Maternal, Prenatal and Genetic Influences on Development of Defect and Disease

LUTFI NA

Congenital and Herediter Disease

Hereditary and Congenital Malformations

- Congenital disease: abnormality present at birth, even though it may not be detected until some time after birth
- Hereditary or genetic disease: resulting from a chromosome abnormality or a defective gene

Congenital Diseases and Disorders

- Present at the time of birth
- May or may not be inherited
  - Causes:
    - Infections
    - Toxins
    - Environmental agents – various chemicals (Mercury or phenols)
    - Drugs – Thalidomide
    - Alcohol
    - Smoking
    - Nutritional

Congenital Diseases and Disorders

- Disorders considered congenital:
  - Club foot
  - Cleft palate
  - Heart abnormalities
  - Fetal alcohol syndrome
  - Hip dislocation
  - Neural tube defects
  - Cerebral palsy

Congenital Diseases and Disorders

- Prevention and minimizing risks
- Non-hereditary congenital disorders may be prevented or minimized by an awareness of risk factors

Hereditary Diseases and Disorders

- Hereditary Diseases and Disorders are evident at birth or soon after, although some do not manifest until later in life
  - Caused by altered genes passed from parent to child
  - Dominate gene expression
  - Recessive gene expression
  - Mutation

Hereditary Diseases and Disorders

- Diseases/Disorders:
  - Diabetes mellitus
  - Cystic fibrosis
  - Sickle cell anemia
  - Huntington's disease
  - Albinism
  - Down's syndrome
  - ADL
  - Tay-Sachs
  - PKU
  - Hemophilia

Factors in Congenital Malformations

- Genetic or hereditary disorders or diseases caused by abnormalities in an individual's genetic material (genome)
- Congenital disease or malformation: any abnormality present at birth
- Four factors in congenital malformations
  - 1. Chromosomal abnormalities
  - 2. Abnormalities of individual genes
  - 3. Intrauterine injury to embryo or fetus
  - 4. Environmental factors

Causes of Congenital Malformations

- 2-3% of all newborn infants have congenital defects
- Additional 2-3% defects: NOT recognized at birth; developmental defects demonstrated later as infants grow older
- 25% to 50% spontaneously aborted embryos, fetuses, and stillborn infants have major malformations

Chromosomal Abnormalities

- Nondisjunction: failure of homologous chromosomes in germ cells to separate in first or second meiotic division
  - May involve either sex chromosomes or autosomes
  - Causes abnormalities in distribution of chromosomes between germ cells
  - One of two germ cells has an extra chromosome while the other lacks a chromosome

Chromosomal Abnormalities

- Monosomy: absence of a chromosome in a cell
- Trisomy: presence of an extra chromosome in a cell
- Deletions: chromosome breaks during meiosis and broken piece is lost
- Translocations: misplaced chromosome or part of it attaches to another chromosome

Sex Chromosome Abnormalities (1 of 3)

- Variations in normal number of sex chromosomes are often associated with some reduction of intelligence
  - Y chromosome: directs masculine sexual differentiation, associated with male body configuration regardless of number of X chromosomes present
  - Extra Y: no significant effect as it mainly carries genes concerned with male sexual differentiation
  - Absent Y: body configuration is female
  - Extra X in female: has little effect (one X chromosome is inactivated)
  - Extra X in male: has adverse effects on male development

Sex Chromosome Abnormalities (2 of 3)

- Two most common ones in the female
  - 1. Turner's Syndrome: absence of one X chromosome
  - 2. Triple X Syndrome: extra X chromosome
- Two most common ones in the male
  - 1. Klinefelter's Syndrome: extra X chromosome
  - 2. XYY Syndrome: extra Y chromosome

Sex Chromosome Abnormalities (3 of 3)

- Fragile X Syndrome (x-linked mental deficiency)
- Not related to either excess or deficiency of sex chromosomes
- Associated with a characteristic abnormality of the X chromosome
- Second to Down syndrome as a major cause of mental deficiency

Autosomal Abnormalities (1 of 3)

- Absence of an autosome results in the loss of several genes that development is generally not possible and the embryo is aborted.
- Deletion of a small part of an autosome may be compatible with development but usually results in multiple severe congenital abnormalities.
- **Down syndrome: most common chromosomal abnormality**, an autosomal trisomy

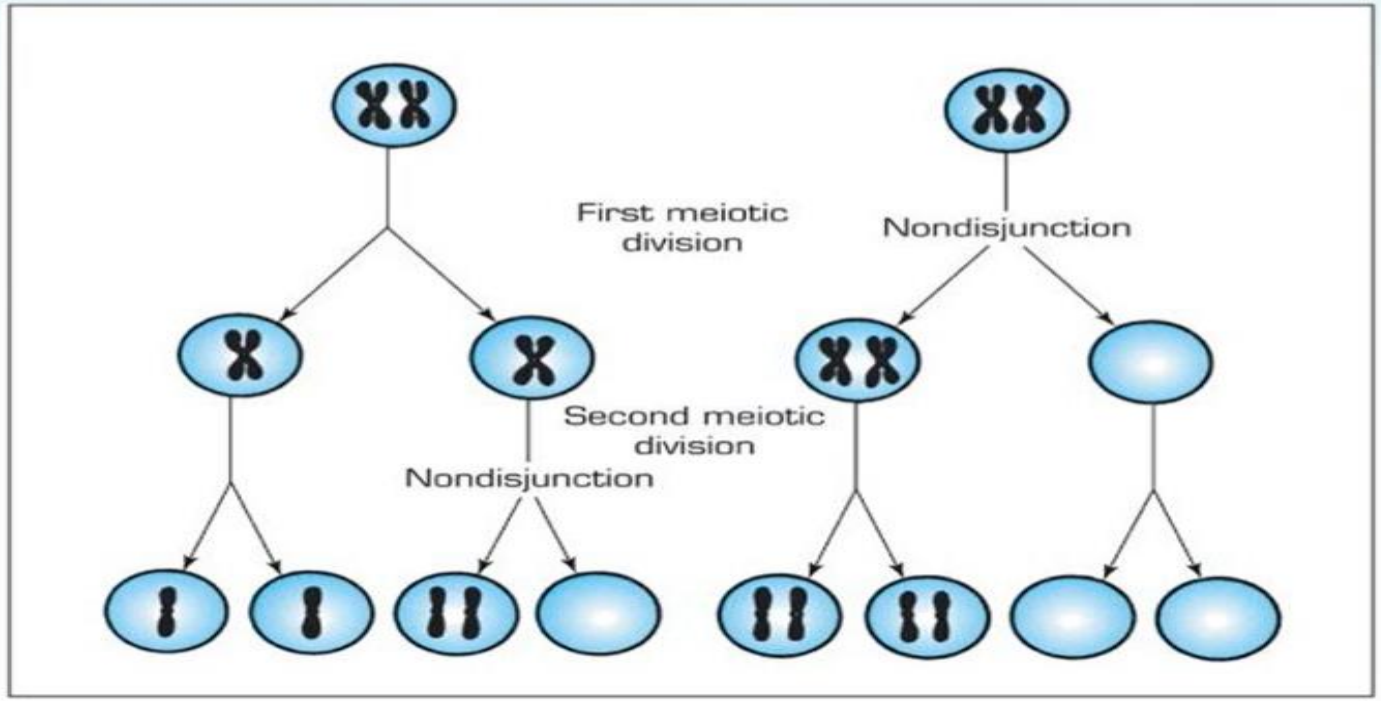
Autosomal Abnormalities (2 of 3)

- With trisomy of small chromosome 21
- Many fetuses are aborted early in pregnancy (70%)
- Those who live have Down syndrome
  - Nondisjunction during oogenesis occurs in 95% of cases
- Increased frequency with advancing maternal age: 1 in 50 if mother is > 40 years old
- Extra chromosome 21 acquired as part of the translocation chromosome

Autosomal Abnormalities (3 of 3)

- Nondisjunction occurring in zygote
  - Most common chromosomal abnormality: 1:600 births
  - Manifestations: mental deficiency, cardiac malformation, major defects in other organ systems
- Trisomy of chromosome 13: Cleft lip and palate; abnormal development of skull, brain, and eyes; congenital heart defect; polydactyly
- Trisomy of chromosome 18:
- Both 13 and 18 trisomies are usually fatal in the neonatal period or in early infancy

Effects of nondisjunction in meiosis, leading to formation of gametes with an extra or missing chromosome.



Transmission of Genetically Determined Diseases

- Autosomal dominant inheritance
- Autosomal recessive inheritance
- Codominant inheritance
- X-linked inheritance
- Most hereditary diseases are transmitted on autosomes
- Few are carried on sex chromosomes

Multifactorial Inheritance

- Combined effect of multiple genes interacting with environmental agents
- Congenital abnormalities
  - Cleft lip, cleft palate, cardiac malformations, clubfoot, dislocation of hip, anencephaly, spina bifida

TABLE 9-2

Mode of inheritance, pathogenesis, and major manifestations of some common genetic diseases

ABNORMALITY	MODE OF INHERITANCE	DEFECT	MANIFESTATIONS
Phenylketonuria	Recessive	Phenylalanine hydroxylase deficiency	Mental retardation
Tay-Sachs disease	Recessive	Hexosaminidase A deficiency	Mental retardation, motor weakness, blindness
Cystic fibrosis of pancreas	Recessive	Dysfunction of mucous and sweat glands, thick mucus obstructs bronchioles, pancreatic ducts, and bile ducts	Chronic broncho-pulmonary infections as a result of bronchial obstruction by mucus; pancreatic and liver dysfunction as a result of thick mucous obstruction of excretory ducts
Achondroplasia	Dominant	Disordered bone growth at ends of long bones (epiphyses)	Dwarfism with disproportionately short limbs
Congenital polycystic kidney disease (one type)	Dominant	Maldevelopment of nephrons and collecting tubules causes formation of multiple cysts in kidneys	Renal failure
Multiple neurofibromatosis	Dominant	Multiple tumors arise from peripheral nerves	Disfigurement and deformities caused by tumors; predisposition to malignant change in tumors
Sickle cell trait	Codominant	Red cells contain mixture of normal (A) and sickle (S) hemoglobin	None
Sickle cell anemia	Codominant	Red cells contain no normal hemoglobin	Severe anemia and obstruction of blood flow to organs by masses of sickled red cells
Hemophilia	X-linked recessive	Deficiency of protein required for normal coagulation of blood	Uncontrolled bleeding into joints and internal organs after minor injuries

Effect of Radiation, Chemical, and Drugs

Intrauterine Injury

- Causes
  - Harmful drugs and chemicals (Table 9-3)
  - Radiation
  - Maternal infections (Figure 9-11)
    - Rubella, cytomegalovirus, *Toxoplasma gondii*
    - 3rd–8th week after conception: embryo is most vulnerable to injury as organ systems are forming

Prenatal Diagnosis of Congenital Abnormalities (1 of 2)

- Examination of fetal cells: determination of biochemical abnormalities in fetal cells
  - Chromosomal abnormalities
  - Biochemical abnormalities
  - Analysis of DNA
- Examination of amnionic fluid: products secreted into fluid by fetus that may indicate fetal abnormality

Prenatal Diagnosis of Congenital Abnormalities (2 of 2)

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- Ultrasound examination: detection of major structural abnormalities
  - Major structural abnormalities of nervous system (anencephaly; spina bifida)
  - Hydrocephalus
  - Obstruction of urinary tract
  - Failure of kidneys to develop
  - Failure of limbs to form normally
- Fetal DNA analysis: determination of biochemical abnormalities by analysis of DNA of fetal cells
  - Amniocentesis
  - Chorionic villus sampling

Thank you……