Disease of development: Genetic errors and human syndromes, genetic and phenotypic heterogeneity, prenatal diagnosis and preimplantation genetics, teratogenesis

Mitesh Shrestha
Genetic errors and human syndromes

• It has been known for centuries that individuals differ, that children tend to resemble their parents and that certain diseases tend to run in families.

• A genetic disorder is a genetic problem caused by one or more abnormalities in the genome, especially a condition that is present from birth (congenital).

• Most genetic disorders are quite rare and affect one person in every several thousands or millions.

• Genes are also known to play a role in the occurrence of infectious diseases like tuberculosis and AIDS as well as some non communicable diseases like cancer and diabetes.

• It is now known, for example, that certain forms of cancer arise from an accumulation of genetic mutations and that many common disorders, such as diabetes and obesity, involve the interaction of many genes as well as environmental factors.
Genetic Disorders

- Chromosomal disorders
- Single-gene disorders
- Polygenic disorders
- Mitochondrial disorders
- Somatic mutations and cancer
- Genomic imprinting disorders
Chromosomal disorders:

• Occur when the entire chromosome, or large segments of a chromosome, is missing, duplicated or otherwise altered. Down Syndrome is a prominent example of a chromosomal abnormality.

• Any abnormality in chromosome number where the chromosome number is an exact multiple of the haploid number (n=23) but exceeds the diploid number (n=46) is called polyploidy.

• If the chromosome number is not an exact multiple of the haploid number then this is called aneuploidy.
<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>92,XXYY</td>
<td>Tetraploidy</td>
</tr>
<tr>
<td>69,XXY</td>
<td>Triploidy</td>
</tr>
<tr>
<td>47,XX+21</td>
<td>Trisomy 21 (Down syndrome)</td>
</tr>
<tr>
<td>47,XY+18</td>
<td>Trisomy 18 (Edward's syndrome)</td>
</tr>
<tr>
<td>47,XX+13</td>
<td>Trisomy 13 (Patau syndrome)</td>
</tr>
<tr>
<td>47,XXY</td>
<td>Klinefelter syndrome</td>
</tr>
<tr>
<td>47,XXX</td>
<td>Trisomy X</td>
</tr>
<tr>
<td>45,X</td>
<td>Turner syndrome</td>
</tr>
</tbody>
</table>
Down Syndrome

• A type of mental retardation caused by extra genetic material in chromosome 21.

• In 95% of cases a person with Down syndrome is born with an extra chromosome 21 in each cell of his or her body (i.e. they have the karyotype 47,XX +21 or 47,XY +21).

• In about 4% of cases of Down syndrome, only an extra part of chromosome 21, the 21q22 region, is present (partial trisomy), rather than the whole of chromosome 21.

• Infants show decreased muscle tone, a flat face, eyes slanting up, irregular shaped ears, ability to extend joints beyond the usual, large space between the big toe and its neighbouring toe, large tongue relative to the mouth, etc.
Down Syndrome

• The estimated incidence of Down Syndrome is between 1 in 1,000 to 1 in 1,100 live births worldwide.

• Each year approximately 3,000 to 5,000 children are born with this chromosome disorder and it is believed there are about 250,000 families in the United States of America who are affected by Down Syndrome.
Numerical Chromosomal Abn.

1. Down syndrome

- Characterized by:
  » decreased muscle tone, stockier build.
  » asymmetrical skull
  » slanting eyes
  » mild to moderate mental retardation
15q11–13 deletion

- Two well-characterized syndromes that result from deletions are Prader–Willi syndrome (frequency 1 in 25000) and Angelman syndrome (exact frequency not known).
- People with Prader–Willi are mentally retarded, have small external genitalia and characteristic facial features, and overeating with obesity occurs.
- In contrast, in Angelman syndrome, there is developmental delay, absent speech, jerky movements, paroxysms of inappropriate laughter and characteristic facial features that differ from those of Prader–Willi.
Single-gene disorders

- Occur when an alteration occurs in a gene causing one gene to stop working. An example of a single gene disorder is sickle-cell anaemia.

- Examples:

- Achondroplasia: Mutations causing chondroplasia have since been found in the FGFR3 gene and it is now known that 99.9% of people with achondroplasia have one of two mutations in the same codon, both of which lead to the glycine at codon 380 of the FGFR3 gene being replaced by arginine. The mutations are either GGG to AGG or GGG to CGG.
Sickle cell anemia

- A blood related disorder that affects the haemoglobin molecule, and causes the entire blood cell to change shape under stressed conditions. In sickle cell anaemia, the haemoglobin molecule is defective. After haemoglobin molecules give up their oxygen, some may cluster together and form long, rod-like structures which become stiff and assume sickle shape.
Sickle cell anemia

• Sickle cell anemia affects millions throughout the world. It is particularly common among people whose ancestors come from Sub-Saharan Africa, South America, Cuba, Central America, Saudi Arabia, India, and Mediterranean countries such as Turkey, Greece, and Italy.

• In the United States, it affects around 72,000 people, most of whose ancestors come from Africa.

• The disease occurs in about 1 in every 500 African-American births and 1 in every 1000 to 1400 Hispanic-American births.

• About 2 million Americans, or 1 in 12 African Americans, carry the sickle cell allele.
Sickle cell anemia

• The sickle cell disease can be diagnosed in a simple blood test. In many cases, sickle-cell anemia is diagnosed when new-borns are screened.
• Vaccines, antibiotics, and folic acid supplements are administered, in addition to pain killers.
• Blood transfusions and surgery are used in severe cases. The only known cure at present is a bone marrow transplant.
Heterozygote advantage

- Describes the case in which the heterozygote genotype has a higher relative fitness than either the homozygote dominant or homozygote recessive genotype.
Polygenic disorders

• Occur as the result of mutations in multiple genes, frequently coupled with environmental causes. An example of a multifactorial disorder is diabetes.

• Examples: Cancer, Cardiovascular disease.
Mitochondrial disorders

- Rare disorders caused by mutations in non-chromosomal DNA located within the mitochondria. (The mitochondria are subcellular organelles.) These disorders can be found to affect any part of the body including the brain and the muscles.
- Bulk of the mitochondrial genome is composed of coding sequence and mutation rates in mitochondrial genes are thought to be about 10 times higher than those in the nuclear genome.
Leber’s hereditary optic neuropathy

• An inherited form of blindness that presents in mid-life and is characterized by rapid bilateral central vision loss due to atrophy of the optic nerve.
Somatic mutations and cancer

• Mutations that occur in certain somatic cells and their descendants are known to play a key role in the cause of many common cancers and may also be involved in disorders of the immune system and the aging process.

• Examples: Mutations in tumor suppressor genes, oncogenes, mutator genes.
Genomic imprinting disorders

- Genomic imprinting is related to the methylation of cytosine bases in the CpG dinucleotides of the DNA molecule which are key regulatory elements of genes.
- These include Prader-Willi and Angelman syndromes (the first examples of genomic imprinting in humans), Silver-Russell syndrome, Beckwith-Weidemann syndrome, Albright hereditary osteodystrophy and uniparental disomy 14.
• Phenotypic heterogeneity describes different mutations in the same gene that can sometimes give rise to strikingly different phenotypes.

• E.g., certain loss-of-function mutations in the RET gene, which encodes a receptor tyrosine kinase, can cause dominantly inherited failure of development of colonic ganglia, leading to defective colonic motility and severe chronic constipation (Hirschsprung disease)
Genetic heterogeneity

- Genetic heterogeneity is a phenomenon in which a single phenotype or genetic disorder may be caused by any one of a multiple number of alleles or non-allele (locus) mutations.
- This is in contrast to pleiotropy, where a single gene may cause multiple phenotypic expressions or disorders. Genetic heterogeneity describes genetic variation from the normal population. Clinically, genetic heterogeneity refers to diseases that result from multiple gene abnormalities.
- Multiple gene abnormalities are seen in disorders such as autism, cystic fibrosis, and retinitis pigmentosa.
Prenatal diagnosis

- Prenatal diagnosis and prenatal screening are aspects of prenatal care that focus on detecting anatomic and physiologic problems with the zygote, embryo, or fetus as early as possible, either before gestation even starts (as in preimplantation genetic diagnosis) or as early in gestation as practicable.
- Use medical tests to detect problems such as neural tube defects, chromosome abnormalities, and gene mutations that would lead to genetic disorders and birth defects, such as spina bifida, cleft palate, Tay–Sachs disease, sickle cell anemia, thalassemia, cystic fibrosis, muscular dystrophy, and fragile X syndrome.
- The screening focuses on finding problems among a large population with affordable and noninvasive methods, whereas the diagnosis focuses on pursuing additional detailed information once a particular problem has been found, and can sometimes be more invasive.
Prenatal diagnosis

• Screening can also be used for prenatal sex discernment. Common testing procedures include amniocentesis, ultrasonography including nuchal translucency ultrasound, serum biomarker testing, or genetic screening. In some cases, the tests are administered to determine if the fetus will be aborted, though physicians and patients also find it useful to diagnose high-risk pregnancies early so that delivery can be scheduled in a tertiary care hospital where the baby can receive appropriate care.
Preimplantation genetics

• Pre-implantation genetic diagnosis (PGD) is generally defined as the testing of pre-implantation stage embryos or oocytes for genetic defects. It has been developed for couples whose potential offspring are at risk of severe Mendelian disorders, structural chromosome abnormalities or mitochondrial disorders.

• Pre-implantation embryo diagnosis requires in vitro fertilization, embryo biopsy and either using fluorescent in situ hybridization or polymerase chain reaction at the single cell level. Therefore, it is a complex procedure which requires much experience.

• Aneuploidy screening to improve medically assisted reproduction (in vitro fertilization/intracytoplasmic sperm injection) is a variant type of PGD. The past, present and future of this development are strongly related to the natural occurrence of chromosomal mosaicism in the pre-implantation embryo. PGD should be included in each reproductive health care programme. It is recognized as an important alternative to pre-natal diagnosis. However, diagnosis from a single cell remains a technically challenging procedure, and the risk of misdiagnosis cannot be eliminated.

• An ethical discussion of the question of whether PGD is acceptable at all-the 'desirability question'-is a rearguard action. Discussion must primarily focus on the conditions of exercising due caution in and the dynamics of PGD.
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.
Definitions

- **Teratology** is the science that studies the causes, mechanisms, and patterns of birth defect.

- **Teratogenesis** is the process with threshold-level effects which are of clinically significant types: malformation, disruption, and deformation.

- **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.
Teratogen

- A teratogen is an exogenous agent that can produce a permanent alteration of structure or function in an organism exposed during embryonic or fetal life.
- Every chemical substance may be teratogenic. This effect depends on quantity. In small amount is without any effect.
- Teratogen is factor that is present in environment in so high amount that it can increase occurrence of embryotoxicity manifestation up to basic frequency in non-exposed population.
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 the agent.
- **Deformation** is an alteration in shape/structure of previously normally formed part.
- **Dysplasia** refers to the enlargement of an organ or tissue by the proliferation of cells of an abnormal type, as a developmental disorder or an early stage in the development of cancer.
- **Syndrome** is a recognized pattern of malformations with a given etiology.
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)
Malformations

- Occurs during formation of structures - Organogenesis
- Result in complete or partial absence of a structure or in alterations of its normal configuration
- For e.g. Holoprosencephaly, caudal dysgenesis, situs inversus, phocomelia
Disruptions

- Disruptions result in morphological alterations of already formed structures
- They are due to destructive processes
- Examples:
  - Vascular accidents leading to bowel atresias
  - Defects produced by amniotic bands
Deformations

- Are due to mechanical forces that mold a part of the fetus over a prolonged period
- Often involve musculoskeletal system
- They may be reversible postnatally

Examples:
- Club feet ---- due to compression in the amniotic cavity
**Syndrome**

Is a group of anomalies occurring together that have a specific common cause.

- In syndrome, the cause is known.
- Diagnosis is made.
- The risk of recurrence is known.

Examples:
- Down’s syndrome
- Fetal alcoholic syndrome
Association

- Is the non-random appearance of two or more anomalies that occur together more frequently than by chance alone.
- Cause is not known.
- They do not constitute a diagnosis.
- Example:
  - VACTERL
- Recognition of one component promotes search for others in the group.
Characteristics of teratogenic agents

- Stage Sensitivity
- Dose-response relationship
  - ↑ dosage, frequency, severity, and duration
- Genetic differences
  - Placental transport, metabolism, distribution
Periods of Teratogenesis

- Fertilization-to-postimplantation Period: low susceptibility to malformations

- Organogenesis Period (3rd – 8th week of gestation in humans): greatest sensitivity to teratogenic agent and peak susceptibility for malformation

- Fetal Period: exposure to teratogenic agent after organ and tissue differentiation leads to functional mutations and fetal death
Weeks of human development

- **Formation of organs** (0-3 weeks)
  - Death of embryo may occur

- **Period of maximal sensitivity to abnormal development** (3-8 weeks)
  - Malformation of embryo may occur (e.g., heart defect)

- **Growth and maturation of organ systems** (8-38 weeks)
  - Functional disturbance of fetus may occur (e.g., mental retardation)
### Etiology of Human Maldevelopment

<table>
<thead>
<tr>
<th>Suspected cause</th>
<th>Percent of total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genetic</strong></td>
<td></td>
</tr>
<tr>
<td>Autosomal genetic disease</td>
<td>15–20%</td>
</tr>
<tr>
<td>Cytogenetic (chromosomal abnormalities)</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td></td>
</tr>
<tr>
<td>Polygenic</td>
<td></td>
</tr>
<tr>
<td>Multifactorial (genetic-environmental interactions)</td>
<td></td>
</tr>
<tr>
<td>Spontaneous errors of development</td>
<td></td>
</tr>
<tr>
<td>Synergistic interactions of teratogens</td>
<td>65%</td>
</tr>
<tr>
<td><strong>Environmental</strong></td>
<td></td>
</tr>
<tr>
<td>Maternal conditions: diabetes, endocrinopathies, nutritional deficiencies, drug and substance addictions</td>
<td>4%</td>
</tr>
<tr>
<td>Maternal infections: rubella, toxoplasmosis, syphilis, herpes, cytomegalic inclusion disease</td>
<td>3%</td>
</tr>
<tr>
<td>Mechanical (deformations): abnormal uterus, amniotic bands, umbilical cord constrictions, disparity in uterine size and uterine contents</td>
<td>1–2%</td>
</tr>
<tr>
<td>Chemicals, drugs, radiation, hyperthermia</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
Birth defects

- 3% of all live-born infants have a major anomaly
- Additional anomalies are detected during postnatal live – 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.
The Six Principles of Teratology

- Susceptibility to teratogenesis **depends on the genotype** of the conceptus and the manner in which this interacts with adverse environmental factors.
- Susceptibility to teratogenesis **varies with the developmental stage** at the time of exposure to an adverse influence. There are critical periods of susceptibility to agents and organ systems affected by these agents.
- Teratogenic agents act in **specific ways on developing cells and tissues** to initiate sequences of abnormal developmental events.
- The access of adverse influences to developing tissues depends on the **nature of the influence**. Several factors affect the ability of a teratogen to contact a developing conceptus, such as the nature of the agent itself, route and degree of maternal exposure, rate of placental transfer and systemic absorption, and composition of the maternal and embryonic/fetal genotypes.
- There are four manifestations of deviant development (**Death, Malformation, Growth Retardation and Functional Defect**).
- Manifestations of deviant development increase in frequency and degree as dosage increases from the **No Observable Adverse Effect Level (NOAEL)** to a dose producing **100% Lethality (LD100)**.
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 syndrom (21) Edwards (18) Patau (13) Turner (X0), Klinenfelter (XXY)
- **Structural chromosomal abnormalities** – chromosome breaks = translocation, deletion (cri du chat syndrome), duplication, inversion.
- **Mutant genes** – achondroplasia, fragile-X syndrome
Anomalies caused by environmental factors

- **Teratogens** are exogeneous 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, toxoplasma, syphilis)
  - *Ionizing radiation* (RTG)
  - *Maternal factors* (diabetes mellitus, hyperthermia, phenylketonuria, hyper-/hypo-thyreosis)
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 (eg, 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.
Process of assessing reproductive or embryo/fetotoxic effect of drug

- A sudden increase in the prevalence of a specific malformation is observed
- An association is established between the introduction or an increased usage of a drug and an increased prevalence of a specific malformation
- Drug use must be taken place in the sensitive period for the introduction of that specific malformation
- Drug or its metabolite suspected of causing malformation has to be proved capable of reaching the embryo or fetus
- It must be established that the drug and not condition (disease) causes the specific malformation
- The finding have to be confirmed by another independent study
- The result of specific laboratory animal studies might support the epidemiological findings
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.
Teratology Information Services (TIS) provide information on the possible risks of exposure to drugs and other exogenous agents during pregnancy and lactation.

Teratology Information Services are consulted by the medical profession and other health care professionals, some of them counsel lay people as well. Answers provided are specifically oriented towards individual patients. Detailed knowledge of dose, time of exposure, adverse effects on the mother related to the exposure, diseases, previous pregnancies, family history of the patient and the pharmacological and toxicological properties of the agents have to be taken into account to make a specific risk assessment.
A TIS deals with the following types of inquiries:

• Before pregnancy
  - A couple is planning a pregnancy and is being exposed to drugs/chemicals.  
    What is the risk? Should this exposure be changed or stopped?  
    Does this exposure decrease fertility?

• During pregnancy

• A pregnant woman has taken a drug before she realises that she is pregnant.  
  What is the risk? Would recommending termination of pregnancy be justified?  
  What prenatal diagnostic procedures can be offered?

• A drug has to be prescribed to a pregnant woman.  
  Is it safe? Is there a less toxic/teratogenic drug with comparable therapeutic efficacy to 
  which the woman should be transferred?  
  Is the risk of taking a drug greater than the risk of the disease for which the drug is taken?  
  Are there risks acceptable to the patient when compared with the spontaneous risk of 
  developmental disorders?

• A pregnant woman has attempted to commit suicide by taking an overdose of a drug.  
  What information should be given to the physician at the emergency department? Can the 
  appropriate antidote be given to her?

• A pregnant woman is addicted to drugs/alcohol.  
  Do they have an adverse effect on the course of pregnancy? What are the effects on fetal 
  development? Can neonatal problems be expected or are there any long-term consequences 
  for the child?
- A pregnant woman is exposed at work to certain chemicals.  

*What is the risk?*  
*Should she continue this work?*

- A pregnant woman is exposed to an infectious agent.  

*What are the risks of a maternal infection for the fetus?*  
*Are techniques available for the diagnosis of a fetal infection and what are the management options?*  
*Similar questions are made for non-infectious maternal diseases.*

- A pregnant woman has been exposed to...  

*What are the risks of certain physical exposures such as heat and radiation (especially x-rays and radioactive materials), vaccinations or environmental pollution?*

- A man has been exposed to chemicals or has been treated with drugs.  

*Are there any paternally mediated risks for the fetus or baby?*
• After Pregnancy
  A baby is born with a birth defect or a neonatal disorder.  
  *Can this be attributed to a drug or chemical to which the mother was exposed before or during pregnancy?*

• A drug has to be prescribed to a mother while she is breastfeeding. A mother uses a prescription drug or is exposed to another exogenous agent, while breastfeeding.  
  *What is the (relative) dose the neonate (infant) is exposed to?*
  *Is this acceptable for its age?*
  *What is the treatment of choice during breastfeeding?*
1. Thalidomide

**EXAMPLES**

- Sedative/hypnotic introduced in 1960 for treatment of nausea during 1st trimester.
- Appearance of newborns in West Germany with phocomelia.
- Drug withdrawn in mid-1962; 5850 cases of malformations
2. Alcohol

- Known as Fetal Alcohol Syndrome
- Craniofacial abnormalities, CNS dysfunction, postnatal growth retardation.
- Most severe effects in children born to alcoholic mothers (25 per 1000).
- Mechanism of toxicity poorly understood; thought to involve cell death and inhibition of cell migration during early pregnancy.
3. Tobacco Smoke

**EXAMPLES**

- Leading cause of environmentally induced developmental disease and morbidity
- Spontaneous abortions, behavioral and attention deficit disorders, and lower birth weight
- Nicotine can by itself produce many of the adverse effects of tobacco smoke
4. Retinoids

- Vitamin A (retinol) and retinoids (used in treatment of acne) are long known to produce malformations.
- Effects include malformations of face, limbs, heart, CNS and skeleton.
- Mechanism of toxicity mediated:
  - Activation of nuclear receptors, retinoic acid receptors (RARs) & retinoid X receptors (RXRs).
  - Activation of homeobox (Hox) genes which direct embryonic pattern development by retinoids at inappropriate times.
4. Retinoids

RXR Signaling Activation

Without RA

Histone deacetylation and repression of transcription

With RA

Histone acetylation and activation of transcription

Typical chordate Hox gene cluster
5. Radiation

- Radiation represents a possible teratogen for the fetus.
- Such as x-rays, γ-rays, and UV.
- Growth retardation, eye malformation, and CNS defect are reported at Hiroshima.
- The risk is dependent on dosage and gestational stage
Principal Mechanisms of Teratogenesis

- Cell growth or proliferation
- Cell death
- Cell migration
- Cell and tissue interactions
- Disruptions
Principal Mechanisms of Teratogenesis

- Mutagenesis
- Mitotic Interference
- Nucleic Acid Alteration
- Nutritional Deficiency
- Enzyme Inhibition
- Osmolar Imbalance
- Others
Useful

- http://mothertobaby.org/fact-sheets-parent/