Drugs & teratogenic agents in pregnancy

By

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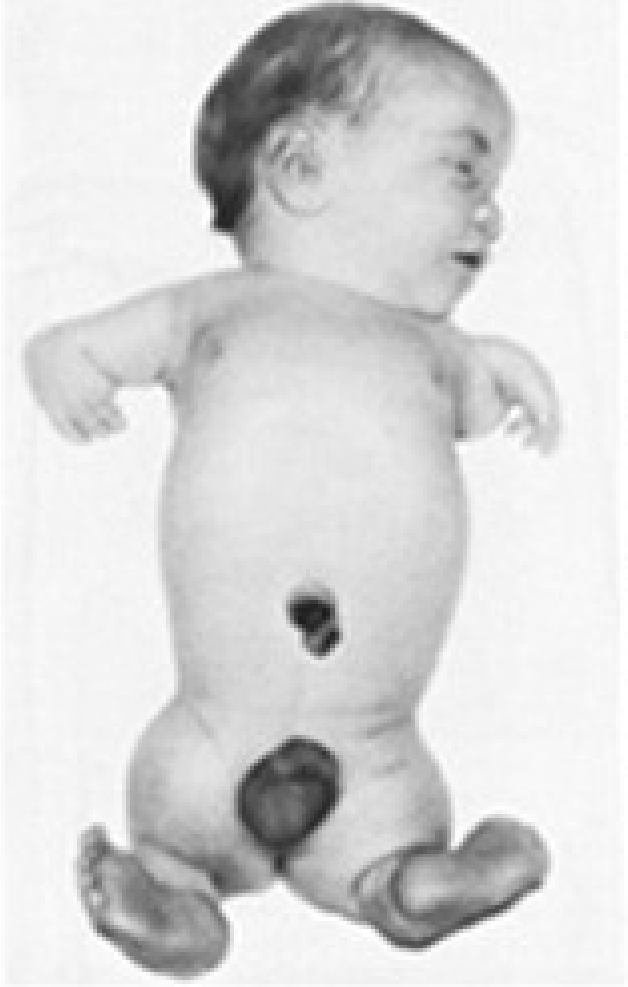
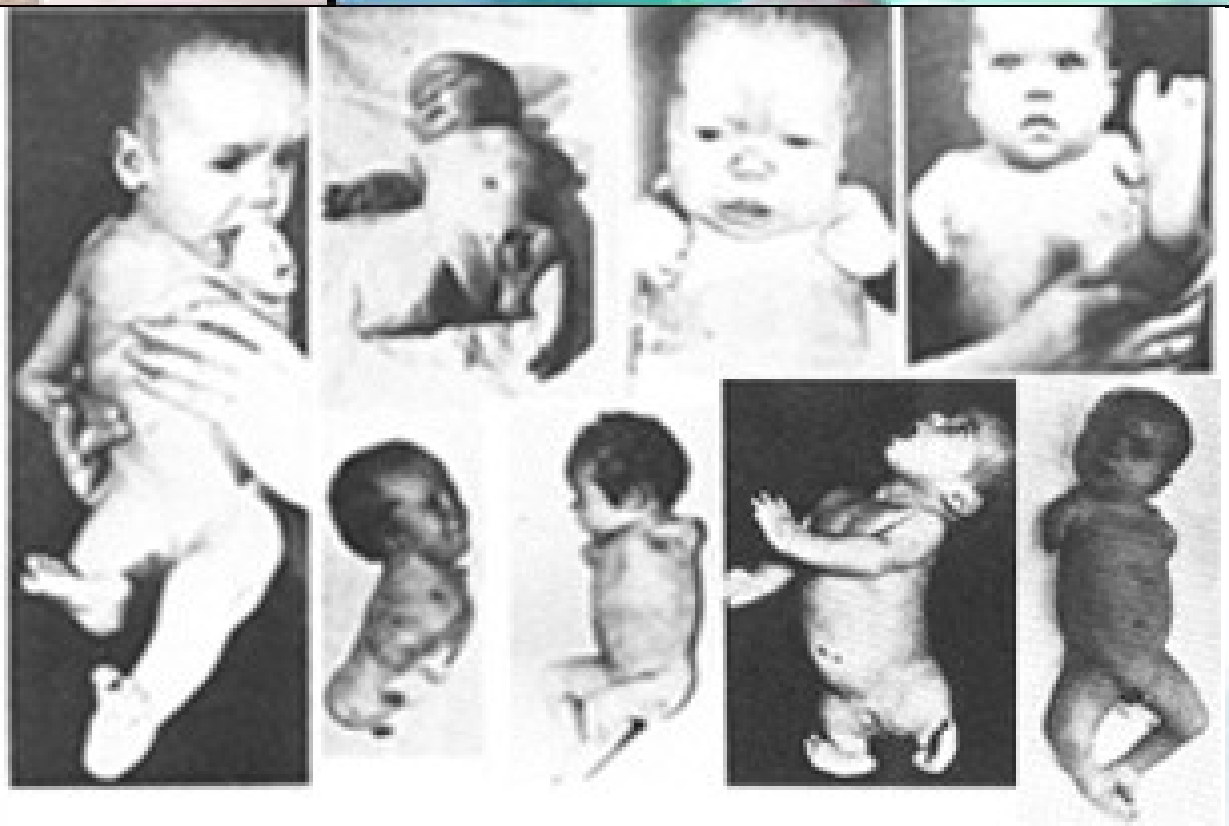
- The terms teratology and teratogen are derived from the Greek word *teratos* that means monster
- *Teratology* is the science that studies the causes, mechanisms, and patterns of abnormal development.
- A *teratogen* is any agent that acts during embryonic or fetal development to produce a permanent alteration of form or function.
- Developmental disorders present at birth are called congenital anomalies, birth defect or congenital malformation.





Malformations due to maternal ingestion of thalidomide (Schardein 1982 and Moore 1993).

Factors That Determine the Effects of Teratogens

1-Dose reaching fetus

2-Time of drug exposure

3-Duration of exposure

4-Environmentall factors e.g age or disease of the mother


Sensitivity to Teratogens according to the stage of development:

The attack by the teratogen could be at any stage of development as follows

1-Pre-implantation Stage *(All or Non)*

From fertilization till implantation

During this stage agents either kill the embryo (embryolethality), or have no effect (i.e. in both cases there is NO teratogenicity) .


2-Embryonic Stage: *(stage of organogenesis)*

from the 3rd to the 8th week of gestation .

*6-7 days after gestation ,implantation occurs followed by gastrulation (formation of ectoderm, mesoderm & endoderm). It is characterized by differentiation and organization. During this stage, the embryo is highly susceptible to teratogens, it produce major morphological changes.

3-Fetal Stage: *(stage of histogenesis)*

It is characterized by growth and functional maturation. During this stage, the fetus is less sensitive to morphologic changes; however minor structural deviation is possible. The teratogen affects mainly growth or functional aspects (e.g. intelligence, reproduction)

FDA Classifications of Drug Risk:

Animal studies cannot be true predictors of teratogenicity due to wide inter- and intra-species variations in the pharmacokinetic properties of drugs, including placental transfer.

Only controlled epidemiological studies can detect a relationship between environmental factors such as drug exposure and pregnancy outcomes.

Drug Risk Categories

Category A:

No fetal risk shown in controlled human studies. Only few drugs, e.g. some vitamin preparations.

Category B:

Animal studies showed no fetal risk, but there are no human studies (OR) adverse effects are demonstrated in animals, but not confirmed in well-controlled human studies e.g. penicillin.

Category C:

There are no adequate studies either animal or human (OR) there are adverse fetal effects in animal studies but no available human data. Many medications taken during pregnancy are in this category.

Drug Risk Categories

Category D:

There is evidence of fetal risk, but benefits are thought to outweight these risks. e.g. carbamazepine phenytoin.

Category X:

Proven fetal risks clearly outweight any benefits, e.g. the acne preparation isotretinoin.


Known teratogens and their effects

- **Aminoglycosides (C) (high dose)……Cranial nerve damage**
- **Androgens (X)…….....Masculinization of female fetus**
- **ACE inhibitors (D)…….....…Renal tubular dysplasia**
- **Antineoplastics (D)**

alkylating agents…… Growth retardation, cleft palate

antimetabolite agents…….. Growth retardation, malformation of ear, eye, nose, cleft palate, malformation of extremities, fingers, brain, skull.

- **Iodides (D)…….Goiter, fetal hypothyroidism**


Known teratogens and their effects

- Lithium (D)……Ebstein's anomaly (tricuspid valve defect)

-Tetracyclines (D)……Weakend fetal bone and, permanent tooth discoloration

-Thalidomide (X) :

- a sedative non-nausiating non-barbiturate
- greatest danger during days 34-56 of pregnancy
-phocomelia and amelia
- deafness ,anomalies of teeth, eyes, intestines, heart, kidney


Mechanism of action of teratogens:

1-Interference with nucleic acids: ***(replication , transcription or RNA translation)***

* ***The antimetabolite : methotrexate.***
* ***alkylating agents : Chlorambucil, cyclophosphamide.***
* ***Active metabolites of Thalidomide***

2- Inhibition of enzymes :

* **Methotrexate (dihydrofolate reductase inhbitor = DHFRI) prevents formation of folinic acid from folic acid which is essential for embryo.**
* **5- flurouracil inhibits thymidylate synthase leading to inhibition of deoxythymidine monophosphate(DTMP) synthesis inhibition of DNA synthesis.**
* **6- aminonicotinamide (G6PD inhibitor) decrease energy production.**


Mechanism of action of teratogens:

3- Deficiency of energy supply needed to build organs :

a- Glucose deficiency :

- Deficiency of glucose in diet
- G6PD inhibitors (6- aminonicotinamide) interfere with glycolysis.
- Drugs affecting Kreb's cycle (fluroacetate)

Interference with O2 s supply or utilization:

b- Interference with internal respiration :

- CN toxicity : cytochrome oxidase inhibitor.

c- Hypoxia:

-CO toxicity (Decrease in both O2 delivery + osmotic pressure to fetus)

- Drug induced (phenytoin).

Mechanism of action of teratogens:

4-Lack of substrates:

Decrease of vitamines or minerals intake.

5- Genetic mutation :

X-ray ,atomic explosion & radiations causing DNA damage, mutation & congenital abnormalities.

E.g.: Achondroplasia. It is characterized by congenital abnormality in ossification of cartilage. Features include :

*** Dwarfism- microcephaly (small head)**

***Kyphosis (arched back)- Polydactylia (6 or more fingers in one hand)**


Mechanism of action of teratogens:

6- Chromosomal aberrations :

A-Numerical abnormalities:

***Aneuploidy** : loss or gain in chromosomes.

-Monosomy = single chromosome instead of a pair

-Trisomy = 3 chromosomes instead of a pair

*** Polyploidy** : when a complete set of chromosomes is gained.

B- Structural abnormalities :


Types of teratogens:

1- pollution

a) physical

Atomic and nuclear explosions e.g.: Hiroshima & Nagasakia.

b) chemical

*lead:

from water pipes, or car exhaust: (miscarriage, stillbirth, and increased mortality rate during the 1st year of life).

*Carbon monoxide CO :

from cigarette smoking, car exhaust, and incomplete combustion of coal. It binds to Hb decreasing O_2 supply to fetus: (spontaneous abortion, stillbirth, growth retardation, premature labor).

Types of teratogens:

1- pollution

**Vinyl chloride:*

Sperm damage (working in vinyl industry, their babies may be malformed) .

**Mercury :*

Eating contaminated fish, the pregnant women gave birth to malformed & mentally retarded babies .


Types of teratogens:

2- infections:

a-Viral :

-German measles (Rubella) : deafness, blindness, cataract, retinopathy, glaucoma, microcephaly, mental retardation . Attenuated virus causes damage to the fetus, so give vaccine before pregnancy by three months

-Hepatitis, small pox, chicken pox : may cause abortion, stillbirth, skin diseases, hepatitis … etc .

Types of teratogens:

2- infections:

b-bacterial :

Syphilis: hydrocephalus & mental retardation, deafness, tooth malformation, meningitis & CNS disturbances .

c-protozoal :

Toxoplasmosis: causing hydrocephalus, microcephaly, hepatosplenomegaly & blindness .

Types of teratogens:

3-Alcohol :

Fetal Alcohol syndrome: delayed development, microcephaly & mental retardation , defects in the eye, face (cleft palate) , congental abnormalities in heart, skin & kidneys .


Types of teratogens:

4- Malnutrition :

Vit. A anophthalmia .

Vit. D bone and teeth malformation .

Folic acid malformations .

Minerals as iron (anemia), Ca 2+ (bone malformation)& K+ (pre-term labour).

5- Drugs:

THANK YOU