Birth Defects & Prenatal Diagnosis

Birth defect, congenital malformation or anomaly

- Structural
- Behavioral
- functional,
- metabolic disorders present at birth
- **Teratology**
- 3%
- 25% of infant deaths
- 5th cause of death before age 65
- major contributor to disabilities

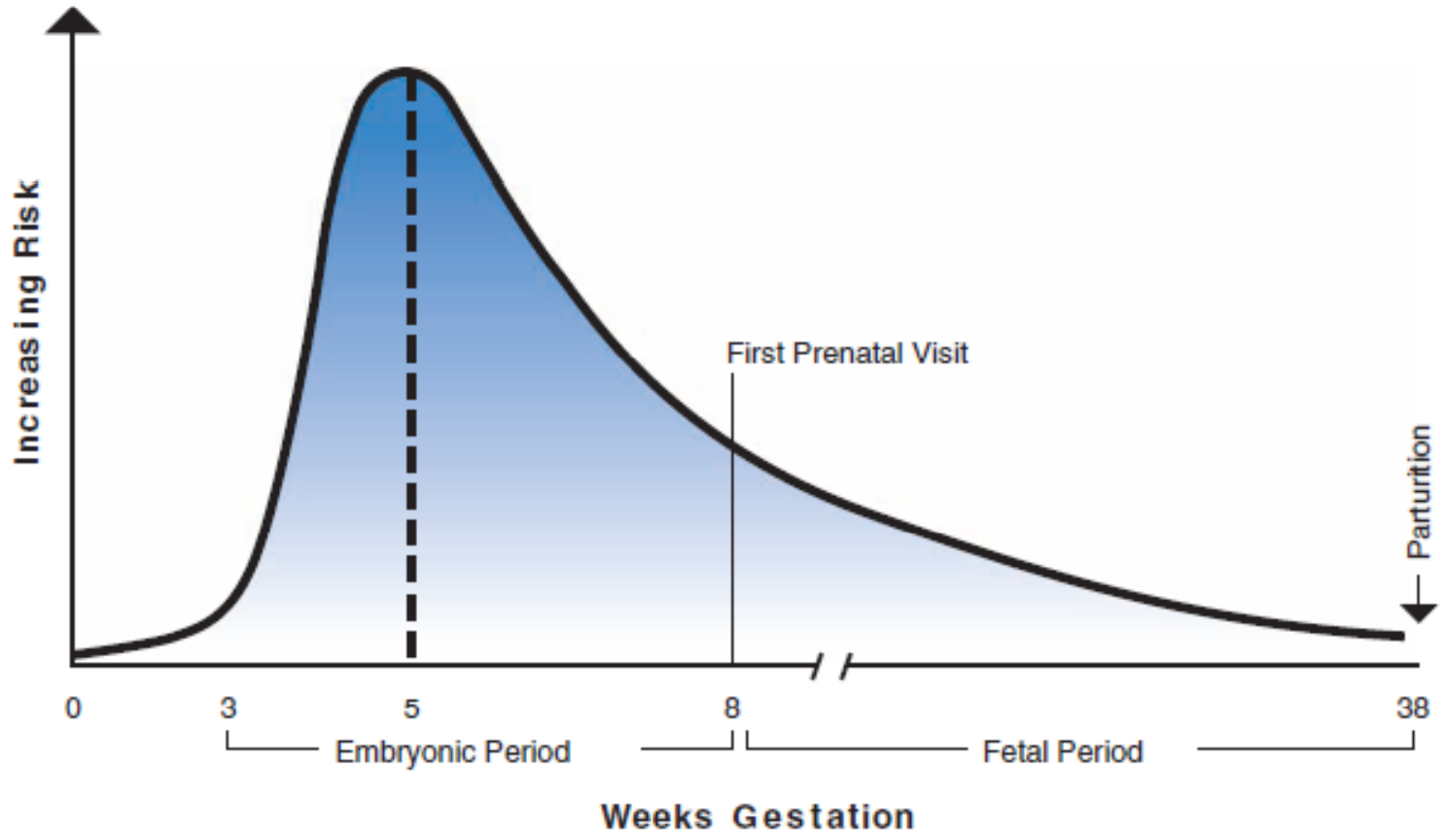
birth defects

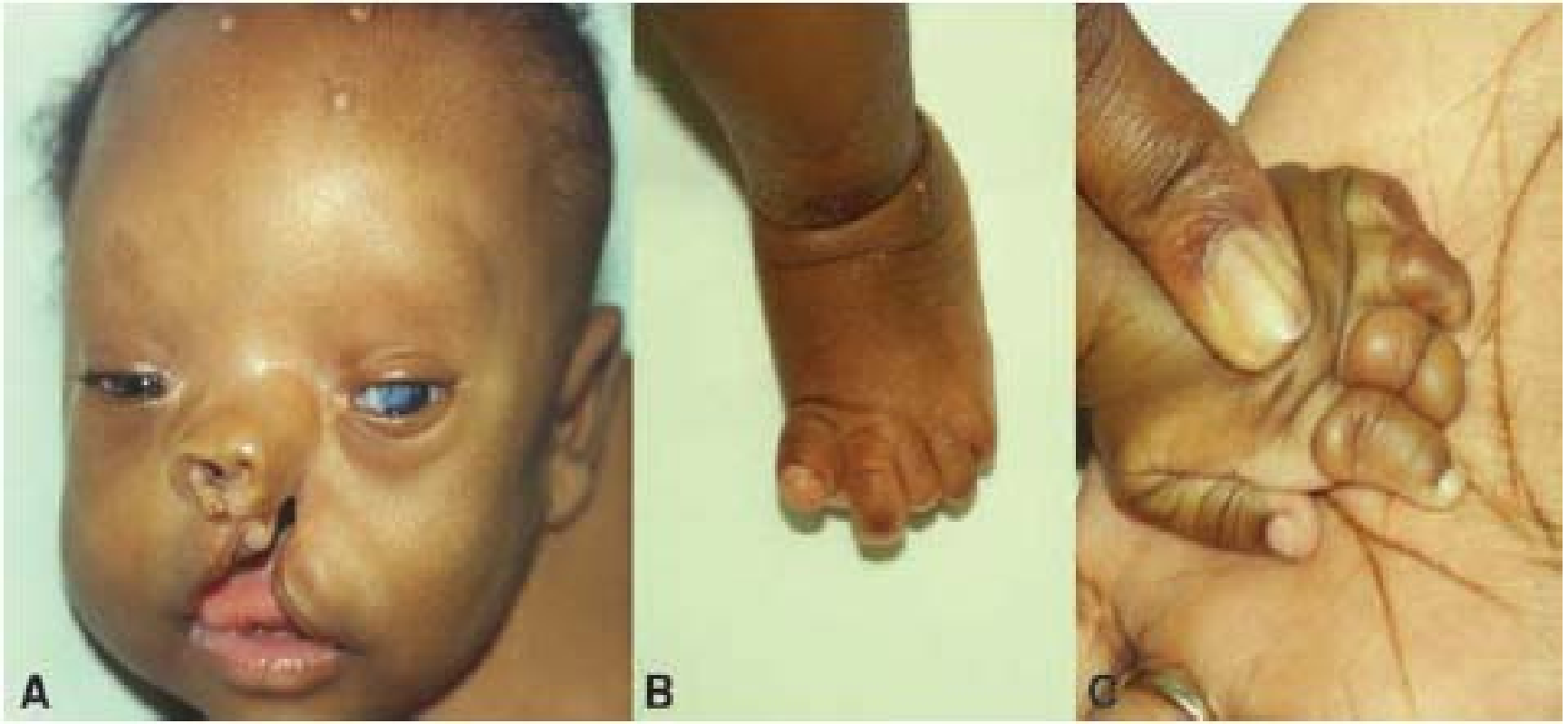
- 30% Genetic factors (chromosome abnormalities & mutant genes)
- 15% environmental Factors
- 55% Combination of genetic & environmental factors

Minor anomalies occur in approximately

- 15% of newborns abnormalities,
- such as microtia, pigmented spots, short palpebral fissures

Risk of Birth Defects Being Induced




A
B
C

Types of Abnormalities

- Malformations
- Disruptions
- Deformations
- Syndrome
- association

Malformations

- complete or partial absence of a structure or
- alterations of its normal configuration.
- caused by environmental and/or genetic factors
- third to 8th weeks of gestation

Disruptions

- morphological alterations of already formed structures
- by destructive processes
- Vascular accidents
- amniotic bands

Deformations

- mechanical forces for a prolonged period
- clubfeet
- Musculoskeletal system
- may be reversible postnatally

Syndrome & Association

Syndrome

- a group of anomalies occurring together that have a specifi c common cause

Association

- the nonrandom appearance of two or more anomalies that occur together more frequently than by chance alone
- No determined cause
- the VACTERL (*vertebral, anal, cardiac, tracheoesophageal, renal,* and *limb anomalies)*

Environmental Factors

- 1940s
- congenital defects are hereditary
- N. Gregg
- rubella (German measles)

- 1961
- W. Lenz
- Thalidomide
- teratogens

TABLE 9.1 *Teratogens Associated With Human Malformations*

Teratogen	Congenital Malformations
Infectious agents	
Rubella virus	Cataracts, glaucoma, heart defects, hearing loss, tooth abnormalities
Cytomegalovirus	Microcephaly, visual impairment, intellectual disability, fetal death
Herpes simplex virus	Microphthalmia, microcephaly, retinal dysplasia
Varicella virus	Skin scarring, limb hypoplasia, intellectual disability, muscle atrophy
Toxoplasmosis	Hydrocephalus, cerebral calcifications, microphthalmia
Syphilis	Intellectual disability, hearing loss
Physical agents	
X-rays	Microcephaly, spina bifida, cleft palate, limb defects
Hyperthermia	Anencephaly, spina bifida, intellectual disability
Chemical agents	
Thalidomide	Limb defects, heart malformations
Aminopterin	Anencephaly, hydrocephaly, cleft lip and palate
Diphenylhydantoin (phenytoin)	Fetal hydantoin syndrome: facial defects, intellectual disability
Valproic acid	Neural tube defects; heart, craniofacial, and limb anomalies
Trimethadione	Cleft palate, heart defects, urogenital and skeletal abnormalities
Lithium	Heart malformations
SSRIs	Heart malformations
Amphetamines	Cleft lip and palate, heart defects
Warfarin	Skeletal abnormalities (nasal hypoplasia, stippled epiphyses)
ACE inhibitors	Growth retardation, fetal death
Mycophenylate mofetil	Cleft lip and palate, heart defects, microtia, microcephaly
Alcohol	Fetal alcohol syndrome (FAS), short palpebral fissures, maxillary hypoplasia, heart defects, intellectual disability
Isotretinoin (vitamin A)	Isotretinoin embryopathy: small, abnormally shaped ears, mandibular hypoplasia, cleft palate, heart defects
Industrial solvents	Low birth weight, craniofacial and neural tube defects
Organic mercury	Neurological symptoms similar to those of cerebral palsy
Lead	Growth retardation, neurological disorders
Hormones	
Androgenic agents	Masculinization of female genitalia: fused labia, clitoral hypertrophy (ethisterone, norethisterone)
DES	Malformation of the uterus, uterine tubes, and upper vagina; vaginal cancer; malformed testes
Maternal diabetes	Various malformations; heart and neural tube defects most common
Maternal obesity	Neural tube defects, heart defects, omphalocele

SSRIs, Selective serotonin reuptake inhibitors; ACE, angiotensin-converting enzyme; DES, diethylstilbestrol.

Principles of Teratology

1. genotype of the conceptus
2. the developmental stage at the time of exposure
3. dose & duration of exposure
4. mechanisms:cell death, decreased cell proliferation, or other cellular phenomena
5. abnormal development: death, malformation, growth retardation, functional disorders

Infectious Agents

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Other Viral Infections & Hyperthermia

- coxsackie virus: spontaneous abortion
- measles & mumps: increase in early and late fetal death and neonatal measles and mumps
- Hepatitis B: fetal and neonatal hepatitis
- hepatitis A, C, and E: rarely transmitted transplacentally

Pyrogenic (cause fevers)
Hyperthermia
caused by fevers or possibly by

- neurulation
- anencephaly & spina bifida

- Toxoplasmosis
- Poorly cooked meat; feces of domestic animals (cats)
- cerebral calcifications
- microcephaly (small head)
- Macrocephaly (large head)
- Hydrocephalus

Radiation

- **Ionizing radiation kills proliferating cells**
- dose and stage of development

- Hiroshima and Nagasaki Atomic bomb explosions
- 28% spontaneously aborted
- 25% gave birth to children who died in their first year of life
- 25% gave birth to children who had severe birth defects (CNS)

- Chernobyl explosion of the nuclear reactor

Pharmaceutical Drugs & Chemical Agents

(1) most studies are retrospective (mother's memory)
(2) pregnant women take a large number of medications

- Only 20% of pregnant women used no drugs taken during pregnancy.
- **Thalidomide (antinauseant & sleeping)**
- **amelia & meromelia**

Diphenylhydantoin (phenytoin), valproic acid, and trimethadione,

- Seizure
- **Trimethadione** & **fetal hydantoin syndromes**
  Facial clefts

- **valproic acid increases the risk of**
- atrial septal defects, cleft palate, hypospadius, polydactyly, and craniosynostosis, neural tube defect, spina bifida.

Pharmaceutical Drugs & Chemical Agents

Antipsychotic & antianxiety agents

- **phenothiazine & lithium**
- congenital heart defects, especially Ebstein anomaly,

Antidepressant drugs that work as selective (serotonin reuptake inhibitors)

- heart defects, spontaneous abortions
- fluoxetine (Prozac), paroxetine (Paxil),

Mycophenolate mofetil (immunosuppressant)

- spontaneous abortions, cleft lip & palate, microtia, microcephaly, & heart defects

anticoagulant warfarin is teratogenic.

- skeletal abnormalities, nasal hypoplasia, abnormal epiphyses in long bones, limb hypoplasia.
- **heparin** does not teratogenic.

Pharmaceutical Drugs & Chemical Agents

Antihypertensive agents (inhibit angiotensin-converting enzyme inhibitors)

- **growth retardation, renal** dysfunction, fetal death, and oligohydramnios
- second or third trimester

- propylthiouracil & potassium iodide (goiter & intellectual disability)
- Streptomycin (hearing loss)
- sulfonamides (kernicterus)
- antidepressant imipramine (limb deformities),
- tetracyclines (bone and tooth anomalies),
- amphetamines (oral clefts and cardiovascular abnormalities)
- quinine (hearing loss).

- social drugs, such as LSD (lysergic acid diethylamide), PCP (phencyclidine, or “angel dust”), marijuana, alcohol, and cocaine.
- LSD, limb abnormalities and CNS malformations

Pharmaceutical Drugs & Chemical Agents

alcohol

- intellectual disability
- brain abnormalities (microcephaly, holoprosencephaly), face, and heart,
- Fetal alcohol syndrome (FAS)
- structural defects, growth deficiency, and intellectual disability
- Dosage & exposure time

Cigarette smoking

- increased risk for orofacial clefts (cleft lip and cleft palate)
- Intrauterine growth retardation
- premature delivery

Isotretinoin (Accutane), vitamin A

- isotretinoin embryopathy
- treatment of cystic acne and other chronic dermatoses

- **Androgenic Agents (synthetic progestins)**
- prevent abortion.
- masculinization of the genitalia in female embryo
- enlarged clitoris
- fusion of the labioscrotal folds

Figure 9.5 Characteristic features of a child with Fetal alcohol syndrome (FAS), including an indistinct philtrum, thin upper lip, depressed nasal bridge, short nose, and flat midface.

Hormones

Endocrine disrupters are exogenous agents

- developmental abnormalities of the central nervous system and reproductive tract
- **Diethylstilbestrol (DES)**
- carcinomas of the vagina and cervix
- Male embryos testes malformations & abnormal sperm analysis

environmental estrogens

- Decreasing sperm counts and increasing incidences of testicular cancer, hypospadias, reproductive tract abnormalities, CNS abnormalities (masculinization of female brains and feminization of male brains

Oral Contraceptives Birth control pills,

- low teratogenic potential

Cortisone

- child with an orofacial cleft.

Maternal Disease

Diabetes

- Stillbirths
- Neonatal deaths
- abnormally large infants
- Congenital malformations (3 to 4 times)
- neural tube defects
- congenital heart defects
- caudal dysgenesis (sirenomelia)

- **insulin is not teratogenic**

Phenylketonuria(PKU)

- Phenylalanine hydroxylase deficiency
- intellectual disability,
- Microcephaly
- cardiac defects

Nutritional Deficiencies

Endemic cretinism

- iodine deficiency
- characterized by stunted mental & physical growth

Methyl-deficient diets alter expression of imprinted genes

- birth defects
- cancer postnatally

Maternal malnutrition

- low birth weight
- 2 to 3 fold increase in schizophrenia

Obesity

- 2 fold increased risk for having a child with a neural tube defect
- maternal metabolic disturbances affecting

Glucose,

Insulin

other factors

- Prepregnancy obesity increases the
- heart defect
- Omphalocele
- multiple congenital anomalies

Hypoxia

- Hypoxia induces congenital malformations in animals
- children born at relatively high altitudes

lighter in weight

Smaller than those born near or at sea level

no increase in the incidence of congenital malformations

- women with cyanotic cardiovascular disease
- small infants but usually without gross congenital malformations.

Heavy Metals

- **organic mercury**

Japan (fish)
United state (corn, Fungicide)
Iraq (fungicide)

- **Lead**

Abortion
Growth retardation
Neurological disorder

Male-mediated teratogenesis

- Ethylnitrosourea
- Iradiation
- Male germ cell mutation

Mercury
Lead
Solvents
Alcohol
Cigarette smoking

- **Spontaneous abortion**
- **Low birth weight**
- **Birth defects**

- **Advanced paternal age**
- Structural birth defects
- Down syndrome
- Autosomal dominant mutation

Clinical Correlates

Prevention of Birth Defects

Many birth defects can be prevented. For example, supplementation of salt with iodine eliminates intellectual disability and bone deformities resulting from **cretinism**. Placing women with diabetes or PKU under strict metabolic control prior to conception reduces the incidence of birth defects in their offspring. **Folate supplementation** lowers the incidence of neural tube defects, such as spina bifida and anencephaly, and also reduces the risk for hyperthermia-induced abnormalities. Avoidance of alcohol during **all** stages of pregnancy reduces the incidence of birth defects. An essential component of all prevention strategies is to initiate interventions **prior to conception**.

It is important for physicians prescribing medications to women of childbearing age to consider the possibility of pregnancy and the potential teratogenicity of the compounds. Hundreds of children have been born with severe birth defects produced by **retinoids (isotretinoin embryopathy)**, compounds used for the treatment of cystic acne (isotretinoin, Accutane). Because patients with acne are usually young and may be sexually active, these agents must be used cautiously

Prenatal diagnosis

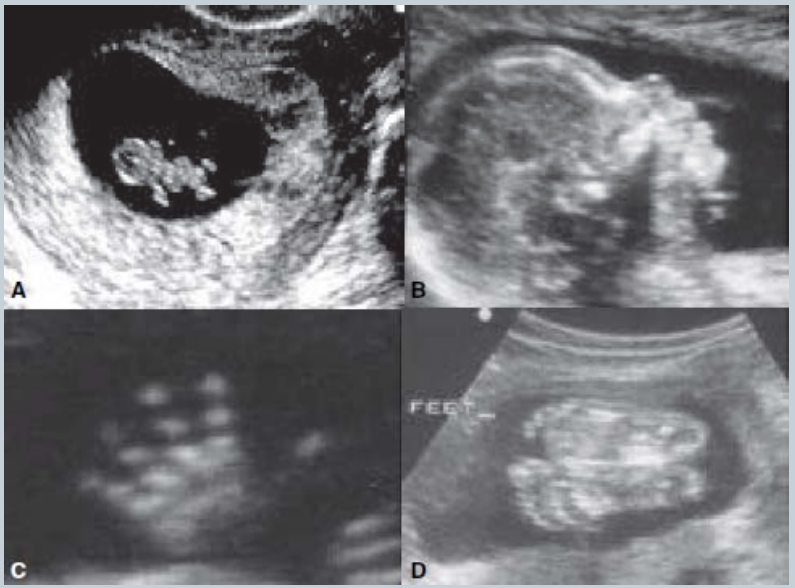
- **Ultrasound**
- **Maternal serum screening**
- **Amniocentesis**
- **Chorionic villus sampling**

Ultrasonography

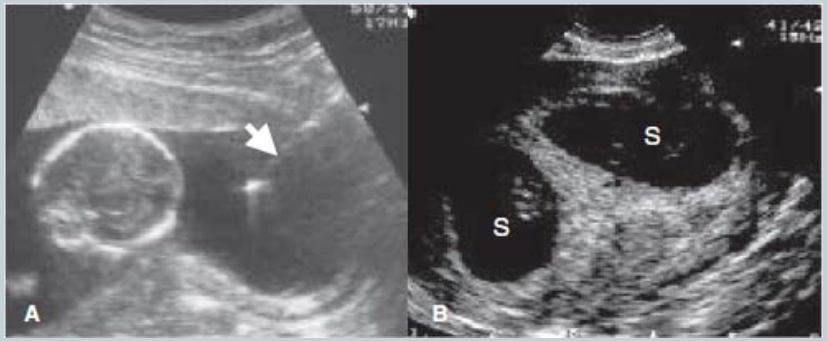
- Transabdominal
- Transvaginal

- Blood flow in large vessel
- Heart valve movement
- Fluid flow in trachea & bronchi

- Fetal age & growth
- Congenital anomalies
- Uterine environment
- Amniotic fluid amount
- Placental position
- Umbilical blood flow
- Multiple gestation



- neural tube defects
- anencephaly
- spina bifida
- abdominal wall defects (omphalocele & gastroschisis)
- heart defect
- facial defects c(left lip and palate)



- Nuchal translucency
- 11^{th} -14^{th} week
- Down syndrome

Maternal Serum Screening

- serum a-fetoprotein (AFP) concentrations
- AFP is produced normally by the fetal liver
- peaks at 14 weeks (second trimester)
- decline after 30 weeks

increased AFP levels

- neural tube defects
- omphalocele
- Gastroschisis
- bladder exstrophy
- Amniotic band syndrome
- sacrococcygeal teratoma
- Intestinal atresia

decreased AFP concentrations

- Down syndrome,
- trisomy 18
- sex chromosome abnormalities
- Triploidy

- second trimester markers
- human chorionic gonadotropin (HCG)
- unconjugated estriol,
- inhibin A

Amniocentesis

- *20 to* 30 mL of fl uid is withdrawn. Because of the

- No before 14 weeks' gestation, when

- risk of fetal loss
- as 1 in 300 to 500

- AFP
- acetylcholinesterase
- metaphase karyotyping (fetal cells)
- 1 to 2 weeks

- major chromosomal alterations

translocations, breaks, trisomies, monosomies

- Giemsa staining
- chromosome-banding patterns
- polymerase chain reaction (PCR)
- genotyping

Chorionic Villus Sampling

- 5 to 30 mg of villus tissue
- high frequency of chromosomal errors in the normal placenta
- cells from the mesenchymal core
- 2 to 3 days
- culture are necessary to permit genetic analysis.

- The risk is like amniocentesis
- limb reduction defects, especially digits

- Advanced maternal age (35 years and older)
- Previous family history of a genetic problem(Down syndrome or neural tube defect)
- The presence of maternal disease, such as diabetes
- An abnormal ultrasound or serum screening test

Fetal Therapy

Fetal Transfusion

- fetal anemia (maternal antibodies)
- Ultrasound is guide insertion of a needle into the umbilical cord vein

Fetal Medical Treatment

- Treatment :
- Infections
- fetal cardiac arrhythmias
- compromised thyroid function

agents may be administered to the fetus directly

- intramuscular injection into the gluteal region
- via the umbilical vein

Fetal Therapy

Fetal Surgery

- advances in ultrasound & surgical procedures

placing shunts to remove fluid from organs & cavities

- obstructive urinary disease of the urethra

Exutero surgery

- repairing congenital diaphragmatic hernias
- removing cystic (adenomatoid) lesions in the lung
- repairing spina bifida defects
- certain congenital heart defects

Stem Cell Transplantation and Gene Therapy

- no immunocompetency before 18 weeks
- tissues or cells transplantation (without rejection)

- hematopoietic stem cells for immunodeficiency treatment & hematologic disorders
- Gene therapy for inherited metabolic diseases (Tay-Sachs & cystic fibrosis)