Birth defects: Causes

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INTRODUCTION — A birth defect is any structural anomaly present at birth. These defects can be caused by genetic abnormalities and/or environmental exposures, although the underlying etiology is often unknown. Birth defects can be isolated or present in a characteristic combination or pattern that may affect one or more organ systems. A genetic disorder or genetic abnormality is caused by a change or mutation in the genome that often leads to a medical consequence. Even though most genetic disorders are congenital, they can have a delayed clinical presentation or even adult onset. These disorders can be inherited or the result of a new mutation.

This topic discusses the causes of birth defects. The epidemiology, types, patterns, and evaluation of birth defects are discussed in detail separately, as are specific congenital anomalies. (See "Birth defects: Epidemiology, types, and patterns" and "Birth defects: Approach to evaluation".)

OVERVIEW — The causes of congenital anomalies are genetic and nongenetic [1].

Genetic abnormalities include:

- Chromosomal disorders (eg, Down syndrome) (see "Down syndrome: Overview of prenatal screening" and "Down syndrome: Clinical features and diagnosis")
- Single gene (monogenic) disorders, including those that are autosomal recessive, autosomal dominant, and X linked. The following are examples of single gene disorders causing limb malformations:
  - Autosomal recessive (eg, some forms of Adams-Oliver syndrome). This rare disorder is characterized by limb reduction defects (limb hypoplasia, absent digits, absent feet, syndactyly) often seen in association with cutis aplasia of the scalp. Although autosomal dominant forms are more common, this syndrome is caused by mutations in many different genes, including dominant and recessive genes. Mutations in the dedicator of cytokinesis 6 (*DOCK6*) gene cause a recessive form [2].
  - Autosomal dominant (eg, ectrodactyly, ectodermal dysplasia, cleft lip, and cleft palate [EEC]). Dominant mutations in the p63 gene are associated with EEC and other related syndromes [3,4]. Ectrodactyly is a major limb malformation characterized by absence or underdevelopment of central metacarpals and/or metatarsals leading to a split hand/foot deformity.
  - X linked (eg, focal dermal hypoplasia or Goltz syndrome). This syndrome is caused by mutations in the protein-serine O-palmitoleoyltransferase porcupine homolog (*PORCN*) gene at Xp11.23, which lead to severe limb malformations (absent digits, polydactyly, syndactyly) as well as cutaneous-dermal defects with fat herniation [5,6].

Nongenetic teratogenic etiologies include:

- Maternal phenylketonuria (PKU) or diabetes (see 'Maternal illnesses' below and "Overview of phenylketonuria", section on 'Phenylalanine embryopathy (maternal PKU)' and "Infant of a diabetic mother")
- Drugs and chemical agents (eg, alcohol, oral isotretinoin) (see 'Drug exposure' below and 'Chemical agents' below)
- Infections (cytomegalovirus [CMV], rubella, Zika virus) (see 'Infectious agents' below and "Overview of TORCH infections" and "Zika virus infection: Evaluation and management of pregnant women")
- Fetal crowding due to multiple gestations (see "Neonatal complications, outcome, and management of multiple births", section on 'Congenital anomalies')

Multifactorial disorders are conditions that result from the interaction of multiple genes and environmental factors. They include:

- Cleft lip/palate (see "Etiology, prenatal diagnosis, obstetrical management, and recurrence of orofacial clefts" and "Facial clefts and holoprosencephaly")

- Congenital heart disease (see "Fetal cardiac abnormalities: Screening, evaluation, and pregnancy management" and "Cardiac causes of cyanosis in the newborn")
- Neural tube defects (see "Open neural tube defects: Risk factors, prenatal screening and diagnosis, and pregnancy management")

GENETIC ABNORMALITIES — Genetic abnormalities can range from a point mutation in a single gene disrupting developmental pathways or proteins to the presence of an additional or missing copy of an entire chromosome. (See "Overview of genetic variation" and "Basic principles of genetic disease".)

Chromosomal disorders — Chromosomal aberrations are due to a change in the normal chromosome number (aneuploidies) or a change in the structure of a chromosome (sizable deletions, microdeletions, duplications, translocations, and inversions).

The syndromes caused by congenital aneuploidies have several common characteristics:

- Greater than 90 percent of embryos/fetuses with congenital chromosomal abnormalities do not survive to term. In trisomy 21, for example, 40 percent of fetuses are lost after 12 weeks of gestation. Even higher embryonic and fetal loss rates are found with monosomy X [7].
- Multiple organ systems tend to be involved, especially the central nervous system. Intellectual disability, in particular, is a common abnormality in viable infants.
- The longevity and fertility of individuals with these conditions tend to be reduced.

Congenital chromosomal disorders are reviewed in greater detail separately. (See "Congenital cytogenetic abnormalities" and "Sex chromosome abnormalities" and "Chromosomal translocations, deletions, and inversions" and "Microdeletion syndromes (chromosomes 1 to 11)" and "Microdeletion syndromes (chromosomes 12 to 22)" and "Microduplication syndromes".)

Disorders due to single gene defects — There is a wide range of birth defects caused by single gene defects. These defects include point mutations as well as small insertions or deletions (indels) that disrupt gene copying and protein synthesis. Inheritance is autosomal dominant, autosomal recessive, or sex linked. A single defect in one copy of a gene on an autosomal chromosome (not a sex X or Y chromosome) causes disease in disorders with autosomal dominant inheritance. In this case, the patient is heterozygous for the genetic defect. In disorders with autosomal recessive inheritance, both alleles of a gene on a autosomal chromosome are mutated, either the same mutation (homozygous mutation) or two different mutations (compound heterozygous). The last form of inheritance is sex linked (X-linked recessive inheritance is most common). Autosomal recessive conditions are more common when there is parental consanguinity (related as second cousins or closer). (See 'Overview' above and "Basic principles of genetic disease" and "Overview of genetic variation" and "Genetic counseling: Family history interpretation and risk assessment".)

Genetic disorders with non-Mendelian patterns of inheritance — Other genetic variations that can cause disorders include imprinting disorders leading to differential expression of genetic material depending upon whether the gene or gene region is imprinted (eg, Beckwith-Wiedemann syndrome). (See "Beckwith-Wiedemann syndrome".)

TERATOGENS — A teratogen is an agent that can cause abnormalities in the form or function of a developing fetus (table 1). It acts by producing cell death, altering normal growth of tissues, or interfering with normal cellular differentiation or other morphologic processes. The consequences of these actions can be fetal loss, fetal growth restriction, birth defects (eg, a limb reduction), or impaired neurologic performance (eg, altered neural connections in the central nervous system in fetal alcohol syndrome).

Approximately 4 to 6 percent of birth defects are caused by exposure to teratogens in the environment [8]. These include maternal illnesses (eg, diabetes mellitus or phenylketonuria [PKU]), infectious agents (eg, TORCH - **T**oxoplasmosis, **O**ther [syphilis, varicella-zoster, parvovirus B19], **R**ubella, **C**ytomegalovirus, and **H**erpes - infections), physical agents (eg, radiation or heat exposure), and drugs (eg, thalidomide, antiepileptic drugs) and chemical agents (eg, mercury).

Response to the teratogenic agent is highly individual and is influenced by multiple factors. These include maternal and fetal genotypes (genetic susceptibility), the dose of the agent, route of exposure, timing of exposure, and concurrent exposures or illnesses during gestation.

Genetic susceptibility — The genetic makeup of both the fetus and the mother determine the relative resistance or susceptibility to teratogenic agents. The degree of genetic susceptibility is separate from any specific genetic conditions that are known direct causes of birth defects.

As an example, albeit an oversimplified one, fetuses with defects in folate metabolism (eg, methylenetetrahydrofolate reductase [*MTHFR*] gene mutations) appear to be at increased risk for structural malformations such as neural tube defects [9], cleft lip and palate, and cardiac malformations [10]. The risk of these malformations may be decreased by maternal supplementation with folic acid in the preconceptional period and in early pregnancy [11,12]. Thus, a malformation such as an open neural tube

defect may result from genetic susceptibility related to a combination of factors consisting of the presence of a fetal *MTHFR* gene defect and a state of inadequate maternal folate intake.

Another example is that some fetuses have low or deficient epoxide hydrolase activity that results in increased levels of teratogenic oxidative metabolites when they are exposed to antiepileptic drugs [13].

Finally, certain birth defects may be seen with different frequencies across races or sexes. For example, postaxial polydactyly is more common in African Americans (approximately 1 percent) than Caucasians (approximately 0.1 percent). Neural tube defects are more common in Caucasians than African Americans. Pyloric stenosis and cleft lip are more common in males than females.

The genetic makeup of the mother and her state of health also play a role in teratogenesis. The production of a malformation is dependent upon the ability of a woman to absorb and metabolize a teratogen. In addition, maternal medical disease states can act as teratogens. (See 'Maternal illnesses' below.)

Route of exposure — The route of exposure can also impact teratogenic effects. For example, the absorption and action of a drug is usually different if exposure is through the dermis versus systemic delivery. The systemic route may cause abnormalities, while the dermal delivery may not. As an example, topical fluconazole applied to the skin is considered safe, but systemic fluconazole is potentially teratogenic [14]. Another example is topical use of retinoic acid versus oral/systemic use.

Dose and duration of exposure — The dose and duration of the embryo's exposure to a teratogen are also important. Most drugs exhibit threshold effects (ie, there is a dose below which the incidence of embryonic death, malformation, growth restriction, or functional impairment is not greater than for unexposed controls). Such thresholds are usually one to three orders of magnitude below the teratogenic dose of the drug [15].

When no human data are available, a dose teratogenic in animals that is less than 10-fold higher than the maximum human therapeutic dose suggests a high risk that the drug may be teratogenic in humans. A 100-fold difference between the animal teratogenic dose and the maximal human dose indicates a low risk of potential human teratogenicity. However, teratogenic agents may have different effects in different species. As an example, thalidomide is not teratogenic in rabbits, but has devastating effects in humans [16]. In addition, many drugs produce malformations in animals when given at 10 to 1000 times the normal dose administered to humans. Extrapolating teratogenic risk using these data is potentially problematic. As an example, high doses of meclizine given to mice cause cleft palate due to appetite suppression, but force feeding the mice prevents the defect [17].

One teratogen may be more harmful in a single large dose than in the same dose spread over several days, while another teratogen may be more harmful when an exposure is prolonged at a lower dose than if the same dose were given all at once. As an example, binge drinking of seven alcoholic beverages may be more harmful to the fetus than daily intake of only one drink for a week. Conversely, an occasional very high maternal blood glucose in an otherwise well-controlled diabetic mother is probably less harmful than a persistently moderately elevated blood glucose. (See "Alcohol intake and pregnancy" and "Pregestational diabetes: Preconception counseling, evaluation, and management".)

Drug-drug interactions can also be important. Two drugs administered together may have synergistic effects, the drugs may act completely independently, or one drug may protect against the teratogenic effects of the other. As an example, the vitamin folic acid may protect against the increased risk of open neural tube defects when taken by women who are taking antiepileptic drugs, such as valproic acid and carbamazepine [18]. However, valproic acid should not be used in pregnancy, if possible [19]. (See "Management of epilepsy and pregnancy".)

Timing — The pattern and type of malformation depend in part upon the time of exposure and/or the site of gene action. A brief review of human embryonic development indicates the system likely to be affected by a problem occurring at that time.

Fertilization is the first step and occurs within 24 hours of ovulation. Of note, embryonic age is counted from fertilization (conception) and starts two weeks before gestational age, which is counted from the first day of the last menstrual period. The following are other important milestones in development (figure 1):

- Preimplantation and implantation on days 5 to 11
- Differentiation into three germ layers (ectoderm, mesoderm, and endoderm) by day 16
- Formation of the neural plate by day 19
- Closure of the neural tube by day 27
- Appearance of limb buds by day 30
- Formation of the branchial arches, clefts, pouches, and optic vesicle between weeks 4 and 5
- Formation of the mature heart and kidneys by weeks 5 to 7
- Achievement of mature limb architecture by week 8
- Sexual differentiation of the internal and external genitalia between weeks 7 to 10
- Rotation of the intestines and return into the abdominal cavity in week 10

A significant exposure that occurs during the first 10 to 14 days after fertilization may result in cell death. If enough cells die, spontaneous abortion may occur (see "Spontaneous abortion: Risk factors, etiology, clinical manifestations, and diagnostic evaluation"). If only a few cells are damaged, then their roles may be compensated by other cells. This is known as the all-or-none theory. An example is an early significant exposure to radiation, which usually results in either pregnancy loss or no abnormalities.

The embryo is most vulnerable to teratogenic insults since organogenesis is occurring during the embryonic period of development. The embryonic period in humans can be defined as from fertilization until the end of the 10th week of gestation (8th week postconception) [20].

During the fetal period, teratogens can cause cell death, retardation of cell growth, or inhibition of normal differentiation. This may result in fetal growth restriction or disorders of the central nervous system that may not be apparent at birth. The eyes, genitalia, central nervous system, and hematopoietic systems continue to develop during the fetal period and remain susceptible to teratogenic insults.

As an example, the risks associated with angiotensin-converting enzyme (ACE) inhibitor exposure are significant during the second and third trimesters (US Food and Drug Administration [FDA] category D) due to blockade of conversion of angiotensinogen I to angiotensin II in the developing fetal kidney. This exposure results in hypotension, renal tubular dysplasia, anuria/oligohydramnios, growth restriction, and calvaria defects. However, these drugs can cause other defects, such congenital heart defects, during the first trimester (FDA category C).

Misoprostol, a prostaglandin E1 analog, can cause severe vascular disruptions in the first trimester (ie, terminal limb defects, Moebius syndrome). It has also been widely used to induce abortions in the first and second trimesters. However, this drug is safe to use during delivery for uterine cervix ripening and to induce labor [21].

Some teratogens act within a narrow window. As an example, the teratogenic effect of thalidomide for limb defects is limited to 21 to 36 days postconception, when limb bud development begins.

Mechanisms of teratogenesis — Teratogenesis is thought to occur after fertilization and results from many diverse mechanisms. These include cell death (eg, radiation), blocking of metabolic processes (eg, thioureas, iodides), and alterations in cellular growth and proliferation, migration, and apoptosis (eg, fetal alcohol syndrome), and interactions between cells or between cells and tissues.

Exposure prior to conception may cause genetic mutations, a process known as toxic mutagenesis, although this is controversial. The timing of this process differs in males and females. In females, DNA replication occurs during oogenesis in the fetus, many years before ovulation. Thus, genetic defects may follow fetal exposure. In contrast, continuing spermatogenesis makes males susceptible to mutations throughout their reproductive life.

Specific teratogens — Numerous teratogens in the environment can lead to birth defects. Common agents are listed below and in the table (table 1).

Infectious agents — Exposure to infectious agents can result in a variety of problems in the fetus and neonate, including malformations, congenital infection, short- and long-term disability, and death. The pathogenesis of the fetal defects is usually direct invasion of fetal tissues leading to damage from inflammation and cell death. Agents known to be toxic to the fetus or embryo are toxoplasmosis, rubella, cytomegalovirus, herpes, and syphilis (the so-called TORCH infections), as well as varicella, parvovirus B19, Zika virus, and lymphocytic choriomeningitis virus (LCMV). (See "Overview of TORCH infections" and "Syphilis in pregnancy" and "Varicella-zoster virus infection in pregnancy" and "Parvovirus B19 infection during pregnancy" and "Rubella in pregnancy" and "Prenatal evaluation of the HIV-infected woman in resource-rich settings" and "Viral meningitis: Clinical features and diagnosis in children", section on 'Other viruses' and "Influenza and pregnancy" and "Zika virus infection: Evaluation and management of pregnant women".)

Nonspecific sonographic signs suggestive of fetal infection include:

- Microcephaly
- Cerebral or hepatic calcifications
- Intrauterine growth restriction
- Hepatosplenomegaly
- Cardiac malformations, limb hypoplasia, hydrocephalus
- Hydrops

Birth defects associated with disorders of movement and muscle tone, chorioretinitis or cataracts, hearing impairment, hepatosplenomegaly, skin rash, thrombocytopenia, jaundice, or low birth weight are suggestive of congenital infection.

Fever associated with infection also can be teratogenic. (See 'Physical agents' below.)

Maternal illnesses — Several maternal illnesses are associated with birth defects. The mechanism is diffusion of a metabolite or antibody across the placenta that is toxic to the fetus.

- Insulin-dependent diabetes mellitus is associated with a two- to threefold increase in risk of congenital anomalies, including congenital heart disease, cleft palate, colobomas, and spina bifida, and, less commonly, caudal regression and focal femoral hypoplasia. (See "Infant of a diabetic mother".)
- Maternal phenylketonuria (PKU) if not diet controlled is associated with microcephaly, intellectual disability, and congenital heart disease. (See "Overview of phenylketonuria".)
- Androgen-producing tumors of the adrenal glands or ovaries can produce virilization of female fetuses.
- Maternal antibodies present in autoimmune disorders can cross the placenta and cause toxicity in the fetus. Examples include myasthenia gravis leading to transient neonatal myasthenia, maternal Grave disease causing fetal and neonatal thyrotoxicosis, immune thrombocytopenia (ITP) resulting in fetal and neonatal thrombocytopenia, and systemic lupus erythematosus causing fetal heart block. (See "Treatment of myasthenia gravis" and "Hyperthyroidism during pregnancy: Treatment" and "Thrombocytopenia in pregnancy" and "Pregnancy in women with systemic lupus erythematosus".)

Maternal obesity is also associated with an increased risk of certain types of birth defects. The mechanism is unknown. (See "Obesity in pregnancy: Complications and maternal management", section on 'Congenital anomalies'.)

Physical agents — Physical agents, such as heat and radiation have been implicated in the pathogenesis of birth defects. Heat exposure may be due to hot tub or sauna use or maternal fever. Elevation of maternal core temperature more than 1.5°C in the first trimester of pregnancy for at least 24 hours may be associated with an increased risk of neural tube defects [22-24]. Other clinical findings associated with high maternal temperature include microcephaly, intellectual disability (mental retardation), hypertonia, hypotonia, and seizures. (See "Intrapartum fever", section on 'Fetal/neonatal consequences'.)

Excessive exposure to ionizing radiation has the potential to produce fetal death, growth disturbances, somatic abnormalities, mutation, chromosome fragmentation, and malignancy. In general, toxic levels are not achieved with diagnostic imaging. However, knowledge of a pregnancy should, in most circumstances, result in a reappraisal of the necessity for and mode of imaging. (See "Diagnostic imaging procedures during pregnancy" and "Radiation-related risks of imaging studies".)

Drug exposure — Maternal drug ingestion, including prescription and over-the-counter medications as well as recreational drugs, can also cause adverse fetal and neonatal outcomes. However, it can be extremely difficult to determine whether a particular substance is teratogenic. A partial list of additional known teratogens is provided in the table (table 1).

The US Food and Drug Administration (FDA) requires that all prescription drugs be tested in animal models, usually one rodent and one nonrodent model. Testing establishes both the lowest observed adverse effect level (LOAEL) and the no observed adverse effect level (NOAEL). If the human exposure level is 100 times lower than the NOAEL, adverse effects in humans are considered unlikely. However, results from animal models may not always apply to humans. As an example, thalidomide is strongly teratogenic in humans, but weakly teratogenic in animals, while the opposite is true for aspirin. A study of drugs approved by the FDA from 2000 to 2010 found that the teratogenic risk in human pregnancy was "undetermined" for 98 percent of the drugs approved for human use [25].

Due to the limitations of drug testing, data regarding the association of drugs or chemicals and birth defects come primarily from case reports of exposed patients. However, these also do not always establish teratogenicity and often need validation by epidemiologic studies. Two promising approaches to providing somewhat better information are prospectively collected exposure data from teratogen information agencies and large-scale birth defects registries [26]. Post-marketing drug registries are also used to monitor for teratogenicity, but these rely on active participation of clinicians and pregnant women and as such are not comprehensive in their surveillance. As previously discussed, some of the drugs can be potentially teratogenic during specific times of fetal development but be innocuous otherwise. (See 'Timing' above.)

The FDA labels prescription drugs during pregnancy in different categories: A, B, C, D, and X. Category A are those drugs that show no risk and have been through well-controlled studies with no adverse defects to the fetus. Category B drugs are those with no defects to humans or with insufficient human studies but that have shown risk to animals. Category C drugs include those in which risk cannot be ruled out, where human studies are lacking and animal studies are positive or lacking as well. In these cases, though, the benefit for the pregnant woman outweighs the risks. Category D drugs are those with positive evidence of risk. Category X includes drugs that are known to be teratogenic based on animal studies and human reports. These drugs have no indication in pregnancy [27]. The effects of the drugs can change category of fetal effects if given during different times in the pregnancy.

Some common teratogenic medications include:

- Angiotensin-converting enzyme (ACE) inhibitors (see "Angiotensin converting enzyme inhibitors and receptor blockers in pregnancy" and 'Timing' above)
- Anticonvulsant agents (see "Risks associated with epilepsy and pregnancy")
- Antineoplastic agents (see "Gestational breast cancer: Epidemiology and diagnosis" and "Management of classical Hodgkin lymphoma during pregnancy")

- Thalidomide, methylene blue, misoprostol, penicillamine, fluconazole, and lithium

Additional known teratogens include the following:

- Folic acid antagonists (eg, trimethoprim, triamterene, carbamazepine, phenytoin, phenobarbital, primidone, methotrexate) increase the risk of neural tube defects and possibly cardiovascular defects, oral clefts, and urinary tract defects [18,28].

- Oral isotretinoin, used to treat severe acne, is associated with ear anomalies (microtia with or without atresia of the ear canal), central nervous system malformations, hydrocephalus, neuronal brain migration defects, cerebellum abnormalities, severe intellectual disability, seizures, optic nerve/retinal abnormalities, conotruncal heart defects, thymic defects, and dysmorphic features [29,30]. (See "Treatment of acne vulgaris", section on 'Pregnancy and acne therapy'.)

- The widely used cholesterol-lowering agents, such as statins (HMG-CoA reductase inhibitors) are completely contraindicated during pregnancy because they may cause severe birth defects due to disruption of cholesterol biosynthesis, which is important in cell membrane morphogenesis. Reported birth defects include limb malformations, congenital heart disease, and CNS abnormalities [31,32].

- Infants whose mothers consume substantial quantities of alcohol during pregnancy can have fetal alcohol effects (FAE), alcohol-related birth defects (ARBD), fetal alcohol syndrome, or they may be normal [33]. (See "Alcohol intake and pregnancy" and "Substance misuse in pregnant women" and "Fetal alcohol spectrum disorder: Clinical features and diagnosis".)

- Cigarette smoking is associated with poor fetal growth mostly due to effects on the placenta [34,35]. Smoking is also linked to increased limb deficiencies in epidemiologic studies [36]. The failure or disruption in formation of limbs or digits may result from vasoactive effects of cigarette compounds on blood vessels. Prenatal exposure can also lead to impaired function of the endocrine, reproductive, respiratory, cardiovascular, and neurologic systems [37]. (See "Cigarette smoking: Impact on pregnancy and the neonate".)

Chemical agents — Chemical agents that can act as teratogens include lead and mercury.

High plasma lead levels are associated with adverse neurobehavioral effects in infants and children. Intrauterine exposure may have similar consequences [38]. Studies of potential associations between parental lead exposure and congenital malformations in offspring have not demonstrated a consistent increase in risk or pattern of defects, but often lack biologic indices of exposure at developmentally significant times [39]. (See "Overview of occupational and environmental risks to reproduction in females", section on 'Lead'.)

Methylmercury exposure, primarily through ingestion of contaminated fish, can cause severe central nervous system damage [40], as well as milder intellectual, motor, and psychosocial impairment [41-43]. Some limitations on fish intake during pregnancy are recommended. (See "Nutrition in pregnancy", section on 'Counseling women about nutrition in pregnancy' and "Fish consumption and docosahexaenoic acid (DHA) supplementation in pregnancy".)

Resources — Several resources are available for information on possible teratogenic exposure. These include:

- National Library of Medicine
  Bethesda, MD
  800-638-8480

- Reproductive Toxicology Center
  REPROTOX
  Columbia Hospital for Women Medical Center
  Washington, DC
  202-293-5137

- Teratogen Information System
  TERIS and Shepard's Catalog of Teratogenic Agents
  Seattle, WA
  206-543-2465

- Pregnancy Exposure Registries

- Organization of Teratology Information Specialists (OTIS)
  877-311-8972

- Motherisk
  The Hospital for Sick Children
  Toronto, Canada
  877-439-2744

- The Teratology Society
  The Teratology Society publishes a free teratology primer

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword (s) of interest.)

- Basics topic (see "Patient education: Newborn appearance (The Basics)")

SUMMARY

- A birth defect is any structural anomaly present at birth. These defects can be caused by genetic abnormalities and/or environmental exposures (teratogens), although the underlying etiology is often unknown. (See 'Introduction' above and 'Overview' above.)
- Specific terms are used to describe congenital anomalies (table 2). In addition, multiple malformations are often grouped in a recognizable pattern (table 3). (See "Birth defects: Epidemiology, types, and patterns", section on 'Types and patterns of defects'.)
- Genetic causes of congenital anomalies include chromosomal disorders, single gene disorders, somatic mutation, and disorders that result from the interaction of multiple genes and environmental factors (multifactorial disorders). (See 'Genetic abnormalities' above.)
- Environmental causes of congenital anomalies include multiple gestation pregnancy and teratogens. A teratogen is an agent that can cause abnormalities in the form or function of a developing fetus (table 1). The pattern and type of malformation depends in part upon the time of exposure and/or the site of gene action. (See 'Teratogens' above.)

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GRAPHICS

Selected agents with potential adverse fetal effects

Reproductive toxin	Alleged effects
Aminopterin, methotrexate	Growth retardation, microcephaly, meningomyelocele, mental retardation, hydrocephalus, and cleft palate
Androgens	Masculinization of the developing female fetus can occur from androgens and high doses of some male-derived progestins.
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers	Fetal hypotension syndrome in second and third trimester resulting in fetal kidney hypoperfusion and anuria, oligohydramnios, pulmonary hypoplasia, and cranial bone hypoplasia. Heart defects from first trimester exposure.
Antidepressants	Recent publications have implicated some of the SSRIs administered in the last trimester with postnatal neurobehavioral effects that are transient and whose long-term effects have not been determined. First-trimester exposures to some SSRIs have been reported to increase the risk of some congenital malformations, predominantly congenital heart disease. The results have not been consistent, but warnings have been issued.
Antituberculous therapy	Isoniazid and paraaminosalicylic acid have an increased risk for some CNS abnormalities.
Caffeine	Moderate caffeine exposure is not associated with birth defects; high exposures are associated with an increased risk of abortion, but the data are inconsistent.
Cobalt in hematemic multivitamins	Fetal goiter.
Cocaine	Vascular disruptive type malformations in very low incidence; pregnancy loss.
Corticosteroids	High exposures administered systemically have a low risk for cleft palate in some studies, but the epidemiologic studies are not consistent.
Cyclophosphamide and other chemotherapeutic agents and immunosuppressive agents (eg, cyclosporine, leflunomide)	Many chemotherapeutic agents used to treat cancer have a theoretical risk for producing malformations in the fetus when administered to pregnant women, especially because most of these drugs are teratogenic in animals, but the clinical data are not consistent. Many of these drugs have not been shown to be teratogenic, but the numbers of cases in the studies are small. Caution is the byword.
Diethylstilbestrol	Administration during pregnancy produces genital abnormalities, adenosis, and clear cell adenocarcinoma of vagina in adolescents. The last has a risk of 1:1000 to 1:10,000, but the other
Tetracycline	This drug produces bone and teeth staining; it does not increase the risk of any other malformations.
Thalidomide	This drug results in an increased incidence of deafness, anotia, preaxial limb-reduction defects, phocomelia, ventricular septal defects, and gastrointestinal atresias. The susceptible period is from the 22nd to the 36th day after conception.
Trimethoprim	This drug was used frequently to treat urinary tract infections and has been linked to an increased incidence of neural tube defects. The risk is not high, but it is biologically plausible because of the drug's effect on lowering folic acid levels, which has resulted in neurologic symptoms in adults taking this drug.
Vitamin A	The malformations reported with the retinoids have been reported with very high doses of vitamin A (retinol). Doses to produce birth defects would have to be in excess of 25,000 to 50,000 units/day.
Warfarin and warfarin derivatives	Early exposure during pregnancy can result in nasal hypoplasia, stippling of secondary epiphysis, intrauterine growth restriction. CNS malformations can occur in late pregnancy exposure because of bleeding.
Anticonvulsants	
Phenytoin	Increases risk of fetal hydantoin syndrome, consisting of facial dysmorphology, cleft palate, ventricular septal defect, and growth and mental retardation.
Trimethadione and paramethadione	Increases the risk of characteristic facial dysmorphology, mental retardation, V-shaped eyebrows, low-set ears with anteriorly folded helix, high-arched palate, irregular teeth, CNS anomalies, and severe developmental delay.
Valproic acid	Increases the risk of spina bifida, facial dysmorphology, autism, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis.
Carbamazepine	Increases the risk facial dysmorphology, neural tube defects, cardiovascular defects, and urinary tract defects.
Chemicals	
Carbon monoxide poisoning	CNS damage has been reported with very high exposures, but the risk seems to be low.*
Lead	Very high exposures can cause pregnancy loss; intrauterine teratogenesis is not established at very low exposures below 20 microgram/percent in the serum of pregnant mothers.
Gasoline addiction embryopathy	Facial dysmorphology, mental retardation
Methyl mercury	Minamata disease consists of cerebral palsy, microcephaly, mental retardation, blindness, and cerebellum hypoplasia. Other epidemics have occurred from adulteration of wheat with mercury-containing chemicals that are used to prevent grain spoilage. Present environmental levels of mercury are unlikely

	effects, such as adenosis, can be quite high.
Ethyl alcohol	Fetal alcohol syndrome consists of microcephaly, mental retardation, growth retardation, typical facial dysmorphogenesis, abnormal ears, small palpebral fissures.
Ionizing radiation	Radiation exposure above a threshold of 20 rad (0.2 Gy) can increase the risk for some fetal effects such as microcephaly or growth retardation, but the threshold for mental retardation is higher.
Insulin shock therapy	Insulin shock therapy, when administered to pregnant women, resulted in microcephaly, mental retardation.
Lithium therapy	Chronic usage for the treatment of manic depressive illness has an increased risk for Ebstein's anomaly and other malformations, but the risk seems to be very low.
Minoxidil	This drug's promotion of hair growth was discovered because administration during pregnancy resulted in hirsutism in newborns.
Methimazole	Aplasia cutis has been reported to be increased in mothers administered this drug during pregnancy.*
Methylene blue intra-amniotic instillation	Fetal intestinal atresia, hemolytic anemia, and jaundice in neonatal period. This procedure is no longer used to identify one twin.
Misoprostol	A low incidence of vascular disruptive phenomenon, such as limb-reduction defects and Mobius syndrome, has been reported in pregnancies in which this drug was used to induce an abortion.
Mycophenolate mofetil	First trimester exposure associated with miscarriage, abnormalities of the ear, distal limbs, heart, esophagus, kidney, and cleft lip/palate.
Penicillamine (D-penicillamine)	This drug results in the physical effects referred to as "lathyrism," the results of poisoning by the seeds of the genus *Lathyrus*. It causes collagen disruption, cutis laxa, and hyperflexibility of joints. The condition seems to be reversible, and the risk is low.
Progestin therapy	Very high doses of androgen hormone-derived progestins can produce masculinization. Many drugs with progestational activity do not have masculinizing potential. None of these drugs have the potential for producing nongenital malformations.
Propylthiouracil	This drug and other antithyroid medications administered during pregnancy can result in an infant born with a goiter.
Radioactive isotopes	Tissue- and organ-specific damage depends on the radioisotope element and distribution (ie, high doses of Iodine-131 administered to a pregnant woman can cause fetal
	to represent a teratogenic risk, but reducing or limiting the consumption of carnivorous fish has been suggested to avoid exceeding the maximum permissible exposure recommended by the Environmental Protection Agency, an exposure level far below the level at which the toxic effects of mercury are seen.
Polychlorinated biphenyls	Poisoning has occurred from adulteration of food products ("Cola-colored babies," CNS effects, pigmentation of gums, nails, teeth, and groin; hypoplastic deformed nails; intrauterine growth retardation; abnormal skull calcification). The threshold exposure has not been determined, but it is unlikely to be teratogenic at the present environmental exposures.
Toluene addiction embryopathy	Facial dysmorphology, mental retardation
Embryonic and fetal infections	
Cytomegalovirus infection	Retinopathy, CNS calcification, microcephaly, mental retardation
Rubella	Deafness, congenital heart disease, microcephaly, cataracts, mental retardation
Herpes simplex	Fetal infection, liver disease, death
HIV	Perinatal HIV infection
Parvovirus infection, B19	Stillbirth, hydrops
Syphilis	Maculopapular rash, hepatosplenomegaly, deformed nails, osteochondritis at joints of extremities, congenital neurosyphilis, abnormal epiphyses, chorioretinitis
Toxoplasmosis	Hydrocephaly, microphthalmia, chorioretinitis, mental retardation
Varicella zoster	Skin and muscle defects; intrauterine growth retardation; limb reduction defects, CNS damage (very low increased risk)
Venezuelan equine encephalitis	Hydranencephaly; microphthalmia; destructive CNS lesions; luxation of hip
Maternal disease states	
Corticosteroid-secreting endocrinopathy	Mothers who have Cushing's disease can have infants with hyperadrenocortism, but anatomic malformations do not seem to be increased.
Iodine deficiency	Can result in embryonic goiter and mental retardation.
Intrauterine problems of constraint and vascular disruption	These defects are more common in multiple-birth pregnancies, pregnancies with anatomic defects of the uterus, placental emboli, or amniotic bands. Possible birth defects include club feet, limb-reduction defects, aplasia cutis, cranial asymmetry, external ear malformations, midline closure defects, cleft palate and muscle aplasia, cleft lip, omphalocele, and encephalocele).
Maternal androgen endocrinopathy (adrenal tumors)	Masculinization of female fetuses
Maternal diabetes with poor glycemic control	Increases the risk of a wide variety of congenital anomalies; cardiac abnormalities are most common.
Maternal folic acid in reduced amounts	An increased incidence of neural tube defects.
Maternal phenylketonuria	

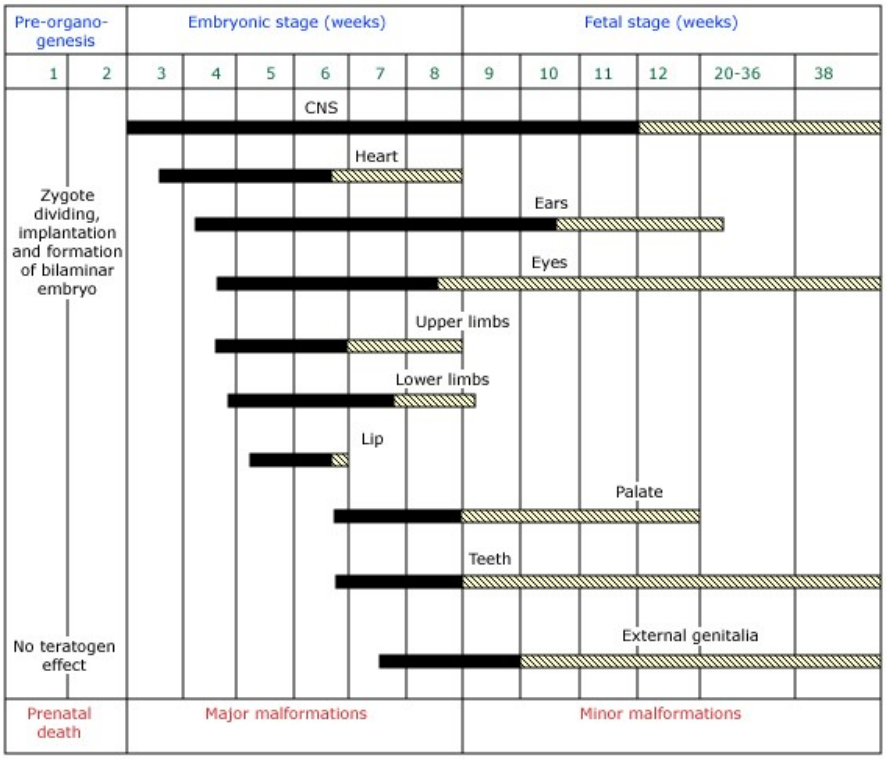
	thyroid hypoplasia after the eighth week of development).		Abortion, microcephaly, and mental retardation; very high risk in untreated patients.
Retinoids	Systemic retinoic acid, isotretinoin, and etretinate can cause increased risk of CNS, cardioaortic, ear, and clefting defects such as microtia, anotia, thymic aplasia, other branchial arch and aortic arch abnormalities, and certain congenital heart malformations.	Maternal starvation	Intrauterine growth restriction, abortion, neural tube defects (Dutch famine experience)
		Tobacco smoking	Abortion, intrauterine growth restriction, stillbirth
		Zinc deficiency*	Neural tube defects*
Retinoids, topical	Topical administration is very unlikely to have teratogenic potential, because teratogenic serum levels cannot be attained by topical exposure to retinoids.		
Streptomycin	Streptomycin and a group of ototoxic drugs can affect the eighth nerve and interfere with hearing; it is a relatively low-risk phenomenon. Children are less sensitive than adults to the ototoxic effects of these drugs.		
Sulfa drugs and vitamin K	These drugs can produce hemolysis in some subpopulations of fetuses.		

SSRI: selective serotonin reuptake inhibitor; CNS: central nervous system; HIV: human immunodeficiency virus.
* Controversial.

Updated July 15, 2010 Gerald Briggs, B.Pharm.

Graphic 73369 Version 12.0

Embryonic development



The black bars represent the critical period during which development may be disrupted by a teratogen resulting in a major structural malformation. Cell differentiation occurs over a longer period (hatched bars); exposure during this period can result in minor structural malformations, growth restriction, or functional deficiency. Note, embryonic age is counted from fertilization, whereas menstrual age (ie, gestational age) is counted from the first day of the last menstrual period. Thus, an embryonic age of six weeks corresponds to a menstrual age (gestational age) of eight weeks.

CNS: central nervous system.

Graphic 65456 Version 4.0

Terms used to describe congenital abnormalities

Term	Definition
Malformation	Defects of organs or body parts due to an intrinsically abnormal developmental process
Deformation	Abnormalities of the position of body parts due to extrinsic intrauterine mechanical forces that modify a normally formed structure
Disruption	Defects of organs or body parts that result from destruction of or interference with normal vascular development
Dysplasia	Anomalies that result from the abnormal organization of cells into tissues

Graphic 57394 Version 3.0

Recognizable patterns of multiple congenital anomalies

Pattern	Definition
Syndrome	Pattern of anomalies that occur together and are associated with a set number of signs and symptoms
Sequence	Pattern of anomalies in which a single known defect in development causes a cascade of subsequent abnormalities
Field defect	Pattern of anomalies caused by disturbance of a developmental field (a region of the embryo that develops in a contiguous physical space)
Association	Two or more anomalies that are not pathogenetically related and occur together more frequently than expected by chance

Graphic 75281 Version 3.0

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