Teratogenicity of Drugs

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Definitions

- **Congenital malformations = non reversible** functional or morphological defects present at birth.

  - may not be detectable at birth

  - may only become evident later in life.

Teratogenicity

- **Teratogenicity is the presence of major congenital malformations.**
- Major malformations are those that are either life-threatening, require major surgery, or have serious cosmetic effects.
- The more inclusive term of all these major defects is congenital anomalies or "birth defects"

Causes of malformations

- **40% ---------- Unknown**
- **12-25% ----------Genetic defects(Down's syndrome is the most common of this group)**
- **20% ----------Interactions between hereditary factors and environmental factors**

- ***5%* - 9% ----------Environmental factors such as maternal disease or infection, chemicals, X-ray and drugs**

Environmental factors

- Maternal disease such as diabetes and seizure disorders.
- Infections such as rubella (German measles), cytomegalovirus, and Toxoplasma gondii (a protozoan).

  Maternal rubella can result in a group of defects, including heart disease, cataracts and deafness, known as fetal rubella syndrome.
- chemicals and drugs: Only a small portion are due to drugs acting as teratogens.

The Risk of Teratogenicity

- **There is no way to predict** drug exposures that result in teratogenesis.
- The effects of many drugs on animal development are not applicable to human pregnancies.
- Several factors determine the teratogenic effects of drugs on the fetus during pregnancy

Factors That Determine the Effects of Teratogens

- Dose reaching fetus
- Point in development when drug exposure occurs
- Duration of exposure
- Environmental factors e.g age or disease of the mother
- Susceptibility of the fetus

The duration of exposure and gestational age at exposure

- These are very critical in the determination of teratogenic potential.
- During the period from conception to implantation (2 weeks), there is a relative resistance to drug effects.

  Exposure during this time produces an "all or none" effect (zygote dies or it is unaffected).

Organogenesis

- Weeks 4 through 10, the period referred to as organogenesis:

  -The remainder of the first trimester

  -The most critical time for organ malformation

  -Unfortunately, this is also a time when many women are unaware of their pregnancy.

- Drugs that reach the embryo at this point may produce abortion, no effect at all, an anatomic defect (teratogenesis), or a metabolic or functional defect that may not be detected until later in life.

Fetal stage (Fetogenesis)

- During the second and third trimester,
  - known as fetogenesis,
  - Drugs are not associated with major malformations, but they may influence neurologic development, growth, physiologic and biochemical functioning, mental development, and reproduction.
- **Little is known about the exact time of the greatest risk for teratogenesis. An exception is thalidomide, which has been shown most harmful during days 34- 56 of gestation.**

Teratogenic Effects

- Some drugs cause a group of effects specific for exposure to that agent.
- These congenital anomalies are named after the drug known to cause them:

"fetal alcohol syndrome"

"fetal warfarin syndrome" or

"fetal hydantoin syndrome."

Fetal alcohol syndrome (D)

Presence of several of the following:

- prenatal and postnatal growth retardation, mental retardation, poor coordination, hypotonia, hyperactivity, microcephaly, short upturned nose, micrognathia or retrognathia in infancy, short palpebral fissures, hypoplastic philtrum, thinned upper lips,

and, less frequently, anomalies of the eyes, mouth, heart, kidneys, gonads, skin, muscle, and joints.'"

- This group of defects is seen in mothers with high-dose alcohol intake during their pregnancies.

Fetal warfarin syndrome(D)

- The anomalies include: nasal hypoplasia, depressed bridge of nose, and bone stippling on x-ray (seen with first trimester exposure).
- A distinctly different pattern is seen with second- and third-trimester exposure to coumarins, featuring optic atrophy, cataracts, mental retardation, microcephaly, microphthalmia, deafness, growth retardation, scoliosis (curvature of the spine), seizures and hemorrhage.

Known teratogens and their effects

- **Aminoglycosides** (C) (high dose)
  VIII cranial nerve damage

Androgens (X)
Masculinization of female fetus

ACE inhibitors (D)
Renal tubular dysplasia, skull hypoplasia oligohydramnios, pulmonary hypoplasia

- **Antineoplastics** (D)

  - **alkylating agents**

    Growth retardation, cleft palate, microphthalmia, cloudy cornea, agenesis of kidney, cardiac defects

  - **antimetabolite agents**

    Growth retardation, malformation of ear, eye, nose, cleft palate, malformation of extremities, fingers, brain, skull

- **Carbamazepine (C)**

  Craniofacial abnormalities, growth retardation, neural tube defects, fingernail hypoplasia
- **Cocaine (C)**

  Premature birth, abruptio placentae, perinatal morbidity, growth retardation, in utero stroke, bowel atresias, defects of genitourinary system, heart, limb, face

- Iodides (D)

  Goiter, fetal hypothyroidism
- Lithium (D)

  Ebstein's anomaly (tricuspid valve defect), other cardiac defects
- Tetracyclines (D)

  Weakend fetal bone and tooth enamel dysplasia, permanent tooth discoloration

- **Retinoids (X)-----**isotretinoin, etretinate

  heart defect, spontaneous abortion, microtia (small external ears), microcephalus, hydrocephalus, cognitive defects
- **Thalidomide (X)---**the first known drug teratogen

  - 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

- **Valproic acid (D)**

  SP1NA BIFIDA (neural tube defect), facial anomalies, slow development
- **Vitamin A** (>18000-25000 IU/day) (X)

  Microtia, craniofacial, CNS and cardiac anomalies, bowel atresia, limb reductions, urinary tract defects

FDA Classifications of Drug Risk

- Animal studies cannot be true predictors of teratogenicity due to wide inter- and intraspecies 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 Category**

  A----No fetal risk shown in controlled human studies in all trimesters. Possibility of harm to fetus is remote.

  B----Animal studies show a risk that is not confirmed in human studies during all trimesters.

  C----Fetal risk shown in controlled animal studies but no controlled human studies are available OR studies in humans and animals are not available. Drugs only given if the potential benefit outweighs the potential risk to the fetus

- **D----Studies show fetal risk in humans**
  (Use of drug may be acceptable even with risks, such as in life-threatening illness or where safer drugs cannot be used or are ineffective)

  X----Risk to fetus clearly outweighs any benefits from these drugs
  The drug is contraindicated in women who are or may become pregnant.


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