Drugs and teratogenic agents in pregnancy

By

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Definitions:

Teratology: is the science that studies the causes, mechanisms, and patterns of abnormal development.

Teratogen: is an agent that acts during embryonic or fetal development to produce a permanent alteration of form or function.

A teratogen may be a drug, chemical agent, an infectious agent or environmental factor. To produce its effect, a teratogen must cross the placenta.

Teratogenic effect is also affected by binding to carrier proteins and metabolism in the placenta.

Many factors may have an influence on the potential teratogenic effect of an agent of interest such as:

*The *dose reaching the fetus*

*D*uration of exposure*

*M*aternal age, her health status*

*The *time of exposure to that agent*, regarding the latter pregnancy is divided into the following periods:

1-Pre-implantation Stage (All or Non): From fertilization till implantation or up to 28 days after the first day of menstruation. 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: from the 3rd to the 8th week of gestation (stage of organogenesis): Implantation occurs followed by formation of ectoderm, mesoderm & endoderm with the differentiation and organization. During this stage, the embryo is highly susceptible to teratogens which can produce major morphological changes.

3-Fetal Stage: 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).

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.

For the purposes of safety and convenience the FDA has introduced classification of drugs and medications to guide physicians putting in mind that a balance should always exist between the risk and benefit and not to deprive pregnant women from essential drugs.

FDA classification of drug risk:

CategoryA:

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

CategoryB:

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

CategoryC:

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. e.g. coriticosteroids.

CategoryD:

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

CategoryX:

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

Mechanisms of action of teratogens:

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

*The antimetabolites: methotrexate.

*Alkylating agents : Chlorambucil, cyclophosphamide.

*Active metabolites of Thalidomide.

2- Inhibition of enzymes:

*Methotrexate a dihydrofolate reductase inhibitor prevents formation of folinic acid from folic acid.

*5- flurouracil inhibits thymidylate synthetase leading to inhibition of DNA synthesis.

3- Deficiency of energy supply needed to build organs:

*Glucose deficiency: G6PD inhibitors (6-aminonicotinamide) which interfere with glycolysis and drugs affecting Kreb's cycle (fluroacetate).

*Interference with O2 supply or utilization: cytochrome oxidase inhibitors.

4- Genetic mutation:

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

5-Lack of substrates:

Decrease of vitamins or minerals intake.

Counseling for teratogen exposure:

--Counseling should include discussion of the possible teratogenic risk of the condition for which the drug is prescribed and its genetic implications which are usually underestimated with overestimation of the possible teratogenic effect of drugs.

Counseling for teratogen exposure:

--women in general have about 3% risk of having a child with a birth defect and through exposure to a confirmed teratogen this increased by 1-2%.

--The concept of risks versus benefits should be introduced (some diseases if un treated may pose serious threat than the theoretical risk resulting from medication exposure).

Known teratogens:

** Drugs:*

Anti concvulsants (carbamazepine, valproic acid and phenytoin "CategoryD"):

These are needed to prevent seizures and if withdrawn recurrence of seizures usually follows. They may result in neural tube defects, orofacial and cardiac anomalies. The risk of teratogenic effect is increased with increasing the number of drugs used and with increasing the serum level.

Anti concvulsants (carbamazepine, valproic acid and phenytoin "CategoryD"):

it is estimated that the risk of fetal anomalies is 5.5%, 11% and 23% when 2, 3 or 4 drugs were used simultaneously. The dose should be carefully diminished to the least possible dose that prevents seizures and if the patient had no seizures in the previous 2 years and her EEG was normal, these can be stopped during pregnancy.

Warfarin "CategoryD"):

About a sixth of exposed pregnancies during the 6^{th}-9^{th} weeks end in abortion or stillbirth and about a sixth result in abnormal live born infant (warfarin embryopathy consisting of nasal, facial, vertebral and femoral deformities). Exposure during the 2^{nd} and 3^{rd} trimesters results CNS dysplasia, optic atrophy and mental retardation.

Androgens "CategoryX":

These may result in virilization of the external genitalia of a female fetus. The most critical period is 7-12 weeks, however partial masculinization and genital ambiguity can develop if exposure occurred between 12-20 weeks. Interestingly late exposure may affect brain receptors and programming of the fetal brain with an impact on gender identity, level of aggression and sexual behavior.

Thalidomide "CategoryX": this is anxiolitic, sedative and antiemetic which was proven to be a strongly teratogenic it produced major anomalies in about 20% in exposed pregnant women mainly phecomelia, amelia and heart defects. Interestingly it caused no congenital malformations in experimental animal studies.

Alcohol "CategoryX"): heavy consumption may result in fetal alcohol syndrome (fetal growth retardation, microcephaly, mental retardation, defects in the face and eyes, renal and cardiac anomalies).

**Ionizing Radiation:*

Exposure to ionizing radiation during pregnancy can result in increased abortion and stillbirth rates and may also result in microcephaly and mental retardation and growth retardation. Doses up to ‘0.56 Gy (5 rads) are allowed and are not teratogenic. Most of the X-ray diagnostic procedures exposes the fetus to amount of radiation less than this allowed dose.

*Infections:

Certain infections are of concern of teratogenicity if caught during pregnancy, notably rubella virus, cytomegalovirus, herpes virus and toxplamosis gondi (TORCH infections). They cause in common similar clinical features; CNS abnormalities, chorioretinitis, osteitis, hepatsplenomegally, cardiac anomalies, deafness and mental retardation

THANK YOU