. Obesity
8. Male mediated teratogenesis

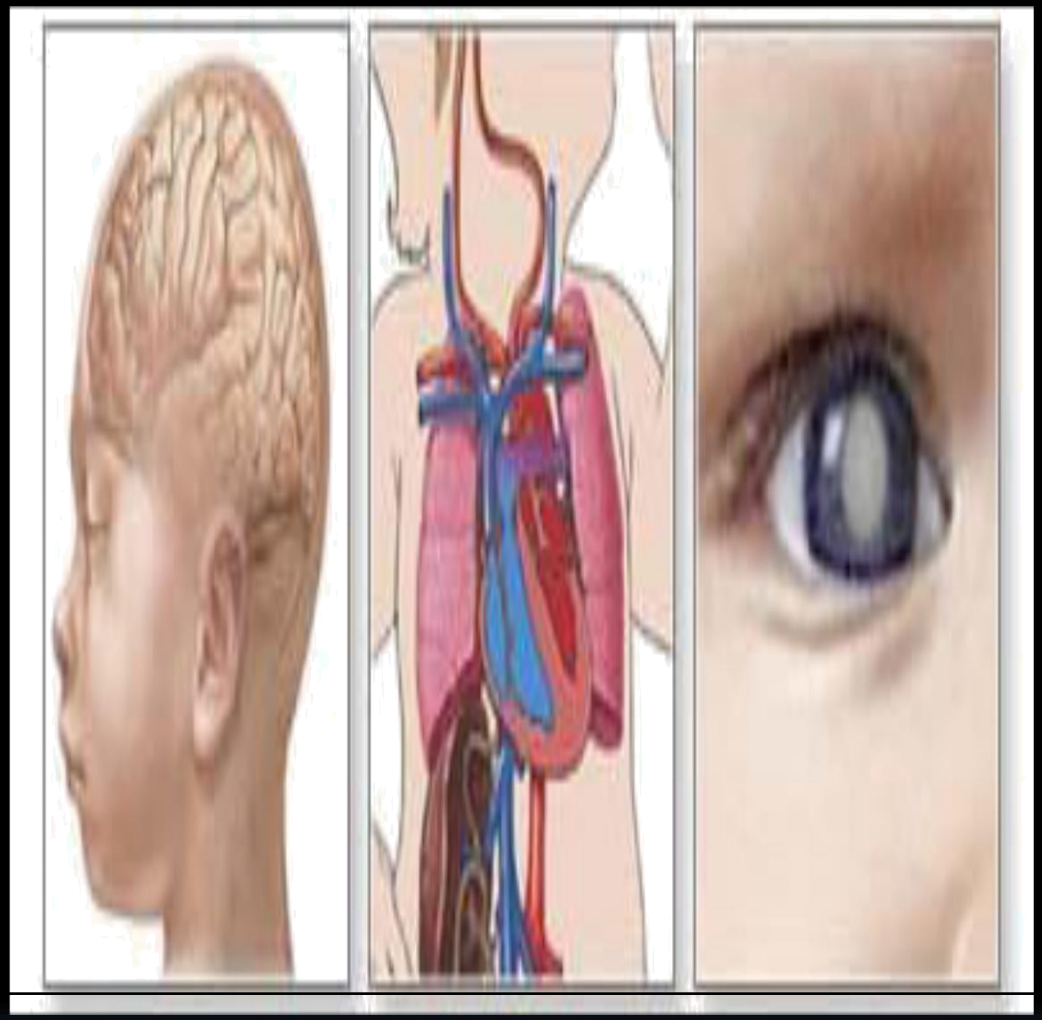
1. Infectious agents

Most are pyrogenic: elevates body temperature

- Rubella Virus (German measles)
- Cytomegalovirus (CMV)
- Herpes Simplex Virus (HSV)
- Varicella virus (Chickenpox)
- HIV
- Toxoplasma gondii (parasitic disease)
- Congenital Syphilis

a) Rubella Virus

- Infective teratogen.
- Approximately 20% risk.
- Vaccine
- Congenital rubella syndrome (CRS)
  - Cataract, glaucoma
  - Cardiac defects
  - Deafness
  - Tooth abnormalities

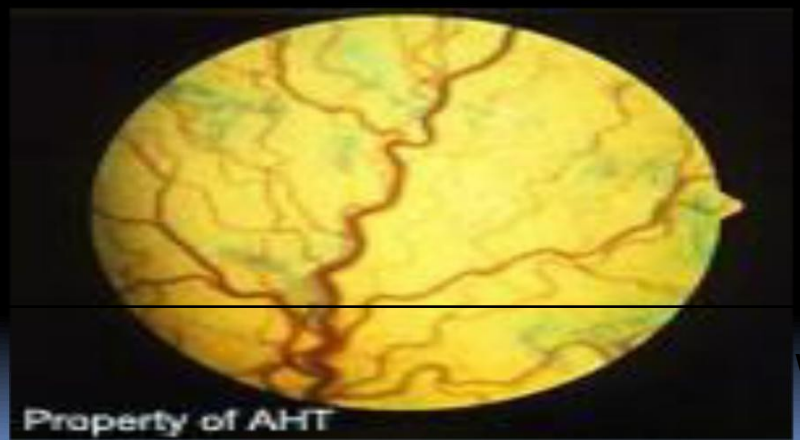


b) Herpes Simplex Virus

Increased rate of abortion (3 fold)

Higher rate of prematurity

- Microcephaly
- Microphthalmia
- Retinal dysplasia.



c) Varicella Virus (Chickenpox)

- Muscle atrophy
- Hypoplasia of the Limbs
- Mental retardation.

FIGURE 4: Icthyosiform plaque in left armpit and bone deformities on ipsilateral limbs

d) HIV

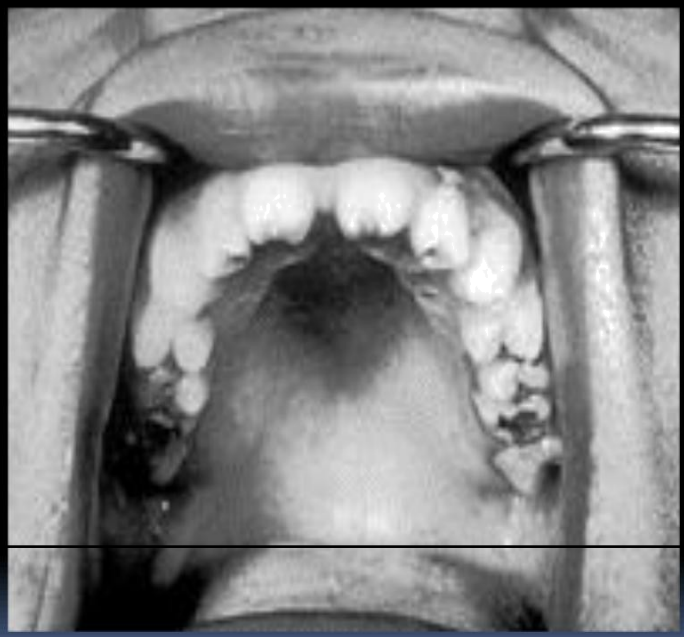
- Growth retardation
- Microcephaly

e) Toxoplasmosis (Toxoplasmosis gondii-a protozoan parasite)

- Hydrocephalus
- Cerebral calcifications
- Microphthalmia
- Chorioretinitis

f) Congenital Syphilis

- Early fetal manifestations:
  - deafness
  - mental retardation
- Late fetal manifestations of untreated congenital syphilis:
  - Abnormal facies (frontal bossing, saddlenose, poorly developed **maxilla).**
  - Destructive lesions of the palate and nasal septum,
  - Hutchinson teeth - (incisors centrally notched, widely spaced)



2. Physical agents

- Radiation (X rays/ ionizing radiations: kills rapidly proliferating cells, mutagenic agent) --- microcephaly, spina bifida, cleft palate, limb defects

- Hyperthermia --- Anencephaly, spina bifida, mental retardation, cleft palate, cleft lip and limb defects - hot bath, sauna

3. Chemical agents / drugs

- Known teratogens
- Possible teratogens

Known teratogenic drugs

- Androgens
- ACE inhibitors
- Antineoplastic agents)
- Anti-epileptic drugs:
  Carbamazepine,
  Phenytoin, Valproic acid
- Cocaine(social drug)
- Coumarins (warfarin)
- Diethylstilboestrol
- Fluconazole (high-dose)
- Ethanol
- Lithium
- Methimazole
- Penicillamine
- Retinoids; isotretinoin,
- Thalidomide
- Tetracyclines

Possible teratogens

- Cigarette smoking
- Colchicine
- Disulfiram
- Ergotamine
- Ethanol
- Glucocorticoids
- Primidone
- Pseudoephedrine
- Streptomycin
- Trimethoprim
- Vitamin A (> 25,000 U/day)
- Zidovudine

Thalidomide (1957-1961)
Sedative & anti nauseant

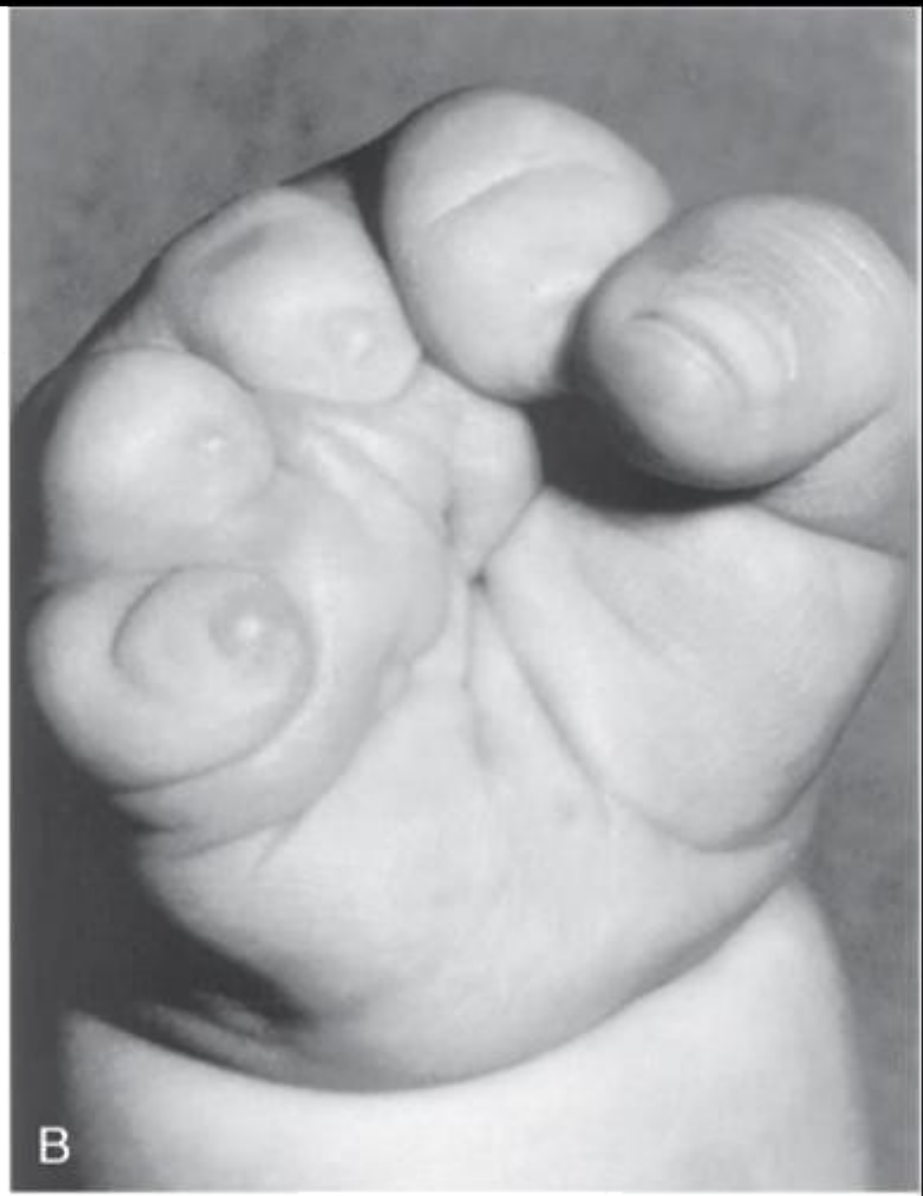
- Critical Periods:
  - 21-22 days: absent external ears, cranial nerve disorders
  - 24-27 days: phocomelia (especially arms)
  - 27-28 days: phocomelia (especially lower limbs)
  - 34-36 days: hypoplastic thumbs, anorectal stenosis
- Withdrawn in 1961; no new cases of these defects

Antiepileptics (diphenylehydantoin i.e Dilantin,valproic acid and trimethadione)

Trimethadione & fetal hydantoin syndromes

- Characteristic dysmorphogenesis
- Facial clefts -- common
- Microcephaly
- Nail dysplasia
- Developmental delay

VALPROIC ACID---- Neural tube defects



Anticoagulants

- All anticoagulants except heparin.
- Warfarin is definitely a teratogen.
  - Hypoplasia of Nasal Cartilage
  - Stippled Epiphyses
  - Various CNS Defects

Tetracyclines

Maternal IV use in pregnancy:

- Acute fatty liver,
- Hepatotoxicity
- Stained decidual teeth
- Under developed enamel
- Heart defects, club foot

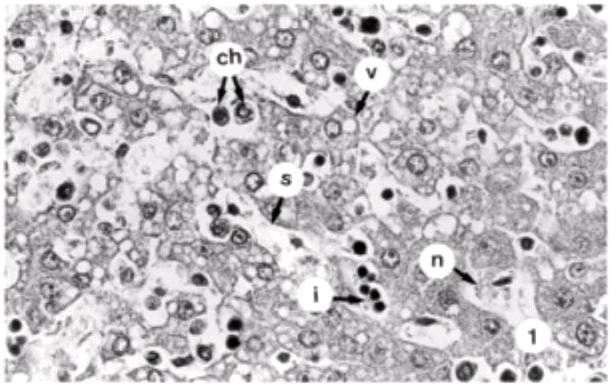


Figure 1- Liver: Newborn - treated – 100mg/Kg – vacuolization in the epatocytes (v), dilated sinusoids (s), focis of necrosis (n), focis of inflammation (i) and focis of ematopoiesis cells (c). HE 630X

Angiotensin-converting enzyme (ACE)inhibitors

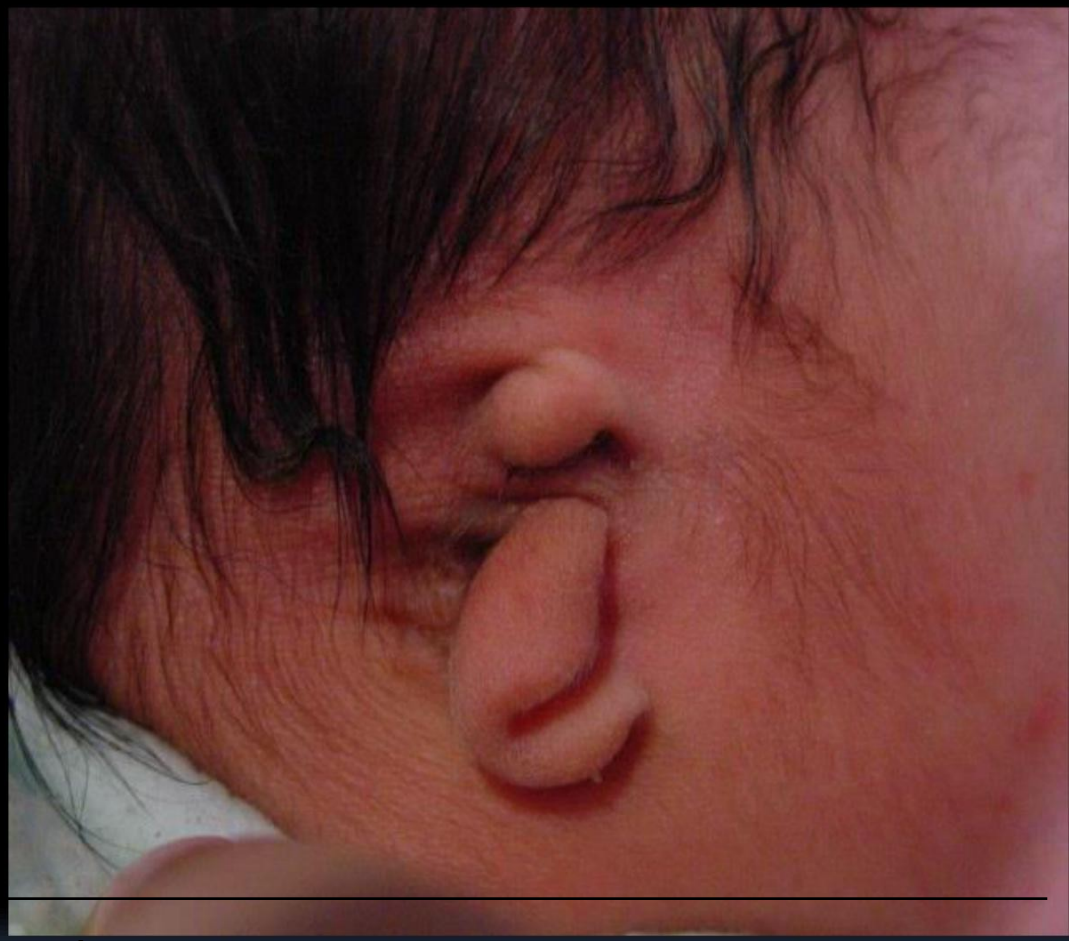
- Oligohydramnios
- Hypoplasia of the skull bones
- IUGR
- Renal dysfunction
- Fetal death

Insulin and Hypoglycemic Drugs

- Insulin is not teratogenic in human embryos.
- Hypoglycemic drugs (e.g., tolbutamide) have been implicated, but evidence of their teratogenicity is weak.
- The incidence of congenital anomalies (e.g., sacral agenesis) is increased two to three times in the offspring of diabetic mothers.

Retinoic Acid (Vitamin A) vitamin A embryopathy

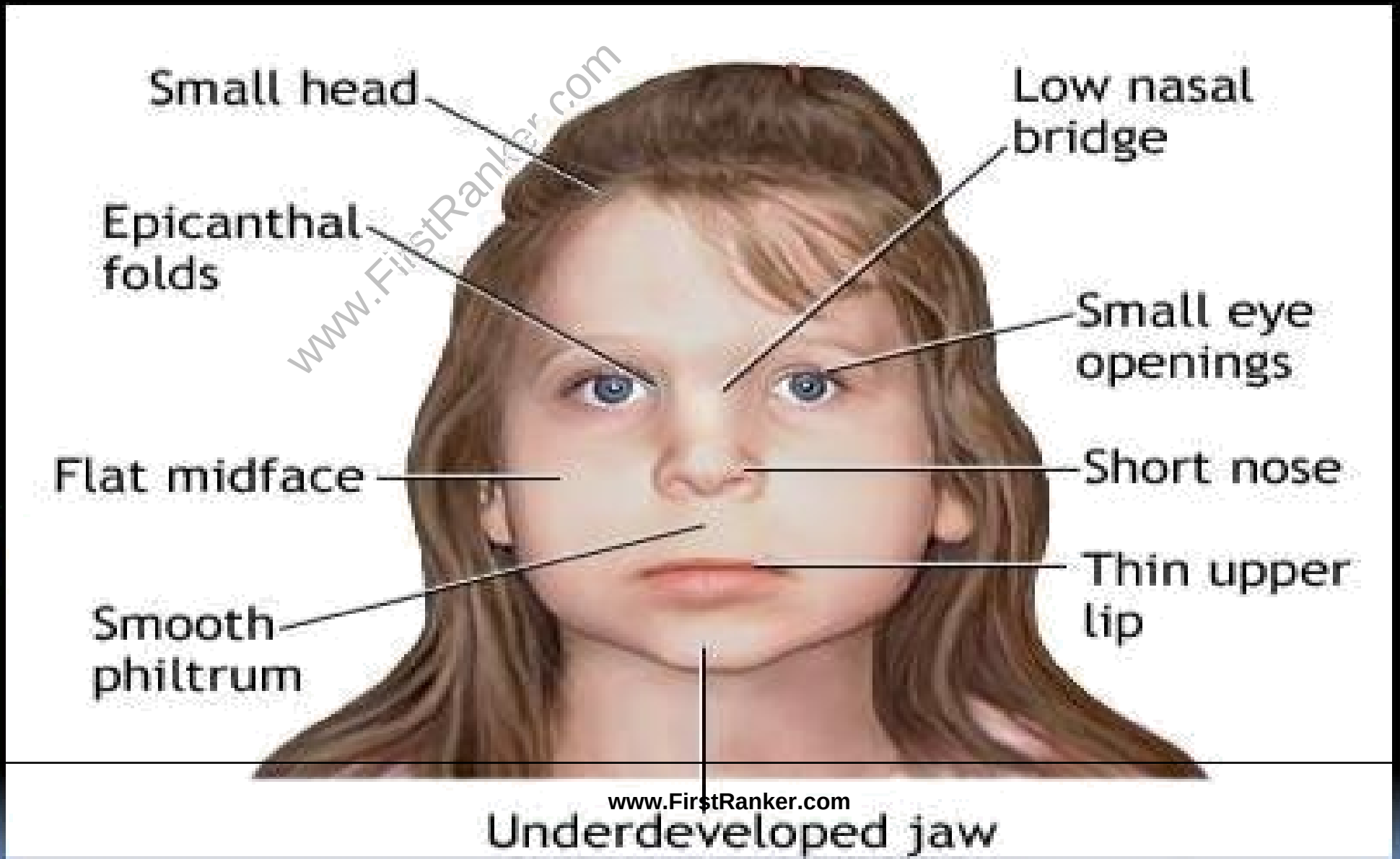
- Isotretinoin (13-cis-retinoic acid), (used for treating severe cystic acne) -- *a known human teratogen*.
- The critical period --- 5 - 7 weeks after the LMP.
- Spontaneous abortion and birth defects --- High.
- Microtia, micrognathia
- Cleft palate and/or thymic aplasia, CVS anomalies, and NTDs.



Fetal Alcohol Syndrome(FAS)

- Severe:
  - Microcephaly
  - Mental retardation (leading cause)
  - Cardiac and renal abnormalities
  - Maxillary hypoplasia
- Mild:
  - Growth retardation
  - Attention deficits with normal intelligence

Fetal Alcohol Syndrome



- **Cocaine**

  causes spontaneous abortion, prematurity, IUGR, microcephaly, cerebral infarction, urogenital anomalies, neurobehavioral disturbances, and neurologic abnormalities.

- **Caffeine**

  not a teratogen

- **Nicotine/cigarette smoking**

  associated with IUGR; behavioral disturbances

5. Hormones

- **Androgenic agents:**

  Synthetic Progestins (ethisterone, norethisterone) to prevent abortion, have androgenic action----- masculinization of female genitalia.

5. Hormones (cont'd)

- **Diethylstilbestrol (DES),** synthetic estrogen, to prevent abortion caused carcinomas of cervix and vagina in women exposed to it in utero.
- **Oral contraceptive pills** (containing estrogen & progestogen) have low teratogenic potential.

5. Hormones (cont'd)

Cortisone

- Causes cleft palate and cardiac defects in susceptible strains of mice and rabbits.
- Low doses of corticosteroids does not induce cleft palate or any other congenital anomaly in human embryos.

6. Maternal disease

- **DIABETES:**
  - Disturbances in carbohydrate metabolism in diabetic mothers during pregnancy--- stillbirths, neonatal deaths, macrosomic babies & congenital malformations (caudal dysgenesis - sirenomelia)
  - Hypoglycemic episodes (even brief) during gastrulation & neurulation --- teratogenic
  - Oral hypoglycaemic agents (Sulfonylureas & biguanides) ---- teratogenic

6. Maternal disease (cont'd)

- **PHENYLKETONURIA:**
  - **Phenylketonuria** (**PKU**) is an autosomal recessive metabolic genetic disorder characterized by a deficiency in the hepatic enzyme phenylalanine hydroxylase. This enzyme is necessary to metabolize the amino acid phenylalanine to the amino acid tyrosine. When PAH is deficient, phenylalanine accumulates and is converted into phenylpyruvate (phenylketone), which is detected in the urine.

7. Heavy metals

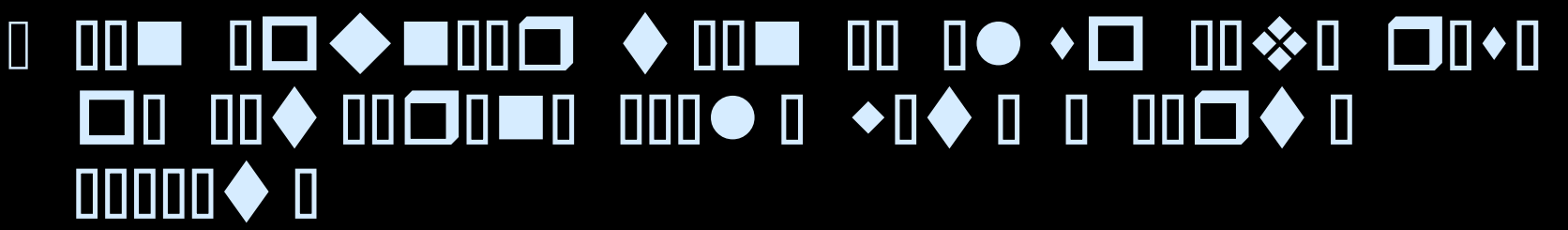
- **Organic Mercury** ---- multiple neurological symptoms
- **Lead** ---- increased abortions, growth retardation, neurological disorders.

8. Hypoxia

- Induces congenital malformations in animals.
- Evidence of congenital malformations in humans needs to be explored

Male mediated teratogenesis

- Exposures to chemicals & radiation can cause mutations in male germ cells ------- spontaneous abortions, LBW & birth defects.
- Advanced paternal age ---- increased risk of limb & NTDs & DOWN syndrome.



THANK YOU