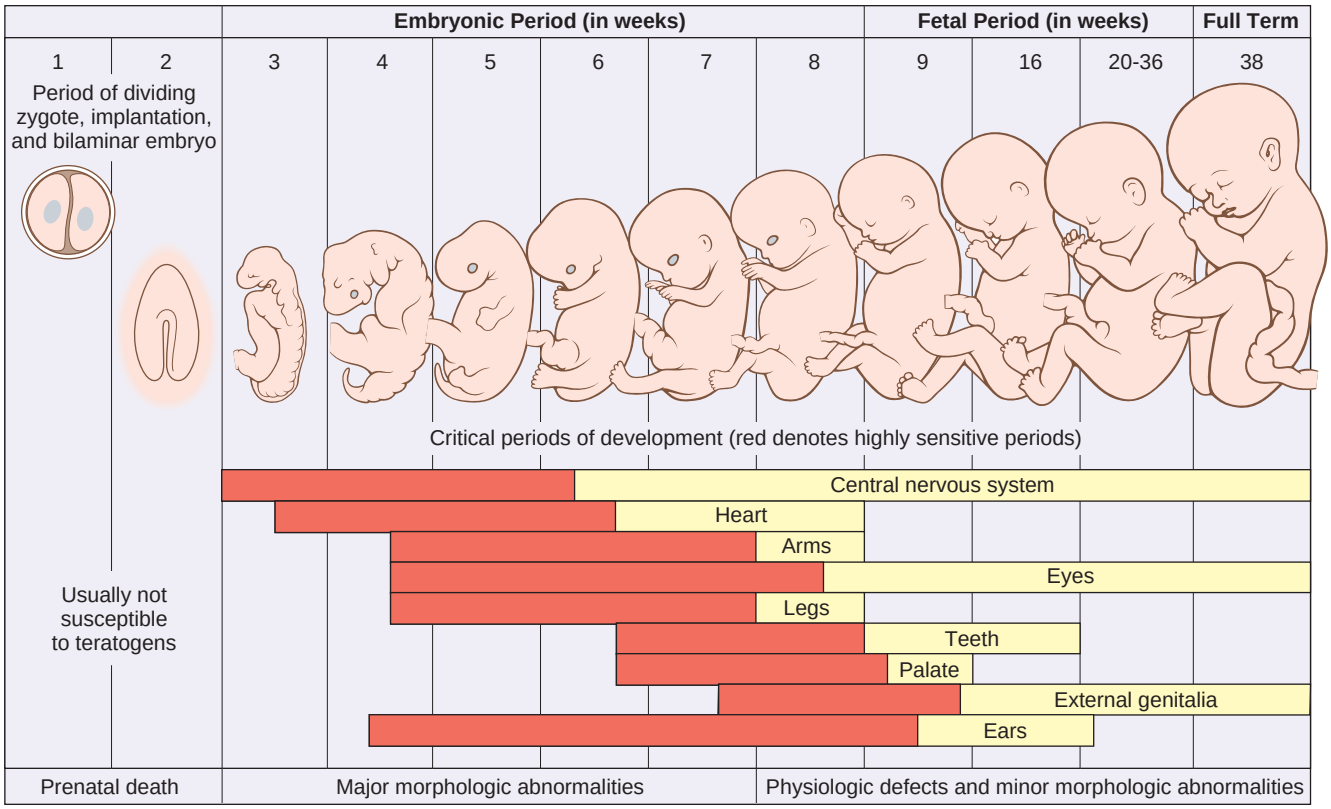

Figure 10-5 Critical periods of development for various organ systems and the resultant malformations. (Modified and redrawn from Moore KL: The Developing Human, 5th ed. Philadelphia, WB Saunders, 1993, p 156.)

hypoplasia), and psychomotor disturbances. These in combination are labeled the *fetal alcohol syndrome* (also discussed in Chapter 9). While cigarette smoke-derived nicotine has not been convincingly demonstrated to be a teratogen, there is a high incidence of spontaneous abortions, premature labor, and placental abnormalities in pregnant smokers; babies born to mothers who smoke often have a low birth weight and may be prone to the SIDS. *In light of these findings, it is best to avoid nicotine exposure altogether during pregnancy.* Among maternal conditions listed in Table 10-2, *diabetes mellitus* is a common entity, and despite advances in antenatal obstetric monitoring and glucose control, the incidence of major malformations in infants of diabetic mothers stands between 6% and 10% in most series. Maternal hyperglycemia-induced fetal hyperinsulinemia results in fetal macrosomia (organomegaly and increased body fat and muscle mass); cardiac anomalies, neural tube defects, and other central nervous system (CNS) malformations are some of the major anomalies seen in *diabetic embryopathy.*

Multifactorial inheritance, which implies the interaction of environmental influences with two or more genes of small effect, is the most common genetic cause of congenital malformations. Included in this category are some relatively common malformations such as cleft lip, cleft palate and neural tube defects. The importance of environmental contributions to multifactorial inheritance is underscored by the dramatic reduction of the incidence of neural tube defects by periconceptional intake of folic acid in the diet.

Pathogenesis. The pathogenesis of congenital anomalies is complex and still poorly understood, but two general principles of developmental pathology are relevant regardless of the etiologic agent.

1. *The timing of the prenatal teratogenic insult has an important impact on the occurrence and the type of anomaly produced* (Fig. 10-5). The intrauterine development of humans can be divided into two phases: (1) the embryonic period occupying the first 9 weeks of pregnancy and (2) the fetal period terminating at birth.
   - In the *early embryonic period* (first 3 weeks after fertilization), an injurious agent damages either enough cells to cause death and abortion or only a few cells, presumably allowing the embryo to recover without developing defects. *Between the third and the ninth weeks, the embryo is extremely susceptible to teratogenesis*, and the peak sensitivity during this period occurs between the fourth and the fifth weeks. During this period organs are being crafted out of the germ cell layers.
   - The *fetal period* that follows organogenesis is marked chiefly by the further growth and maturation of the organs, with greatly reduced susceptibility to teratogenic agents. Instead, the fetus is susceptible to growth retardation or injury to already formed organs. It is therefore possible for a given agent to produce different anomalies if exposure occurs at different times of gestation.