2. The interplay between environmental teratogens and intrinsic genetic defects is exemplified by the fact that *features of dysmorphogenesis caused by environmental insults can often be recapitulated by genetic defects in the pathways targeted by these teratogens.* This is illustrated by the following representative examples.
   - *Cyclopamine* is a plant teratogen and pregnant sheep who feed on this plant give birth to lambs that have severe craniofacial abnormalities including holoprosencephaly and "cyclopia" (single fused eye, hence the origin of the moniker cyclopamine). This compound is an inhibitor of Hedgehog signaling in the embryo, and as stated earlier, mutations of Hedgehog genes are present in subsets of patients with holoprosencephaly.
   - *Valproic acid* is an antiepileptic and a recognized teratogen during pregnancy. Valproic acid disrupts expression of a family of highly conserved developmentally critical transcription factors known as *homeobox* (HOX) proteins. In vertebrates, HOX proteins have been implicated in the patterning of limbs, vertebrae, and craniofacial structures. Not surprisingly, mutations in *HOX* family of genes are responsible for congenital anomalies that mimic features observed in *valproic acid embryopathy*.
   - The vitamin A (retinol) derivative *all-trans-retinoic acid* is essential for normal development and differentiation, and its absence during embryogenesis results in a constellation of malformations affecting multiple organ systems, including the eyes, genitourinary system, cardiovascular system, diaphragm, and lungs (see Chapter 9 for effects of for vitamin A deficiency in the postnatal period). Conversely, *excessive exposure to retinoic acid is also teratogenic*. Infants born to mothers treated with retinoic acid for severe acne have a predictable phenotype *(retinoic acid embryopathy)*, including CNS, cardiac, and craniofacial defects, such as *cleft lip and cleft palate*. The latter may stem from retinoic acid–mediated deregulation of components of the transforming growth factor-β (TGF-β) signaling pathway, which is involved in palatogenesis. Mice with knockout of the *Tgfb3* gene uniformly develop cleft palate, once again illustrating the functional relationship between teratogenic exposure and signaling pathways in the causation of congenital anomalies.

Prematurity and Fetal Growth Restriction

Prematurity, defined by a gestational age less than 37 weeks, is the second most common cause of neonatal mortality, behind only congenital anomalies (Table 10-1). The American College of Obstetrics and Gynecology estimates that 12% of all births in the United States are preterm deliveries, and despite extensive research into this area, this rate has increased over the last two decades. The major risk factors for prematurity include:

- *Preterm premature rupture of placental membranes* (PPROM): PPROM complicates about 3% of all pregnancies and is responsible for as many as a third of all preterm deliveries. Rupture of membranes (ROM) before the onset of labor can be spontaneous or induced. PPROM refers to spontaneous ROM occurring *before* 37 weeks' gestation (hence the annotation "preterm"). In contrast, PROM refers to spontaneous ROM occurring *after* 37 weeks' gestation. This distinction is important because after 37 weeks the associated risk to the fetus is considerably decreased. Several clinical risk factors have been identified for PPROM, including a prior history of preterm delivery, preterm labor and/or vaginal bleeding during the current pregnancy, maternal smoking, low socioeconomic status, and poor maternal nutrition. The fetal and maternal outcome after PPROM depends on the gestation age of the fetus (second-trimester PPROM has a dismal prognosis), and the effective prophylaxis of infections in the exposed amniotic cavity.
- *Intrauterine infection:* This is a major cause of preterm labor with and without intact membranes. Intrauterine infection is present in approximately 25% of all preterm births, and the earlier the gestational age at delivery, the higher the frequency of intra-amniotic infection. The histologic correlates of intrauterine infection are inflammation of the placental membranes *(chorioamnionitis)* and inflammation of the fetal umbilical cord *(funisitis)*. The most common microorganisms implicated in intrauterine infections leading to preterm labor are *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Gardnerella vaginalis* (the dominant organism found in "bacterial vaginosis," a polymicrobial infection), *Trichomonas*, gonorrhea, and *Chlamydia*. In developing countries, malaria and HIV are significant contributors to the burden of preterm labor and prematurity. Recent studies have begun to elucidate the molecular mechanisms of inflammation-induced preterm labor. Endogenous Toll-like receptors (TLRs), which bind bacterial components as natural ligands (Chapter 6), have emerged as key players in this process. It is postulated that signals produced by TLR engagement deregulate prostaglandin expression, which in turn induces uterine smooth muscle contractions.
- *Uterine, cervical, and placental structural abnormalities:* Uterine distortion (e.g., uterine fibroids), compromised structural support of the cervix ("cervical incompetence"), *placenta previa*, and *abruptio placentae* (Chapter 22) are associated with an increased risk of prematurity.
- *Multiple gestation* (twin pregnancy).

The hazards of prematurity are manifold for the newborn and may give rise to one or more of the following:

- Neonatal respiratory distress syndrome, also known as hyaline membrane disease
- Necrotizing enterocolitis
- Sepsis
- Intraventricular and germinal matrix hemorrhage

Fetal Growth Restriction

Although preterm infants have low birth weights, it is usually appropriate once adjusted for their gestational age. In contrast, as many as one third of infants who weigh less than 2500 gm are born at term and are therefore undergrown rather than immature. These