

Genetics

Biology Dept.3rd stage

Asst. Professor. Dr. Kazhal M. Sulaiman

Lec-13- Teratogenesis

1. Teratogenesis: the formation of an abnormal embryo.
2. Teratology: that aspect of embryology involved with the study of abnormal development.
3. Teratogen: any agent which overtly causes the production of a congenital malformation or which increase the incidence of a particular CD.

:(A teratogen (terat = monster or ugly animal)

It is a substance that alters embryonic or fetal development resulting in structural or functional alterations.

Teratogenic agents

Teratogenic agents can be divided into two categories, environmental or genetic, based on their etiology. Each category of agents utilizes different pathological .processes that result in embryopathology

Genetic Teratogenic Agents

About 20-25% of human malformations observed in the first year of life are caused by genetic agents. Birth defects caused by these teratogenic agents have a range of pathological processes that are determined prior to conception, due to the presence of inherited or newly acquired genetic abnormalities. The causal mechanisms underlying these processes include, but are not limited to: gene deficiency, gene abnormality, chromosome rearrangement, chromosome deletion and chromosome

Genetics

Biology Dept.3rd stage

Asst. Professor. Dr. Kazhal M. Sulaiman

excess. Although environmental factors may modify the development of the genetically abnormal embryo, the genetic abnormality is the major contributor to the pathologic process.

Environmental Teratogenic Agents

Approximately 10% of human malformations observed in the first year of life are caused by environmental agents, which have several characteristics in common.

•**Stage sensitivity**- There are three defined stages of human embryonic development which are divided into fertilization & implantation, organogenesis and fetal period. The susceptibility of the embryo as well as the degree of the adverse effect caused by the agent depends on the stage at which the exposure occurred.

•**Dose response relationships**- There exists a quantitative correlation between the magnitude of embryopathic effects and the dose of the teratogenic agent, such that the higher the dose, the more severe the teratogenic effect.

•**Genetic variability**- There are differences in the placental transport, metabolism, absorption and distribution of an agent in mammals and these differences must be accounted for when extrapolating data between different species.

- Dose reaching fetus
- Time of drug exposure
- Duration of exposure
- Environmental factors e.g age or disease of the mother

Genetics

Biology Dept.3rd stage

Asst. Professor. Dr. Kazhal M. Sulaiman

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 inhibitor = DHFRI) prevents formation of folinic acid from folic acid which is essential for embryo.

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)*

4-Lack of substrates:

1-**Decrease of vitamins or minerals intake.**

2-**Failure of absorption from GIT as in GIT infection e.g. diarrhea or bile acid deficiency.**

Genetics

Biology Dept.3rd stage

Asst. Professor. Dr. Kazhal M. Sulaiman

5- Genetic mutation :

X-ray ,atomic explosion & radiations 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)- Polydactyilia (6 or more fingers in one hand)

6- Chromosomal aberrations :

The abnormalities may be in number (numerical) or structure (structural)

A-Numerical abnormalities:

Normal no. of chromosomes= 23 pairs. Pairs from 1-22 are called somatic or autosomal chromosomes. Pair 23 is called sex chromosomes (XX=female) & (XY= male) Abnormalities in no. may be called:

*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.

‣The numerical abnormality may be in the autosomes (1st 22 pairs) or in the sex chromosomes (pair no.23)

Genetics

Biology Dept.3rd stage

Asst. Professor. Dr. Kazhal M. Sulaiman

i-Autosomal abnormalities

*Autosomal abnormalities may be caused by X-ray, viruses, F in drinking H₂O ,
maternal diabetes & age*

Trisomy 21 : (Mongolism = Down's syndrome)

It is characterized by mental retardation, heart malformations, susceptibles to infections, acute leukemia & death in childhood.

Trisomy 17& 18 :

mental retardation, defects in heart, ears & finger.

Trisomy 13 : mental retardation & microcephaly.

ii Sex chromosome (genosomal) abnormalities

Turner;s syndrome : (XO)- (Monosomy 23)

B- Structural abnormalities :

In this case the no. is normal, but there may be a breakage or a loss of a part from chromosomes mental retardation or deformity.

E.g.: Cri- du chat syndrome (cat cry syndrome):.

It is characterized by mental retardation & mewling sound crying.

Structural abnormalities may be caused by atomic explosion, radioactive materials,, heavy smoking & viruses.

Genetics

Biology Dept.3rd stage

Asst. Professor. Dr. Kazhal M. Sulaiman

Types of Teratogenes

1- pollution

a) physical

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

b) chemical

*lead (pb²⁺) :

from water pipes, or car exhaust : miscarriage (spontaneous abortion), stillbirth (delivery of a dead baby), 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 O₂ supply to fetus hypoxia spontaneous abortion, stillbirth, growth retardation, premature labor.

Vinyl chloride :

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

*Mercury :

Minamata syndrome : A plastic factory poured its wastes, containing Hg, in Minamata Bay Hg is converted by microorganisms in H₂O to methyl Hg which contaminated fish eating contaminated fish, the pregnant women eating contaminated fish, the pregnant women gave birth to malformed & mentally retarded babies .