Birth Defects and Prenatal Diagnosis
Birth Defects:

Birth defect, congenital malformation, and congenital anomaly are synonymous terms used to *describe structural, behavioral, functional, and metabolic disorders present at birth*.
Teratology and dysmorphology are terms used to describe the study of these disorders.

Major structural anomalies
occur in 2% to 3% of liveborn infants, and an additional 2% to 3% are recognized in children by age 5 years, for a total of 4% to 6%.

Etiology

In 40% to 60% of persons with birth defects, the cause is unknown.

Genetic factors, such as chromosome abnormalities and mutant genes, account for approximately 15%;
Environmental factors produce approximately 10%;
a combination of genetic and environmental influences (multifactorial inheritance) produces 20% to 25%; and twinning causes 0.5% to 1%.

Minor anomalies

occur in approximately 15% of newborns. These structural abnormalities, such as microtia (small ears), pigmented spots, and short palpebral fissures, are not themselves detrimental to health but, in some cases, are associated with major defects. For example, infants with one minor anomaly have a 3% chance of having a major malformation; those with two minor anomalies have a 10% chance; and those with three or more minor

anomalies have a 20% chance. Therefore, minor anomalies serve as clues for diagnosing more serious underlying defects.

In particular, ear anomalies are easily recognizable indicators of other defects and are observed in virtually all children with syndromic malformations.

Types of Abnormalities   P.112

Malformations occur during formation of structures, for example, during organogenesis. They may result in complete or partial absence of a structure or in alterations of its normal configuration.

Malformations are caused by environmental and/or genetic factors acting independently or in concert.

Most malformations have their origin during the third to eighth weeks of gestation (see Fig. 8.1).

Disruptions result in morphological alterations of already formed structures and are due to destructive processes. Vascular accidents leading to bowel atresias (see Chapter 14) and defects produced by amniotic bands are examples of destructive factors that produce disruptions.

Deformations are due to mechanical forces that mold a part of the fetus over a prolonged period. Clubfeet, for example, are due to compression in the amniotic cavity. Deformations often involve the musculoskeletal system and may be reversible postnatally.

Syndrome is a group of anomalies occurring together that have a *specific common cause*. This term indicates that a diagnosis has been made and that the risk of recurrence is known.

In contrast, association is the nonrandom appearance of two or more anomalies that occur together more frequently than by chance alone, but whose *cause has not been determined*. An example is the VACTERL association (vertebral, anal, cardiac, tracheoesophageal, renal, and limb anomalies). Although they do not constitute a diagnosis, associations are important because recognition of one or more of the components promotes the search for others in the group.

Environmental Factors

Until the early 1940s, it was assumed that congenital defects were caused primarily by hereditary factors. With the discovery by N. Gregg that German measles affecting a mother during early pregnancy caused abnormalities in the embryo, it suddenly became evident that

congenital malformations in humans could also be caused by environmental factors.

In 1961, observations by W. Lenz linked limb defects to the sedative thalidomide and made it clear that drugs could also cross the placenta and produce birth defects (see Fig. 8.2).

Since that time, many agents have been identified as teratogens (Table 8.1). P.113

TABLE 8.1 Teratogens Associated with Human

Teratogen	Congenital Malformations
Infectious agents	
Rubella virus	Cataracts, glaucoma, heart defects,
Cytomegalovirus	Microcephaly, blindness, mental re
Herpes simplex virus	Microphthalmia, microcephaly, ret
Varicella virus	Limb hypoplasia, mental retardatio
HIV	Microcephaly, growth retardation
Toxoplasmosis	Hydrocephalus, cerebral calcificati
Syphilis	Mental retardation, deafness
Physical agents	
X-rays	Microcephaly, spina bifida, cleft p

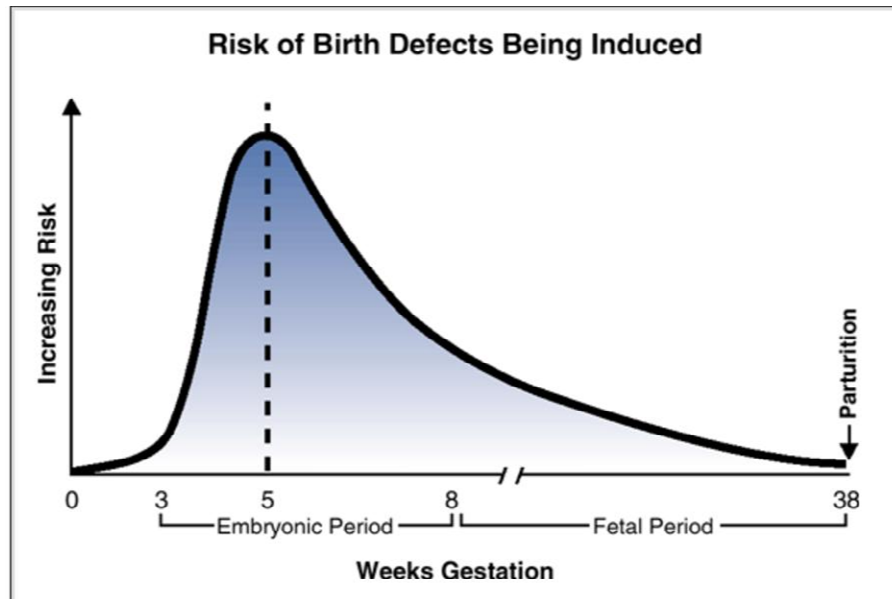|	
Hyperthermia	Anencephaly, spina bifida, ment... abnormalities, omphalocele, limb ...
Chemical agents	
Thalidomide	Limb defects, heart malformations
Aminopterin	Anencephaly, hydrocephaly, cleft ...
Diphenylhydantoin (phenytoin)	Fetal hydantoin syndrome: facial d...
Valproic acid	Neural tube defects, heart, craniofa...
Trimethadione	Cleft palate, heart defects, urogeni...
Lithium	Heart malformations
Amphetamines	Cleft lip and palate, heart defects
Warfarin	Chondrodysplasia, microcephaly
ACE inhibitors[a]	Growth retardation, fetal death
Cocaine	Growth retardation, microce... gastroschisis
Alcohol	Fetal alcohol syndrome, short pal... heart defects, mental retardation
Isotretinoin (vitamin A)	Vitamin A embryopathy: small, ab... hypoplasia, cleft palate, heart defe...
Industrial solvents	Low birth weight, craniofacial and ...
Organic mercury	Neurological symptoms similar to ...
Lead	Growth retardation, neurological d...
Hormones	
Androgenic agents (ethisteron... norethisterone)	Masculinization of female genitali...
Diethylstilbestrol (DES)	Malformation of the uterus, uteri... cancer; malformed testes
Maternal diabetes	Variety of malformations; heart an...
Maternal obesity	Heart defects, omphalocele

Principles of Teratology

Factors determining the capacity of an agent to produce birth defects have been defined and set forth as the principles of teratology. They include the following:

- Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this genetic composition interacts with the environment.
- The maternal genome is also important with respect to drug metabolism, resistance to infection, and other biochemical and molecular processes that affect the conceptus.

- Susceptibility to teratogens varies with the developmental stage at the time of exposure. The most sensitive

period for inducing birth defects is the third to eighth weeks of gestation, the period of embryogenesis.

- Each organ system may have one or more stages of susceptibility. For example, cleft palate can be induced at the blastocyst stage (day 6), during gastrulation (day 14), at the early limb bud stage (fifth week), or when the palatal shelves are forming (seventh week).

- Furthermore, while most abnormalities are produced during embryogenesis, defects may also be induced before or after this period; no stage of development is completely safe (Fig. 8.1).

Risk of Birth Defects Being Induced

Increasing Risk

Parturition

0   3   5   8   38

Embryonic Period   Fetal Period

Weeks Gestation

- Manifestations of abnormal development depend on dose and duration of exposure to a teratogen.
- Teratogens act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis (pathogenesis). Mechanisms may involve inhibition of a specific biochemical or molecular process;

- pathogenesis may involve cell death, decreased cell proliferation, or other cellular phenomena.
- Manifestation of abnormal development are:
- death, malformation, growth retardation, and functional disorders.

Infectious Agents

Infectious agents that cause birth defects (Table 8.1) include a number of viruses. Rubella used to be a major problem, but the ability to detect serum antibody titers and development of a vaccine have significantly lowered the incidence of birth defects from this cause. Today approximately 85% of women are immune.

Cytomegalovirus is a serious threat. Often, the mother has no symptoms, but the effects on the fetus can be devastating. The infection is often fatal,

and if it is not, meningoencephalitis caused by the virus produces mental retardation.

Herpes simplex virus, varicella virus, and human immunodeficiency virus (HIV) can cause birth defects. Herpes-induced abnormalities are rare, and usually infection is transmitted as a venereal disease to the child during delivery.

Similarly, HIV (the cause of acquired immuno-deficiency syndrome, or AIDS) appears to have a low teratogenic potential.

Infection with varicella causes a 20% incidence of birth defects.

Other Viral Infections and Hyperthermia

Malformations following maternal infection with measles, mumps, hepatitis, poliomyelitis, echovirus, Coxsackie virus, and influenza virus have been described. Prospective studies indicate

that the malformation rate following exposure to these agents is low if not nonexistent.

A complicating factor introduced by these and other infectious agents is that most are pyrogenic, and elevated body temperature (hyperthermia) is teratogenic. Defects produced by exposure to elevated temperatures include anencephaly, spina bifida, mental retardation, microphthalmia, cleft lip and palate, limb deficiencies, omphalocele, and cardiac abnormalities.
In addition to febrile illnesses, use of hot tubs and saunas can produce sufficient temperature elevations to cause birth defects.

Toxoplasmosis and syphilis cause birth defects. Poorly cooked meat; domestic animals, especially cats; and feces in contaminated soil can carry the

protozoan parasite Toxoplasmosis gondii. A characteristic feature of fetal toxoplasmosis infection is cerebral calcifications.

Radiation

Ionizing radiation kills rapidly proliferating cells, so it is a potent teratogen, producing virtually any type of birth defect depending upon the dose and stage of development of the conceptus at the time of exposure.

Radiation from nuclear explosions is also teratogenic. Among women survivors pregnant at the time of the atomic bomb explosions over Hiroshima and Nagasaki, 28% aborted, 25% gave

birth to children who died in their first year of life, and 25% gave birth to children who had severe birth defects involving the central nervous system.

Radiation is also a mutagenic agent and can lead to genetic alterations of germ cells and subsequent malformations.

Chemical Agents

The role of chemical agents and pharmaceutical drugs in the production of abnormalities in humans is difficult to assess for two reasons:

(a) most studies are retrospective, relying on the mother's memory for a history of exposure and

(b) pregnant women take a large number of pharmaceutical drugs.

Thalidomide, an antinauseant and sleeping pill. In 1961, it was noted in West Germany that the frequency of amelia and meromelia (total or partial absence of the extremities), a rare hereditary abnormality, had suddenly increased (Fig. 8.2).

This observation led to examination of the prenatal histories of affected children and to the discovery that many mothers had taken thalidomide early in pregnancy. The causal relation between thalidomide and meromelia was discovered only because the drug produced such an unusual abnormality.

Anticonvulsants diphenylhydantoin (phenytoin), valproic acid, and trimethadione, which are used by epileptic women. Specifically, trimethadione and diphenylhydantoin produce a broad spectrum of abnormalities that constitute distinct patterns of dysmorphogenesis known as the trimethadione and fetal hydantoin syndromes. Facial clefts are particularly common to these syndromes.

Valproic acid also causes craniofacial abnormalities but has a particular propensity for producing neural tube defects.

Antipsychotic and antianxiety agents are suspected producers of congenital malformations.

The antipsychotics phenothiazine and lithium have been implicated as teratogens. In any case, it has been strongly suggested that use of these

agents during pregnancy carries a high risk.

Antianxiety agents meprobamate, chlordiazepoxide, and diazepam (Valium). A prospective study showed that severe anomalies occurred in 12% of fetuses exposed to meprobamate and in 11% of those exposed to chlordiazepoxide, compared with 2.6% of controls. Likewise, retrospective studies demonstrate up to a fourfold increase in cleft lip with or without cleft palate in offspring whose mothers took diazepam during pregnancy.

The anticoagulant: warfarin is teratogenic, whereas heparin does not appear to be.

Antihypertensive agents that inhibit angiotensin-converting enzyme (ACE inhibitors) produce growth retardation, renal dysfunction, fetal death, and oligohydramnios.

Other compounds that may damage the embryo or fetus. The most prominent among these are propylthiouracil and potassium iodide (goiter and mental retardation), streptomycin (deafness), sulfonamides (kernicterus), the antidepressant imipramine (limb deformities), tetracyclines (bone and tooth anomalies), amphetamines (oral clefts and cardiovascular abnormalities), and quinine (deafness).

Finally, there is increasing evidence that aspirin (salicylates), the most commonly ingested drug during pregnancy, may harm the developing offspring when used in large doses.

One of the increasing problems in today's society is the effect of social drugs, such as LSD (lysergic acid diethylamide), PCP (phencyclidine, or "angel dust"), marijuana, alcohol, and cocaine. In the case of LSD, limb

abnormalities and malformations of the central nervous system have been reported. A similar lack of conclusive evidence for teratogenicity has been described for marijuana and PCP. Cocaine has been reported to cause a number of birth defects, possibly due to its action as a vasoconstrictor that causes hypoxia.

Alcohol may induce a broad spectrum of defects, ranging from mental retardation to structural abnormalities, the term fetal alcohol spectrum disorder (FASD) is used to refer to any alcohol-related defects.

Fetal alcohol syndrome (FAS) represents the severe end of the spectrum and includes structural defects, growth deficiency, and mental retardation (see Fig. 8.3).

Alcohol-related neurodevelopmental disorder (ARND) represents a less severe example of alcohol-related abnormalities.

The incidence of FAS and ARND together is 1 in 100 live births. Furthermore, alcohol is the leading cause of mental retardation.

Figure 8.3 Characteristic features of a child with fetal alcohol syndrome, including an indistinct philtrum, thin upper lip, depressed nasal bridge, short nose, and flat midface.

Cigarette smoking has not been linked to major birth defects, but it does contribute to intrauterine growth retardation and premature delivery. There is also evidence that it causes behavioral disturbances.

Isotretinoin embryopathy or vitamin A embryopathy. The drug Isotretinoin is prescribed for the treatment of cystic acne and other chronic dermatoses, but it is highly teratogenic and can produce virtually any type of malformation. Even topical retinoids, such as etretinate, may have the potential to cause abnormalities.

Hormones

ANDROGENIC AGENTS.

In the past, synthetic progestins were frequently used during pregnancy to prevent abortion. The progestins ethisterone and norethisterone have considerable androgenic activity, and many cases of masculinization of the genitalia in female embryos have been reported. The abnormalities consist of an enlarged clitoris associated with varying degrees of fusion of the labioscrotal folds.

ENDOCRINE DISRUPTERS.

 Most commonly, these agents interfere with the action of estrogen through its receptor to cause developmental abnormalities of the central nervous system and reproductive tract. synthetic estrogen diethylstilbestrol, which was used to prevent abortion, raised the incidence of carcinomas of the vagina

and cervix in women exposed to the drug in utero. Furthermore, a high percentage of these women had reproductive dysfunction due in part to congenital malformations of the uterus, uterine tubes, and upper vagina.

Male embryos exposed in utero can also be affected, as evidenced by an increase in malformations of the testes and abnormal sperm analysis among these individuals. In contrast to women, however, men do not demonstrate an increased risk of developing carcinomas of the genital system.

ORAL CONTRACEPTIVES.

Birth control pills, containing estrogens and progestogens, appear to have a low teratogenic potential. Since other hormones such as diethylstilbestrol produce abnormalities, however, use of oral contraceptives should be discontinued if pregnancy is suspected.

CORTISONE. Experimental work has repeatedly shown that cortisone injected into mice and rabbits at certain stages of pregnancy causes a high percentage of cleft palates in the offspring. However, it has been impossible to implicate cortisone as an environmental factor causing cleft palate in humans.

Maternal Disease

DIABETES.

Disturbances in carbohydrate metabolism during pregnancy in diabetic mothers cause a high incidence of stillbirths, neonatal deaths, abnormally

large infants, and congenital malformations.

The risk of congenital anomalies in children of diabetic mothers is three to four times that for the offspring of nondiabetic mothers and has been reported to be as high as 80% in the offspring of diabetics with long-standing disease. The variety of observed malformations includes caudal dysgenesis .

Factors responsible for these abnormalities have not been delineated, altered glucose levels may play a role and that insulin is not teratogenic. In this respect, a significant correlation exists between the severity and duration of the mother's disease and the incidence of malformations. Also, strict control of maternal metabolism with aggressive insulin therapy prior to conception reduces the occurrence of malformations. Such therapy, however, increases the

frequency and severity of hypoglycemic episodes. Numerous animal studies have shown that during gastrulation and neurulation, mammalian embryos depend on glucose as an energy source, so that even brief episodes of low blood glucose are teratogenic. Therefore, caution must be exercised in managing the pregnant diabetic woman.

In the case of non–insulin-dependent diabetes, oral hypoglycemic agents may be employed. These agents include the sulfonylureas and biguanides. Both classes of agents have been implicated as teratogens.

PHENYLKETONURIA.

Mothers with phenylketonuria (PKU), in which the enzyme phenylalanine hydroxylase is deficient, resulting in increased serum concentrations of phenylalanine, are at risk for having infants with mental retardation,

microcephaly, and cardiac defects. Women with PKU who maintain their low-phenylalanine diet prior to conception reduce the risk to their infants to that observed in the general population.

Nutritional Deficiencies

Although many nutritional deficiencies, particularly vitamin deficiencies, have been proven to be teratogenic in laboratory animals, the evidence in humans is sparse. Thus, with the exception of endemic cretinism, which is related to iodine deficiency, no analogies to animal experiments have been discovered. However, the evidence suggests that poor maternal nutrition prior to and during pregnancy contributes to low birth weight and birth defects.

Obesity

Prepregnancy obesity, defined as having a body mass index (BMI) >30 kg/m^2, is associated with a two- to threefold increased risk for having a child with a neural tube defect. Causation has not been determined but may relate to maternal metabolic disturbances affecting glucose, insulin, or other factors. Studies also have shown that prepregnancy obesity increases the risk for having a baby with a heart defect, omphalocele, and multiple anomalies.

Hypoxia

Hypoxia induces congenital malformations in a great variety of experimental animals. Whether the same is valid for humans remains to be seen. Although children born at relatively high altitudes are usually lighter in weight and smaller than those born near or at sea level, no increase in the incidence of congenital malformations has been

noted. In addition, women with cyanotic cardiovascular disease often give birth to small infants, but usually without gross congenital malformations.

Heavy Metals

Several years ago, researchers in Japan noted that a number of mothers with diets consisting mainly of fish had given birth to children with multiple neurological symptoms resembling cerebral palsy. Further examination revealed that the fish contained an abnormally high level of organic mercury, which was spewed into Minamata Bay and other coastal waters of Japan by large industries. Many of the mothers did not show any symptoms themselves, indicating that the fetus was more sensitive to mercury than the mother. *In Iraq*, several thousand babies were affected after mothers ate grain treated with mercury-containing fungicides.

Lead has been associated with increased abortions, growth retardation, and neurological disorders.

Male-mediated Teratogenesis

A number of studies have indicated that exposures to chemicals and other agents, such as ethylnitrosourea and radiation, can cause mutations in male germ cells. Epidemiological investigations have linked paternal occupational and environmental exposures to mercury, lead, solvents, alcohol, cigarette smoking, and other compounds to spontaneous abortion, low birth weight, and birth defects.

Advanced paternal age is a factor for an increased risk of limb and neural tube defects, Down syndrome, and new autosomal dominant mutations. Interestingly, men younger than 20 also

have a relatively high risk of fathering a child with a birth defect. Even transmission of paternally mediated toxicity is possible through seminal fluid and from household contamination from chemicals brought home on work clothes by the father. Studies also show that men with birth defects themselves have a greater than twofold risk of having an affected child.

Prenatal Diagnosis

The perinatologist has several approaches for assessing growth and development of the fetus in utero, including ultrasound, maternal serum screening, amniocentesis, and chorionic villus sampling. In combination, these techniques are designed to detect malformations, genetic abnormalities, overall fetal growth, and complications of pregnancy, such as placental or

uterine abnormalities. The use and development of in utero therapies have heralded a new concept in which the fetus is now a patient.

Ultrasonography

Ultrasonography is a relatively noninvasive technique that uses high-frequency sound waves reflected from tissues to create images. The approach may be transabdominal or transvaginal, with the latter producing images with higher resolution (see Fig. 8.4). In fact, the technique, which was first developed in the 1950s, has advanced to a degree where detection of blood flow in major vessels, movement of heart valves, and flow of fluid in the trachea and bronchi is possible. The technique is safe and commonly used, with approximately 80% of pregnant women in the United States receiving at least one scan.

Important parameters revealed by ultrasound include characteristics of fetal

age and growth; presence or absence of congenital anomalies; status of the uterine environment, including the amount of amniotic fluid (see Fig. 8.5A); placental position and umbilical blood flow; and whether multiple gestations are present (Fig. 8.5B). All of these factors are then used to determine proper approaches for management of the pregnancy.

Determination of fetal age and growth is crucial in planning pregnancy management, especially for low–birth-weight infants. In fact, studies show that ultrasound screened and managed pregnancies with low–birth-weight babies reduced the mortality rate by 60% compared with an unscreened group. Fetal age and growth are assessed by crown-rump length during the 5th to 10th weeks of gestation. After that, a combination of measurements— including the biparietal diameter (BPD)

of the skull, femur length, and abdominal circumference—are used (see Fig. 8.6). Multiple measures of these parameters over time improve the ability to determine the extent of fetal growth.

Congenital malformations that can be determined by ultrasound include the neural tube defects anencephaly and spina bifida (see Chapter 17); abdominal wall defects, such as omphalocele and gastroschisis (see Chapter 14); and heart (see Chapter 12) and facial defects, including cleft lip and palate (see Chapter 16).

P.119

Maternal Serum Screening

A search for biochemical markers of fetal status led to development of maternal serum screening tests. One of the first of these tests assessed serum a-fetoprotein (AFP) concentrations. AFP is produced normally by the fetal liver, peaks at approximately 14 weeks, and "leaks" into the maternal circulation via the placenta. Thus, AFP concentrations increase in maternal serum during the second trimester and then begin a steady decline after 30 weeks of gestation. In cases of neural tube defects and several other abnormalities, including omphalocele, gastroschisis, bladder exstrophy, amniotic band syndrome, sacrococcygeal teratoma, and intestinal atresia, AFP levels increase in amniotic fluid and maternal serum. In other instances, AFP concentrations decrease, as, for example, in Down syndrome, trisomy 18, sex chromosome abnormalities, and triploidy. These

conditions are also associated with lower serum concentrations of human chorionic gonadotropin (hCG) and unconjugated estriol. Therefore, maternal serum screening provides a relatively noninvasive technique for an initial assessment of fetal well-being.

Amniocentesis

During amniocentesis, a needle is inserted transabdominally into the amniotic cavity (identified by ultrasound; Fig. 8.5A), and approximately 20 to 30 mL of fluid is withdrawn. Because of the amount of fluid required, the procedure is not usually performed before 14 weeks gestation, when sufficient quantities are available without endangering the fetus. The risk of fetal loss as a result of the procedure is 1%, but it is less in centers skilled in the technique.

The fluid itself is analyzed for biochemical factors, such as AFP and acetylcholinesterase. In addition, fetal cells, sloughed into the amniotic fluid, can be recovered and used for metaphase karyotyping and other genetic analyses (see [Chapter 2](#)). Unfortunately, the harvested cells are not rapidly dividing, and therefore, cell cultures containing mitogens must be established to provide sufficient metaphase cells for analysis. This culture period requires 8 to 14 days, and consequently, making a diagnosis is delayed. Once chromosomes are obtained, major chromosomal alterations, such as translocations, breaks, trisomies, and monosomies, can be identified. With special stains (Giemsa) and high-resolution techniques, chromosome banding patterns can be determined. Furthermore, now that the human genome has been sequenced, more sophisticated molecular analyses

using polymerase chain reaction (PCR) and genotyping assays will increase the level of detection for genetic abnormalities.

Chorionic Villus Sampling

Chorionic villus sampling (CVS) involves inserting a needle transabdominally or transvaginally into the placental mass and aspirating approximately 5 to 30 mg of villus tissue. Cells may be analyzed immediately, but accuracy of results is problematic because of the high frequency of chromosomal errors in the normal placenta. Therefore, cells from the mesenchymal core are isolated by trypsinization of the external trophoblast and cultured. Because of the large number of cells obtained, only 2 to 3 days in culture are necessary to permit genetic analysis. Thus, the time for

genetic characterization of the fetus is reduced compared with amniocentesis. However, the risk of fetal loss from CVS is approximately twofold greater than with amniocentesis, and there have been indications that the procedure carries an increased risk for limb reduction defects.

Generally, these prenatal diagnostic tests are not used on a routine basis (although ultrasonography is approaching routine use), being reserved
P.121

instead for high-risk pregnancies. Indications for using the tests include the following: (1) advanced maternal age (35 years and older); (2) previous family history of a genetic problem, such as the parents having had a child with Down syndrome or a neural tube defect; (3) the presence of maternal disease, such as

diabetes; and (4) an abnormal ultrasound or serum screening test.

Fetal Therapy
Fetal Transfusion
In cases of fetal anemia produced by maternal antibodies or other causes, blood transfusions for the fetus can be performed. Ultrasound is used to guide insertion of a needle into the umbilical cord vein, and blood is transfused directly into the fetus.

Fetal Medical Treatment
Treatment for infections, fetal cardiac arrhythmias, compromised thyroid function, and other medical problems is usually provided to the mother and reaches the fetal compartment after crossing the placenta. In some cases,

however, agents may be administered to the fetus directly by intramuscular injection into the gluteal region or via the umbilical vein.

Fetal Surgery

Because of advances in ultrasound and surgical procedures, operating on fetuses has become possible. However, because of risks to the mother, infant, and subsequent pregnancies, procedures are only performed in centers with well-trained teams and only when there are no reasonable alternatives. Several types of surgeries may be performed, including placing shunts to remove fluid from organs and cavities. For example, in obstructive urinary disease of the urethra, a pigtail shunt may be inserted into the fetal bladder. One problem is diagnosing the condition early enough to prevent renal damage.

Ex utero surgery, where the uterus is opened and the fetus is operated upon

directly, has been used for repairing congenital diaphragmatic hernias, removing cystic (adenomatoid) lesions in the lung, and repairing spina bifida defects. Repairs of hernias and lung lesions have good outcomes if proper selection criteria for cases are employed, and one of these is the fact that without surgery, fetal demise is almost certain. Surgery for neural tube defects is more controversial because the abnormalities are not life threatening. Also, the evidence is not conclusive that repair of the lesion improves neurological function, although it does alleviate the accompanying hydrocephalus by freeing the tethered spinal cord and preventing herniation of the cerebellum into the foramen magnum (see Chapter 17).

Stem Cell Transplantation and Gene Therapy

Because the fetus does not develop any immunocompetence before 18 weeks' gestation, it may be possible to transplant tissues or cells before this time without rejection. Research in this field is focusing on hematopoietic stem cells for treatment of immunodeficiency and hematologic disorders.

Gene therapy for inherited metabolic diseases, such as Tay-Sachs and cystic fibrosis, is also being investigated.

Q1: What factors influence the action of a teratogen