

23. TERATOGENS AND THEIR EFFECTS

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SUMMARY

A congenital malformation is an anatomical or structural abnormality present at birth. Congenital malformations may be caused by genetic factors or environmental insults or a combination of the two that occur during prenatal development. Most common congenital malformations demonstrate multifactorial inheritance with a threshold effect and are determined by a combination of genetic and environmental factors. During the first two weeks of gestation, teratogenic agents usually kill the embryo rather than cause congenital malformations. Major malformations are more common in early embryos than in newborns; however, most severely affected embryos are spontaneously aborted during the first six to eight weeks of gestation. During organogenesis between days 15 to 60, teratogenic agents are more likely to cause major congenital malformations. The variety of these associated syndromes with specific teratogenic agents is discussed below.

LEARNING OBJECTIVES:

At the end of the lecture you should be able to:

1. Describe the frequency and significance of major and minor congenital malformations.
2. Discuss the etiology of congenital malformations and the importance of developmental timing of exposure.
3. Learn to recognize the most frequent genetic and environmental causes of congenital malformation syndromes and exposures to be avoided during and prior to pregnancy.

GLOSSARY:

Chorioretinitis: inflammation of the choroid and retina

Hemangioma: benign tumor made up of newly formed blood vessels

Hepatosphenomegaly: enlarged liver and spleen

Meromelia: congenital absence of any part of a limb

Micromelia: abnormal smallness or shortness of the limb(s)

Microphthalmia: abnormal smallness of the eyes

TEXT:

Teratology is the study of abnormal development in embryos and the causes of congenital malformations or birth defects. These anatomical or structural abnormalities are present at birth although they may not be diagnosed until later in life. They may be visible on the surface of the body or internal to the viscera. Congenital malformations account for approximately 20% of deaths in the perinatal period. Approximately 3% of newborn infants will have major malformations and another 3% will have malformations detected later in life.

There are a variety of causes of congenital malformations including: 1) genetic factors (chromosomal abnormalities as well as single gene defects); 2) environmental factors (drugs, toxins, infectious etiologies, mechanical forces); and 3) multifactorial etiologies including a combination of environmental and genetic factors. The graph below (Fig. 23-1) divides these etiologies by percentages.

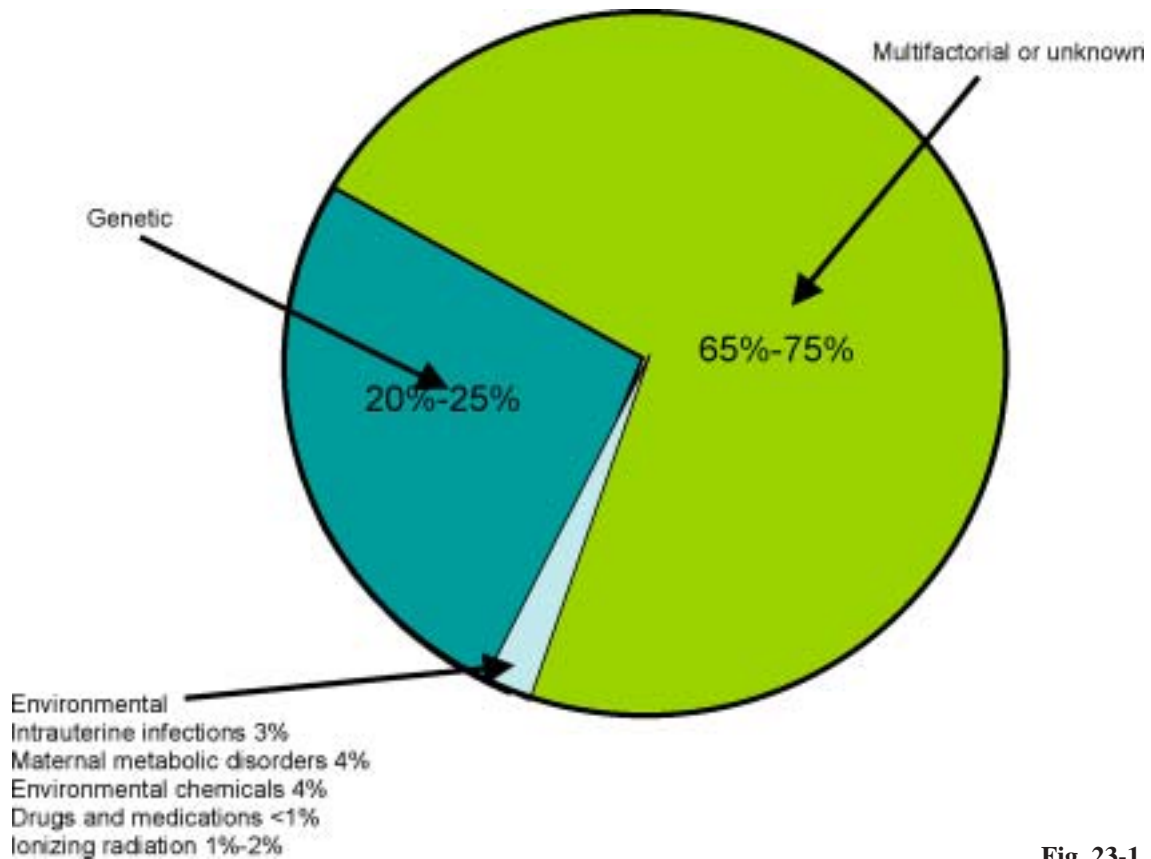


Fig. 23-1

Malformations may be single or multiple and have major or minor clinical significance. Single minor malformations are observed in approximately 14% of newborns. These malformations are usually of no clinical consequence and may include features such as a simian crease or ear tags. Specific minor malformations suggest the possibility of an associated major malformation. For instance, the finding of a single umbilical artery should suggest the possibility of associated congenital heart problems. The greater the number of minor malformations, the greater the likelihood of an associated major malformation. The more severe and the greater the number of major malformations, the greater the likelihood of a spontaneous miscarriage or shortened life span.

Genetic etiologies of malformations

Genetic factors are the most common causes of congenital malformations and account for approximately one fourth of all congenital malformations. Chromosomal abnormalities including numerical and structural abnormalities are a common cause of congenital malformations. Specific genetic syndromes are associated with the most common of these chromosomal defects. Trisomy 21 is referred to as Down syndrome and has associated characteristic facial features, congenital heart disease, growth retardation, and mental retardation. Monosomy of the X-chromosome is referred to

as Turner syndrome and is associated with webbing of the neck, lymphedema of the hands and feet, and later in life short stature and infertility. Trisomy 13 is associated with midline defects including cleft lip and cleft palate, central nervous system malformations, microphthalmia, and congenital heart disease. Infants with this disorder rarely live beyond the first year of life. Trisomy 18 is associated with intrauterine growth restriction, clenched hands, rocker bottom feet, and congenital heart disease. Similar to trisomy 13, infants with the syndrome also rarely live beyond the first year of life. Other chromosomal abnormalities including interstitial deletions, interstitial duplications, and unbalanced translocations are often associated with congenital anomalies. The most common deletions have named clinical syndromes with which they are associated.

In addition to gross chromosomal abnormalities, there are multiple single gene defects that can result in congenital malformations. Many of these genes include developmentally important transcription factors and genes important in intermediary metabolism.

Teratogenic agents cause approximately 7% of congenital malformations. A *teratogenic agent* is a chemical, infectious agent, physical condition, or deficiency that, on fetal exposure, can alter fetal morphology or subsequent function. Teratogenicity depends upon the ability of the agent to cross the placenta. Certain medications such as heparin cannot cross the placenta due to its high molecular weight and are therefore not teratogenic. The embryo is most susceptible to teratogenic agents during periods of rapid differentiation. The stage of development of the embryo determines susceptibility to teratogens. The most critical period in the development of an embryo or in the growth of a particular organ is during the time of most rapid cell division. The critical period for each organ is pictured below (Fig. 23-2). For instance, the critical period for brain growth and development is from three to 16 weeks. However the brain's differentiation continues to extend into infancy. Teratogens can produce mental retardation during both embryonic and fetal periods (Fig. 23-2).

Specific types of major malformations and the times of development usually associated with exposure to the teratogenic agent are outlined in the table below (Table 23-1).

Each organ of an embryo has a critical period during which its development may be disrupted. The type of congenital malformation produced by an exposure depends upon which organ is most susceptible at the time of the teratogenic exposure. For instance, high levels of radiation produce abnormalities of the central nervous system and eyes specifically at eight to 16 weeks after fertilization. Embryological timetables such as the one above are helpful in studying the etiology of human malformations. However, it is wrong to assume that malformations always result from a *single* event occurring during a single critical sensitive period or that one can determine the exact day on which a malformation was produced.

A teratogen is any agent that can induce or increase the incidence of a congenital malformation. Recognition of human teratogens offers the opportunity to prevent exposure at critical periods of development and prevent certain types of congenital malformations. In general, drugs, food additives, and pesticides are tested to determine their teratogenicity to minimize exposure of pregnant women to teratogenic agents. To prove that a specific agent is teratogenic means to prove that the frequency of congenital malformations in women exposed to the agent is prospectively greater than the background frequency in the general population. These data are oftentimes not available for humans and thus cannot be determined in an unbiased fashion. Therefore, testing is often done in animal models and often times administered at higher than the usual therapeutic doses. There are clearly species differences between teratogenic effects, limiting this testing in animals. Based upon

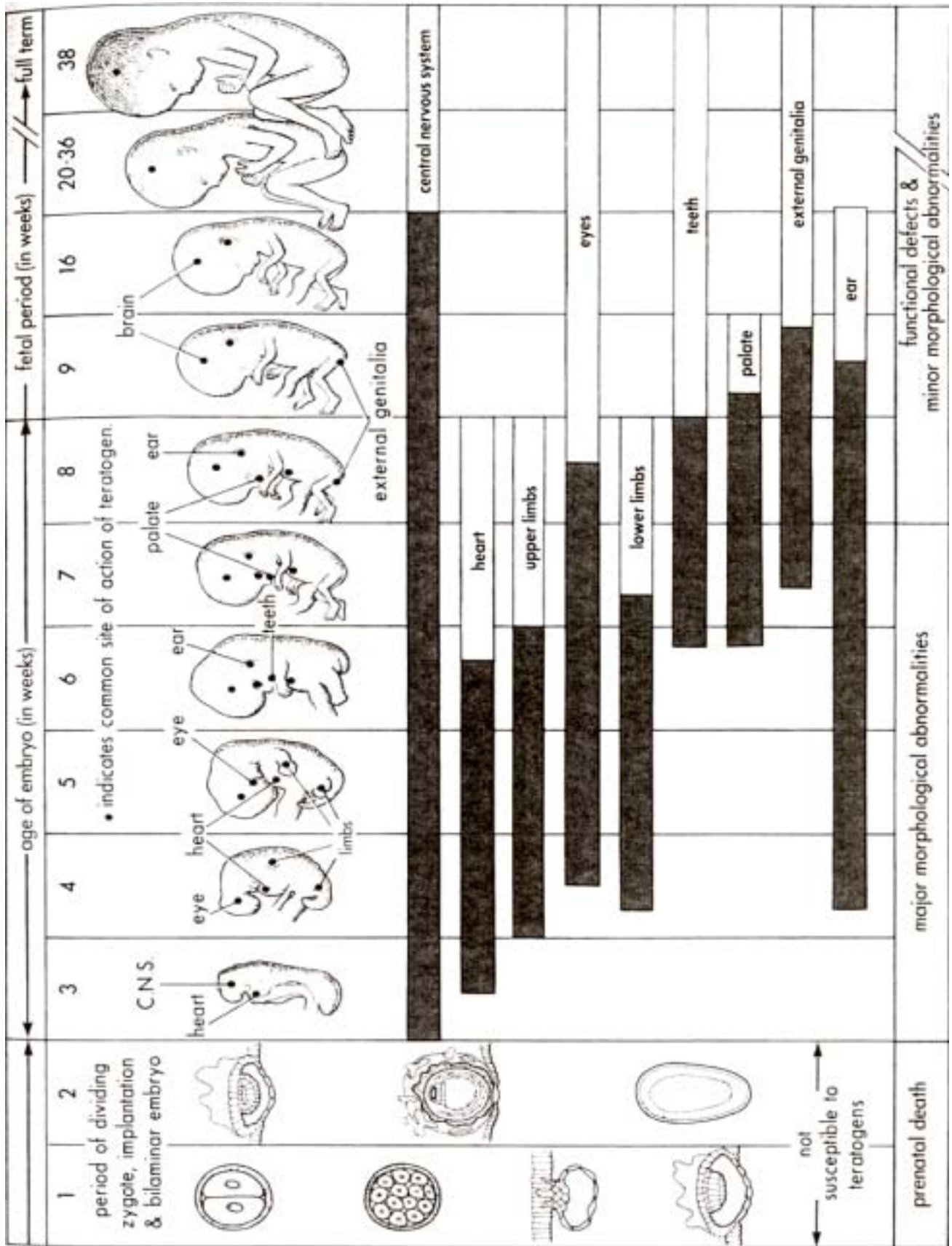


Fig. 23-2

Tissue	Malformation	Defect	Timing of Cause	Additional Information
Central nervous system	Holoprosencephaly	Prechordal mesoderm	23 days	Associated facial defects
	Anencephaly	Closure of anterior neural tube	26 days	Subsequent degeneration of forebrain
	Meningomyelocele	Closure in portion of posterior neural tube	28 days	80% lumbosacral
Face	Cleft lip	Closure of lip	36 days	42% associated with cleft palate
	Branchial sinus or cyst	Resolution of branchial cleft	8 weeks	Preauricular and along line anterior to sternocleidomastoid
	Robin sequence	Early mandibular hypoplasia	9 weeks	U-shaped posterior cleft palate
Neck	Cleft maxillary palate	Fusion of maxillary palatal shelves	10 weeks	
	Esophageal atresia and tracheoesophageal fistula	Lateral septation of foregut into trachea and foregut	30 days	
Abdomen	Posterior nuchal cystic hygroma	Lymphaticovenous communication	40 days	Common in XO Turner's syndrome
	Rectal atresia with fistula	Lateral septation of cloaca into rectum and urogenital sinus	6 weeks	
	Diaphragmatic hernia	Closure of pleuroperitoneal canal	6 weeks	
	Duodenal atresia	Recanalization of duodenum	7-8 weeks	
	Malrotation of gut	Rotation of intestinal loop so that cecum lies to right	10 weeks	Associated incomplete or aberrant mesenteric attachments
	Omphalocele	Return of midgut from yolk sac to abdomen	10 weeks	
	Meckel diverticulum	Obliteration of vitelline duct	10 weeks	May contain gastric or pancreatic tissue
Genitourinary system	Extroversion of bladder	Migration of infraumbilical mesenchyme	30 days	Associated müllerian and wolffian duct defects
	Urethral obstruction sequence	Usually prostatic urethra valves	9 weeks	More common in males
	Bicornuate uterus	Fusion of lower portion of müllerian ducts	10 weeks	
	Hypospadias	Fusion of urethral folds (labia minora)	12 weeks	
	Cryptorchidism	Descent of testicle into scrotum	7-9 months	
Heart	D-transposition of great vessels	Directional development of bulbus cordis septum	34 days	
	Ventricular septal defect	Closure of ventricular septum	6 weeks	
	Patent ductus arteriosus	Closure of ductus arteriosus	9-10 months	
Limb	Aplasia of radius	Genesis of radial bone	38 days	Often accompanied by other defects of radial side of distal limb
	Severe syndactyly	Separation of digital rays	6 weeks	

Table 23-1

either anecdotal information on exposures in humans or on the basis of testing in animals, drugs are classified as to their teratogenic potential. It should be emphasized that less than 2% of congenital malformations are caused by drugs or chemicals. There are small numbers of drugs that have been positively implicated as teratogenic agents that should be avoided either during or prior to conception. However, because of the unknown, subtle effects of many agents, women preparing to conceive or already pregnant refrain from taking any medications that are not absolutely necessary. Women are especially urged to avoid using all medications during the first 8 weeks after conception unless there is a strong medical reason. Effects of teratogens during this period of developmental often times results in an “all or none effect.” That is, the effect of the teratogen, if it is to have any effect, will be so profound as to cause a spontaneous abortion.

Some examples of teratogens known to cause human malformations are listed in the table below (Table 23-2). A few of the most common examples will be discussed below.

Teratogens	Congenital Malformations
Androgenic Agents	
Ethisterone	Varying degrees of masculinization of female fetuses: ambiguous external genitalia caused by labial fusion and clitoral hypertrophy.
Norethisterone	
Testosterone	
Drugs and Chemicals	
Alcohol	<i>Fetal alcohol syndrome</i> : intrauterine growth retardation (IUGR); mental retardation; microcephaly; ocular anomalies; joint abnormalities; short palpebral fissures.
Aminopterin	Wide range of skeletal defects; IUGR; malformations of the central nervous system, notably meroanencephaly (a large part of the brain is absent).
Busulfan	Stunted growth; skeletal abnormalities; corneal opacities; cleft palate; hypoplasia of various organs.
Phenytoin (Dilantin)	<i>Fetal hydantoin syndrome</i> : IUGR; microcephaly; mental retardation; ridged metopic suture; inner epicanthal folds; eyelid ptosis; broad depressed nasal bridge; phalangeal hypoplasia.
Lithium carbonate	Various malformations, usually involving the heart and great vessels.
Methotrexate	Multiple malformations, especially skeletal, involving the face, skull, limbs, and vertebral column.
Large doses of retinoic acid (vitamin A).	Facial abnormalities; neural tube defects, such as spina bifida cystica (see Fig. 18-14).
Tetracycline	Stained teeth; hypoplasia of enamel.
Trimethadione	Developmental delay; V-shaped eyebrows; low-set ears; cleft lip and/or palate.
Infectious Agents	
Cytomegalovirus	Microcephaly; hydrocephaly; microphthalmia; microgyria; mental retardation; cerebral calcifications.
Herpes simplex virus	Microcephaly; microphthalmia; retinal dysplasia.
Rubella virus	Cataracts; glaucoma; chorioretinitis; deafness; microphthalmia; congenital heart defects.
Varicella	Skin scarring; muscle atrophy; mental retardation.
Venezuelan equine encephalitis	Cataracts; brain destruction.
<i>Toxoplasma gondii</i>	Microcephaly; mental retardation microphthalmia; hydrocephaly; chorioretinitis; cerebral calcifications.
<i>Treponema pallidum</i>	Hydrocephalus; congenital deafness; mental retardation; abnormal teeth and bones.
High levels of ionizing radiation	Microcephaly; mental retardation; skeletal malformations.

Table 23-2

Nicotine does not produce congenital malformations but nicotine does have an effect on fetal growth. Maternal smoking is a well-established cause of intrauterine growth restriction. Heavy cigarette smokers were also more likely to have a premature delivery. Nicotine constricts uterine blood vessels and causes decreased uterine blood flow thereby decreasing the supply of oxygen and nutrients available to the embryo. This compromises cell growth and may have an adverse effect on mental development.

Alcohol is a common drug abused by women of childbearing age. Infants born to alcoholic mothers demonstrate prenatal and postnatal growth deficiency, mental retardation, and other malformations. There are subtle but classical facial features associated with fetal alcohol syndrome including short palpebral fissures, maxillary hypoplasia, a smooth philtrum, and congenital heart disease. Even moderate alcohol consumption consisting of 2 to 3 oz. of hard liquor per day may produce the fetal alcohol effects. Binge drinking also likely has a harmful effect on embryonic brain developments at all times of gestation.

Tetracycline, the type of antibiotic, can cross the placental membrane and is deposited in the embryo in bones and teeth. Tetracycline exposure can result in yellow staining of the primary or deciduous teeth and diminished growth of the long bones. Tetracycline exposure after birth has similar effects.

Anticonvulsant agents such as phenytoin produce the fetal hydantoin syndrome consisting of intrauterine growth retardation, microcephaly, mental retardation, distal phalangeal hypoplasia, and specific facial features.

Anti-neoplastic or chemotherapeutic agents are highly teratogenic as these agents inhibit rapidly dividing cells. These medications should be avoided whenever possible but are occasionally used in the third trimester when they are urgently needed to treat the mother.

Retinoic acid or vitamin A derivatives are extremely teratogenic in humans. Even at very low doses, oral medications such as isotretinoin, used in the treatment of acne, are potent teratogens. The critical period of exposure appears to be from the second to the fifth week of gestation. The most common malformations include craniofacial dysmorphisms, cleft palate, thymic aplasia, and neural tube defects.

The tranquilizer thalidomide is one of the most famous and notorious teratogens. This hypnotic agent was used widely in Europe in 1959, after which an estimated 7000 infants were born with the thalidomide syndrome or meromelia. The characteristic features of this syndrome include limb abnormalities that span from absence of the limbs to rudimentary limbs to abnormally shortened limbs. Additionally, thalidomide also causes malformations of other organs including absence of the internal and external ears, hemangiomas, congenital heart disease, and congenital urinary tract malformations. The critical period of exposure appears to be 24 to 36 days after fertilization.

Infectious agents can also cause a variety of birth defects and mental retardation when they cross the placenta and enter the fetal blood stream. Congenital rubella or German measles consists of the triad of cataracts, cardiac malformation, and deafness. The earlier in the pregnancy that the embryo is exposed to maternal rubella, the greater the likelihood that it will be affected. Most infants exposed during the first four to five weeks after fertilization will have stigmata of this exposure. Exposure to rubella during the second and third trimester results in a much lower frequency of malformation, but continues to pose a risk of mental retardation and hearing loss.

Congenital cytomegalovirus infection is the most common viral infection of the fetus. Infection of the early embryo during the first trimester most commonly results in spontaneous termination. Exposure later in the pregnancy results in intrauterine growth retardation, micromelia, chorioretinitis, blindness, microcephaly, cerebral calcifications, mental retardation, and hepatosplenomegaly.

Ionizing radiation can injure the developing embryo due to cell death or chromosome injury. The severity of damage to the embryo depends on the dose absorbed and the stage of development at which the exposure occurs. Study of survivors of the Japanese atomic bombing demonstrated that exposure at 10 to 18 weeks of pregnancy is a period of greatest sensitivity for the developing brain. There is no proof that human congenital malformations have been caused by diagnostic levels of radiation. However, attempts are made to minimize scattered radiation from diagnostic procedures such as x-rays that are not near the uterus. The standard dose of radiation associated with a diagnostic x-ray produces a minuscule risk to the fetus. However, all women of childbearing age are asked if they are pregnant before any exposure to radiation.

Maternal medical conditions can also produce teratogenic risks. Infants of diabetic mothers have an increased incidence of congenital heart disease, renal, gastrointestinal, and central nervous system malformations such as neural tube defects. Tight glycemic control during the third to sixth week post-conception is critical. Infants of mothers with phenylketonuria who are not well controlled and have high levels of phenylalanine have a significant risk of mental retardation, low birth weight, and congenital heart disease.

Mechanical forces can also act as teratogens. Malformations of the uterus may restrict fetal movements and be associated with congenital dislocation of the hip and clubfoot. Oligohydramnios can have similar results and mechanically induce abnormalities of the fetal limbs. These abnormalities would be classified as deformations or abnormal forms, shapes, or positions of body parts caused by physical constraints. Amniotic bands are fibrous rings and cause intrauterine amputations or malformations of the limbs as well. These abnormalities would be classified as disruptions or defects from interference with a normally developing organ system usually occurring later in gestation.

Most common congenital malformations have familial distributions consistent with multifactorial inheritance. Multifactorial inheritance may be presented by a model in which liability to a disorder is a continuous variable that is dependent on a combination of environmental and genetic factors. Development of the malformation is dependent upon passing a threshold that is the sum of a combination of many of these factors. Traits that demonstrate this mode of inheritance include cleft lip, cleft palate, neural tube defects, pyloric stenosis, and congenital dislocation of the hip.