TERATOLOGY

2010
Teratology

- Teratology is the science that studies the causes, mechanisms, and patterns of abnormal development.
- Developmental disorders present at birth are called congenital anomalies, birth defect or congenital malformation.
- Congenital anomalies are of four clinically significant types: malformation, disruption, deformation and dysplasia.
Malformation - definition

- Congenital malformation are structural defects present at birth. They may be gross or microscopic, on the surface of the body or within it, familiar or sporadic, hereditary or nonhereditary, single or multiple. (Warkany 1947)

- A major congenital anomaly is one that is incompatible with survival, is life-threatening, or seriously compromises an individual’s capacity to function normally in society (Otake et al. 1990)
Teratology - terms

- **Malformation** is a primary structural defect resulting from a localized error of morphogenesis.
- **Disruption** is a specific abnormality that results from disruption of normal developmental processes. It depends on time, not on agent.
- **Deformation** is an alteration in shape/structure of previously normally formed part.
- **Syndrome** is a recognized pattern of malformations with a given etiology.
Birth defects

- 3% of all live-born infants have a major anomaly
- Additional anomalies are detected during postnatal life – about 6% at 2 year-olds, 8% in 5 year-olds, other 2% later
- Single minor anomalies are present in about 14% of newborns
Birth defects

- Major anomalies are more common in early embryos (up to 15%) than they are in newborns (3%). Most severely malformed embryos are spontaneously aborted during first 6 to 8 weeks.
Causes of congenital anomalies

Figure 9-1. Graphic illustration of the causes of human congenital anomalies. Note that the causes of most anomalies are unknown and that 20 to 25% of them are caused by a combination of genetic and environmental factors (multifactorial inheritance).
Anomalies caused by genetic factors

- Chromosomal aberrations are common and are present in 6 to 7% of zygotes – (result = abort)
- Numerical chromosomal abnormalities – usually non-disjunction - error in cell division
  - Down syndrome (21) Edwards (18) Patau (13)
  - Turner (X0), Klinefelter (XXY)
- Structural chromosomal abnormalities – chromosome breaks = translocation, deletion (cri du chat syndrome), duplication, inversion.
- Mutant genes – achondroplasia, fragile-X syndrome
Down syndrome
Teratogen

- Teratogenesis is a process with threshold-level effect.
- Every chemical substance may be a teratogen. This effect depends on quantity. In small amounts, it is without any effect.
- Teratogen is a factor that is present in the environment in such high amounts that it can increase the occurrence of embryotoxicity manifestation up to the basic frequency in the non-exposed population.
- Teratogenicity is a manifestation of developmental toxicity representing a particular case of embryo/fetotoxicity, by the induction or the increase of frequency of structural disorders in the progeny.
Basic principles in teratogenesis

- Critical periods of development
- Dosage of the drug or chemical
- Genotype (genetic constitution) of the embryo and mother
Critical and sensitive periods of development
Figure 9-12. Schematic illustration of critical periods in human prenatal development. During the first 2 weeks of development, the embryo is usually not susceptible to teratogens; a teratogen either damages all or most of the cells, resulting in death of the embryo, or damages only a few cells, allowing the conceptus to recover and the embryo to develop without birth defects. Meave denotes highly sensitive periods when major defects may be produced (e.g., amelia, absence of limbs). Green indicates stages that are less sensitive to teratogens when minor defects may be induced (e.g., hypoplastic thumbs).
Dose-response relation in teratology

- A - afflicted
- B - malformed
Course of losses

![Graph showing the course of losses over time, with a decreasing curve indicating the percentage change over weeks. The graph includes error bars indicating variability at different time points.](image)
Consequences of exposure to teratogens

- Death – abortion or miscarriage
- Malformation
- IUGR – intrauterine growth retardation
- Functional defects in the newborn
- Normal newborn
Anomalies caused by environmental factors

- **Teratogens** are exogenous agents that may cause developmental defects:
  - *Drugs* (warfarin, valproic acid, phenytoin, vitamin A, thalidomide, cytostatic drugs – cyclophosphamide, lithium carbonate)
  - *Chemicals* (PCBs, methylmercury, alcohols)
  - *Infections* (rubella, cytomegalovirus, herpes virus, toxoplasma, syphilis)
  - *Ionizing radiation* (X-rays)
  - *Maternal factors* (diabetes mellitus, hyperthermia, phenylketonuria, hyper-/hypo-thyreosis)
Thalidomide

- Firm Gruenewald brought it on market in 1957
- 1958-1961 cases of irreversibile polyneuropathia
- W.Lenz (1961) reports on accumulation of specific malformations (focomelia)
- Thalidomide was gone out of market
- 8000 -12000 malformed newborns
- Critical period 38. – 50. day after ovulation
- Risk 1-2:10 if exposed during critical period
  - ie. 20% risk.
- It probably blocks the expression of growth factors (IGF1,FG2,integrins) and formation of vessels
Testing for teratogenicity

- Standardized procedures for testing drugs for teratogenic potential are used.
- They use at least two common mammalian laboratory species that are given several different doses of the test agent once or several successive days during organogenesis and early fetal period.
- Conventionally 3 doses are administered; the highest causing maternal toxicity.
- Evaluation of human case reports and epidemiological investigation (retrospective and prospective).
Labeling of some prescription drugs includes information about the level of risk for the fetus and the extent of caution necessary in their use. The FDA has established five categories (A, B, C, D, and X) to indicate a drug's potential for causing teratogenicity. This format was first announced in the September 1979 FDA Drug Bulletin. Because of labeling revisions, many products now use this format.

A similar, but somewhat expanded, classification system was adopted by the Australian Drug Evaluation Committee (ADEC) in 1989. Germany set forth its own classification system.
US FDA Pregnancy Category Definitions

- **A** - Adequate, well-controlled studies in pregnant women fail to demonstrate a risk to the fetus in the first (second, third, or all) trimester(s), and the possibility of fetal harm appears remote.

- **B** - Animal studies do not indicate a risk to the fetus; however, there are no adequate, well-controlled studies in pregnant women. OR Animal studies have shown an adverse effect on the fetus but adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus. Despite the animal findings, the possibility of fetal harm appears remote, if used during pregnancy.

- **C** - Animal studies have shown that the drug exerts teratogenic or embryocidal effects, and there are no adequate, well-controlled studies in pregnant women, OR No studies are available in either animals or pregnant women.

- **D** - Positive evidence of human fetal risk exists, but benefits in certain situations (e.g., life-threatening situations or serious diseases for which safer drugs cannot be used or are ineffective) may make use of the drug acceptable despite its risks.

- **X** - Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on human experience, or both, and the risk clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.
Drug classification by risk factors

- The rating according to FDA classification does not provide sufficient useful therapeutic guidance.
- The characterization of different categories of drugs are ambiguous and difficult to evaluate whether reader is physician.
- The anxiety may even lead to unnecessary termination of pregnancy.
Drugs

QUALITY OF DATA

Proportion

None
Very Poor
Poor
Very limited
Limited
Poor to fair
Limited to fair
Fair
Fair to good
Good
Good to excellent
Excellent

90%

n=2240

1%
About 80% pregnant women use prescribed or over-the-counter drugs.

The drugs should only be taken when essential thereby avoiding unnecessary and unknown risks.

The same is obviously applied to social drugs like tobacco, alcohol and additive drugs.
Surveillance and monitoring

- EUROCAT (European Concerted Action on Congenital Abnormalities and Multiple Births – 1979)
ENTIS

In 1990, two networks of Teratology Information Services were established, OTIS (USA and Canada) and ENTIS (Europe).

- They provide information relating to the pertinent situation of the person involved.
- They carry out follow-up studies to learn about what happened during the course of pregnancy and health of the newborn.
Recommendation

- Disease have to be treated in all cases! Disease without treatment is more risky than appropriate treatment.
- We should use drugs with well-known effect on pregnancy without signs of embryotoxicity. It is not recommended to change quickly a lot of drugs.
- It is not recommended to use combinations of various drugs. Undesirable effects may be multiplied.
- Any woman in reproductive age may be pregnant!!
Drugs classified X according to FDA:

- Thalidomide
- Cytostatics
- Warfarin and other coumarin derivatives
- Anti-epileptic drugs
- Retinoids
- Alcohol
- Androgens
- ACE inhibitors
- Diethistilbestrol
Fetal valproate syndrome

- epicanthal folds
- short nose
- anteverted nostrils
- long philtrum
- small mouth
Fetal alcoholic syndrome
Embryopathy caused by retinoid acid

Alterations due to fetal exposure to isotretinoin (Scherdein 1993).
Fetal warfarin syndrome

Fetal Warfarin Syndrome - infant with hypoplastic nose, flat face and low nasal bridge as well as altered calcification (Smith 1982).
Thalidomide
Thalidomide is currently used in France and I suppose in other European countries for a large number of indications in severe aphtosis, leprosy, Behçet and Jessner-Kanoff diseases, cutaneous lupus, multiple myeloma, graft versus host disease. In France, the prescription is limited to a restricted panel of hospital physicians under very specific administrative conditions.
Sirenomelia and caudal regression syndrome

• It occurs in diabetic women more often
CZTIS