Fetal, Intrapartum, and Neonatal Deaths

4

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Contents

Abstract

Due to differences and inconsistencies in the interpretation of definitions, different classification systems, various international registration systems, and an overall dispute over epidemiological metrics, it is a challenge if not an impossibility to fully understand fetal, intrapartum, and neonatal mortality data. However, as medical practitioners, we can take the science and evidence-based research and attempt to categorize the current knowledge for a methodical assessment of these entities. This chapter will examine these three divisions of child death with a focus on risk factors, causes, autopsy findings, and ancillary studies.

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Introduction

Fetal, intrapartum, and neonatal deaths are particularly challenging because of the numerous variables involved: from a sterile, intrauterine environment "feeding and breathing" by way of a complex maternal–placental–fetal circulation; to the process of labor and delivery with a sudden change to respiration and digestion; to the vulnerable neonatal period when a child's systems must function independently in constantly changing, often hostile, surroundings. During these few weeks, numerous fetal, maternal, and placental factors are involved in every aspect of a child's pathophysiology.

Definitions

Embryonic period: Time from fertilization to the end of the 8th week of gestation.

Fetal death: Death after 20 weeks gestational age. Some areas in the world use 22 weeks gestational age (Reddy et al. 2009; The Stillbirth Collaborative Research Network Writing Group 2011a).

Late fetal death: Death after 28 weeks gestation.

Neonate: A child from birth to 1 month, or 28 days, of age (Lawn et al. 2005, 2006; Bryce et al. 2005).

Neonatal death: Death during the first month, or 28 days, of life (Lawn et al. 2005, 2006; Bryce et al. 2005).

Early neonatal period: The first week of life (Lawn et al. 2005, 2006; Bateman and Seed 2010).

Infant: A child from 1 month to 1 year of age (Coté 2010).

Very low birth weight infant = <1,500 g.

Extremely low birth weight infant = <1,000 grams.

Small for gestational age (SGA) = <10th percentile (McCowan and Horgan 2009).

Intrapartum death: Death which occurs during labor and delivery (Reddy et al. 2009).

Premature: Born less than 37 weeks gestational age (Reddy et al. 2009).

Stillbirth: Fetus born with no signs of life after 28 weeks gestational age (Varli et al. 2008; Ishaque et al. 2011).

Full term: Child born between 37 and 42 weeks gestation (Reddy et al. 2009; Rutherford 2001).

Viability: The ability of a neonate to survive outside the mother.

Fetal Death

Fetal death is defined as intrauterine death after 20 weeks gestation. Some countries use 22 weeks gestation. Late fetal death is death after 28 weeks gestation.

Table 4.1 Risk factors for fetal death

Maternal age over 35 years
Maternal hypertension
Maternal thyroid disease (hypo- or hyperthyroidism)
Maternal cholestasis, fatty liver
Maternal diabetes mellitus (especially late fetal death)
Maternal malnutrition, obesity
Maternal tobacco use (especially 3 months prior to and during pregnancy)
Maternal alcohol and drug use
Maternal third trimester radiation (over 100 rads)
Maternal thrombophilias
Maternal AB blood type
Previous stillbirth or preterm birth
Preeclampsia/eclampsia
Maternal periodontal disease
Maternal iron-deficiency anemia
Maternal folate deficiency
Small for gestational age fetus
Intrauterine growth restriction
Congenital malformations/deformations
Chromosomal/genetic abnormalities
Multiple gestations

Approximately half of fetal deaths occur prior to 28 weeks gestation, and about 20 % are at or near term (The Stillbirth Collaborative Research Network Writing Group 2011b; Pardi et al. 2002; Reddy et al. 2010; Silver 2007).

The sterile fetus has no bacterial flora. It grows and develops in sterile amniotic fluid contained within the amniotic membranes. The fetus' development is determined by its genetic makeup, blood supply (maternal-placental-fetal circulation), and the composition/volume of amniotic fluid (Pardi et al. 2002). Any disease of the mother or abnormality of the placenta/umbilical cord can impact the development and survival of the fetus.

Intrauterine fetal death (IUFD) has many causes and associated risk factors. Many fetal deaths cannot be predicted or prevented, but risk factors are known and can be assessed for early intervention (Table 4.1) (Varli et al. 2008; McCowan and Horgan 2009; Ishaque et al. 2011; The Stillbirth Collaborative Research Network Writing Group 2011b; Reddy et al. 2010; Silver 2007; Silver et al. 2007; Huang et al. 2000; Saugstad 2011; Yakoob et al. 2010; Fretts et al. 1995; Zera et al. 2011).

Often, the causes and risks overlap as a risk factor for death can sometimes be the proximate cause of death. At other times, a risk factor may be present but is not the cause of death. The risk factors and causes of fetal death can be divided into fetal, maternal, and placental.

Fetal Factors

Approximately one fifth of fetal deaths are due to inherent fetal anomalies (Pauli 2010). These include malformations, deformations, genetic/chromosomal abnormalities, nonimmune hydrops, metabolic disorders, and malignancies (Pauli 2010; Sebire and Jauniaux 2009; Michels and Tiu 2007). Genetic/chromosomal abnormalities are present in up to 13 % of fetal deaths (Korteweg et al. 2012). Common chromosomal anomalies are similar to those seen in live births: monosomy X, trisomy 21, trisomy 18, and trisomy 13 (Varli et al. 2008; Silver 2007; Michels and Tiu 2007; Wapner and Lewis 2002). Approximately 10 % of fetal deaths result from multiple gestations (Silver 2007). Multiple gestations may cause growth restriction, preterm labor, preterm rupture of membranes, preeclampsia, twin-to-twin transfusion syndrome, and fetal death (Varli et al. 2008; Huang et al. 2000; Fretts et al. 1995). Tumors can cause fetal death due to their location or potential for malignancy. These include neuroblastoma (the most common fetal malignancy, accounting for 30 % of all fetal tumors), hepatoblastoma, leukemia (especially in Down syndrome and usually acute myeloblastic leukemia – AML), lipoma, lymphangioma, teratoma (especially sacrococcygeal), hemangioma, cardiac fibroma, and rhabdomyoma (especially cardiac and associated with tuberous sclerosis) (Sebire and Jauniaux 2009; Woodward et al. 2005).

Maternal Factors

Knowing the mother's past medical and prenatal/obstetric history is important in the death investigation and certification of the cause of death. Maternal risks or causes of fetal death are trauma, malnourishment, advanced age, obesity, drug/alcohol and tobacco use, infections, diabetes mellitus, hypo-/hyperthyroidism, hypertension, and thrombophilias (Table 4.1) (Reddy et al. 2009; Ishaque et al. 2011; Reddy et al. 2010; Huang et al. 2000; Yakoob et al. 2010; Zera et al. 2011). Malnourishments that adversely affect the fetus are maternal deficiencies of folate, iron, lysine, protein, and omega-3 fatty acids (Ishaque et al. 2011). At the other end of the spectrum, maternal obesity is also associated with complications of hypertension, preeclampsia, diabetes, macrosomia, and fetal death. Numerous drugs are known teratogens; however, drugs (prescription and drugs of abuse) can also compromise the uteroplacental circulation or cross the placenta to result in toxic fetal levels and death.

Maternal thrombophilias can result in placental damage (necrosis, infarction, vascular thrombi) and uteroplacental insufficiency. These include antiphospholipid syndrome, prothrombin gene promoter G20210A mutation, factor V Leiden mutation, protein C deficiency, protein S deficiency, and antithrombin III deficiency (Varli et al. 2008; Silver 2007; Battinelli and Bauer 2011). Objective evidence of uteroplacental insufficiency includes intrauterine growth restriction, delay in central nervous system (CNS) maturation, thrombosis, and placental infarction. Resultant fetal death is highest during the second and third trimester.

Placental Factors

In one third to three fourths of fetal deaths, the cause can be determined by examination of the placenta and umbilical cord, especially after 24 weeks gestation (Horn et al. 2004). Therefore a complete autopsy with placental examination is critical (The Stillbirth Collaborative Research Network Writing Group 2011a, b) (See ▶ Chap. 5, "Placental and Maternal Conditions in Perinatal Deaths"). Placental causes of fetal death include structural developmental abnormalities, chorioamnionitis, abruption, villitis, placental infarction, atherosis, maternal floor "infarction"/perivillous fibrin deposition, fetal thrombotic vasculopathy, uteroplacental insufficiency, confined placental mosaicism, and amnion rupture sequence (Fig. 4.1) (Varli et al. 2008; Pardi et al. 2002). Primary placental neoplasms can also occur (Sebire and Jauniaux 2009). Umbilical cord abnormalities include funisitis, true knots, prolapse, abnormal insertions, hemorrhage/hematoma, thrombosis, torsion, and nuchal cords (Silver et al. 2007; Huang et al. 2000). Of note, nuchal cords are reported in up to one third of uncomplicated pregnancies (Reddy et al. 2009; The Stillbirth Collaborative Research Network Writing Group 2011a; Silver 2007; Silver et al. 2007; Carey and Rayburn 2000).

Infections

Infections have been reported to account for 10–25 % of fetal deaths in developed countries (Reddy et al. 2009, 2010; Ishaque et al. 2011; Silver et al. 2007; McClure et al. 2012; Tita and Andrews 2010; Lamont et al. 2011) (Table 4.2). The proportion is higher in developing countries (Ishaque et al. 2011; Silver 2007; Yakoob et al. 2010). Infections can cause fetal death by direct infection of the fetus, placental damage, or severe maternal illness (Varli et al. 2008; Silver 2007; McClure et al. 2012; Lamont et al. 2011). Infections can lead to congenital deformity and damage to a vital organ such as the brain or heart. Placental infection can prevent oxygen and nutrients from reaching the fetus. Infections can also precipitate preterm labor and fetal death (Fig. 4.2) (Reddy et al. 2009). Infections can be divided into hematologic/transplacental and ascending infections. The TORCH infections (Toxoplasmosis, "other," rubella, cytomegalovirus, and herpes) are causes of fetal abnormalities and may cause death (Ishaque et al. 2011). The "other" category is expanding to include not only syphilis but also parvovirus and human immunodeficiency virus – HIV (Ishaque et al. 2011; Yakoob et al. 2010; Lamont et al. 2011). Cytomegalovirus is the most common fetal and neonatal viral infection, but it rarely results in fetal death. Likewise, herpes rarely causes fetal death (Ishaque et al. 2011). The virus most commonly associated with fetal death is parvovirus B19 (Lamont et al. 2011). Ascending infections are usually bacterial, especially Group B streptococcus and Listeria (Tita and Andrews 2010). Cultures, nucleic acid tests, polymerase chain reaction, serology, as well as immunohistochemistry and immunofluorescence can positively identify these infectious agents.

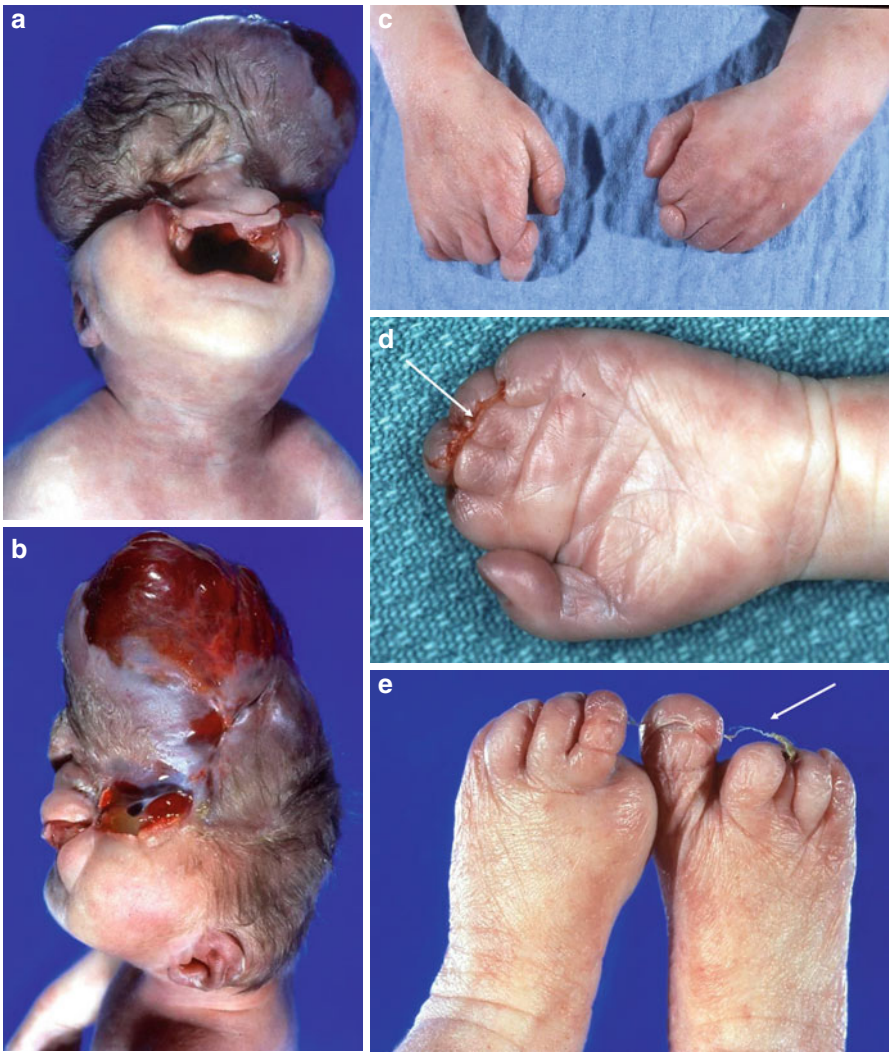

Fig. 4.1 (**a**–**e**). Fibrous bands of amnion cause entrapment of the fetus, constricting body parts as the fetus grows. (**a** and **b**) Frontal and left side view of the cranial distortion. Fetal hands: (**c**) (dorsal) and (**d**) (ventral): Deformation and amputation of the fingers. See amniotic band at *arrow*. (**e**) Deformation and amputation of the toes. Note the amniotic band still intact (*arrow*) (Courtesy of Patrick E. Lantz, MD)

Fetomaternal Hemorrhage

Fetomaternal hemorrhage is defined as the transplacental passage of fetal blood and cells into the maternal circulation before or during delivery (Samadi et al. 1999; Ahmed and Abdullatif 2011). It has been attributed as the cause of 5–14 % of all

Table 4.2 Infectious causes of fetal death

Escherichia coli
Group B streptococcus
Ureaplasma urealyticum and *Mycoplasma hominis*
Toxoplasma gondii
Listeria monocytogenes
Leptospirosis
Parvovirus (B-19)
Enteroviruses (Coxsackie A and B)
Cytomegalovirus
Herpes
Syphilis, malaria, HIV, rubella, measles, mumps

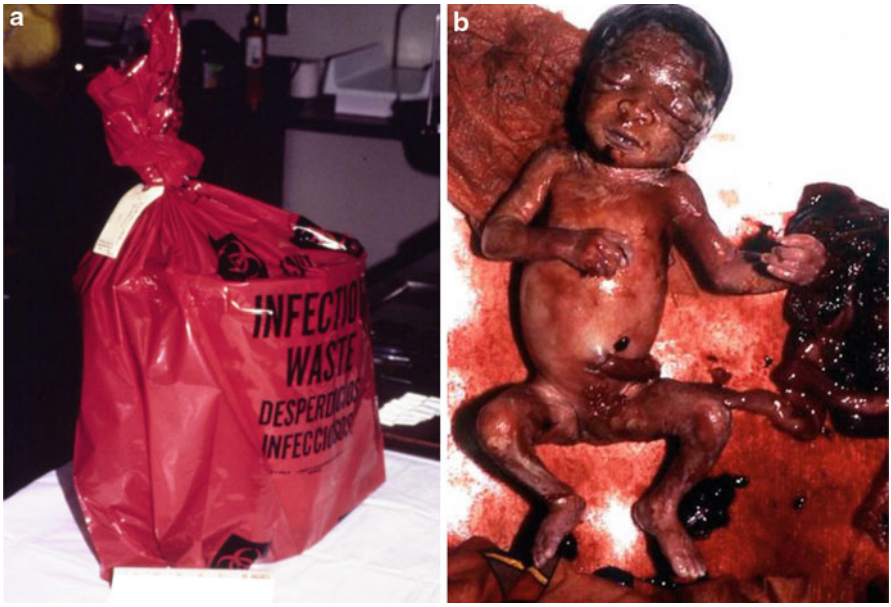

Fig. 4.2 (**a**) 14-year-old mother prematurely delivered a stillborn fetus and placed it in a bucket. She had concealed both the pregnancy and the home delivery. Later, she hemorrhaged and confessed to the delivery. (**b**) The fetus was well-developed and without trauma. The autopsy confirmed that the fetus was a stillbirth. Toxicology was negative. The placenta, membranes, and umbilical cord showed marked acute inflammation. The cause of death was acute chorioamnionitis and funisitis. The manner of death was classified as natural

fetal deaths and can cause intrapartum and early neonatal death (Reddy et al. 2009; Varli et al. 2008; Silver et al. 2007; Carey and Rayburn 2000; Samadi et al. 1999; Ahmed and Abdullatif 2011). The cause of the fetomaternal hemorrhage is a breach of the integrity of the placental circulation. This breach can be secondary to trauma, abruption, chorionic villus sampling, amniocentesis, choriocarcinoma, vasa previa, or external cephalic version (Ahmed and Abdullatif 2011). Transplacental passage

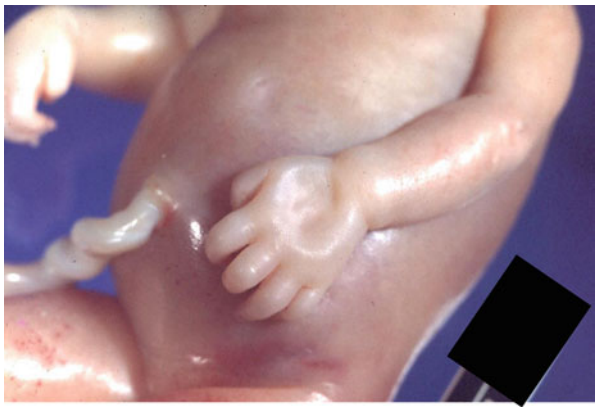

Fig. 4.3 Hydrops fetalis secondary to heart failure. Marked anasarca. Note the pitting edema when the left hand is pressed by the pathologist

Table 4.3 Histopathology of chronic fetal stress

Loss of thymic cortical lymphocytes, decreased thymic weight
Macrophage infiltration of thymic cortex and Hassall bodies
Adrenal gland cortical pseudofollicular change (cortical cytolysis)
Nucleated red blood cells in fetal vessels
Foci of hemorrhagic necrosis in liver, adrenals, kidney, spleen
Intrathoracic serosal petechiae[a]
Intrauterine growth retardation

[a]Intrathoracic serosal petechiae may resolve several days after insult and not be present at the time of autopsy

of fetal cells into the maternal circulation occurs. The threshold for fetomaternal hemorrhage severe enough to cause stillbirth is unknown and is affected by the rate (acute or chronic) of the bleed and the gestational age. The volume of fetal blood that has passed into the maternal circulation can be estimated by various tests such as the Kleihauer-Betke test. A small leak is <0.1 mL up to 2 mL of fetal blood loss (Ahmed and Abdullatif 2011). A massive fetomaternal hemorrhage is >150 mL, or some use 20 mL/kg, of fetal blood loss (Ahmed and Abdullatif 2011). The mechanism of death is severe anemia, neurological injury, nonimmune hydrops fetalis with heart failure, or massive acute exsanguination (Fig. 4.3).

Histological Indicators of Chronic Fetal Stress

If a fetus has been stressed for several days to weeks prior to death and delivery, certain histopathological changes may be seen at autopsy. These could indicate such entities as poor oxygenation, infection, anemia, or cardiovascular stress (Ahmed and Abdullatif 2011) (Table 4.3).

Fig. 4.4 Maceration with epidermal sloughing and a red underlying dermis

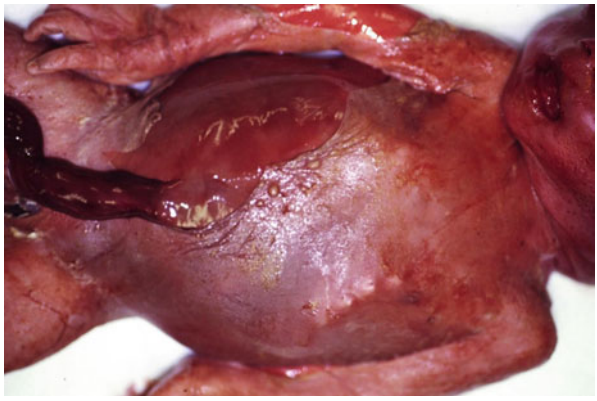

Fig. 4.5 Maceration with blister formation, skin sloughing, red discoloration of the dermis, and red-brown discoloration of the umbilical cord

Autopsy Findings of IUFD

At autopsy, the appearance of the fetus depends largely upon the postmortem interval or the death-to-delivery interval. Maceration is the degeneration of fetal tissues after death. Autolysis (due to endogenous proteolytic enzymes) and putrefaction (due to the action of bacteria) may both be involved, depending on the sterility of the fetus and the postmortem environment. The umbilical stump will change color to a red–brown within 6 h (Genest and Singer 1992; Wainwright 2006). The epidermis will separate from the dermis and slough with a loss of 1 cm $\geq$ 6 h (Genest and Singer 1992; Wainwright 2006). The underlying dermis will be moist and red (Fig. 4.4). Desquamation of the face, back, or abdomen will occur by 12 h (Genest and Singer 1992; Wainwright 2006). Fluid will accumulate beneath the epidermis resulting in bullae formation (Fig. 4.5). Generalized desquamation

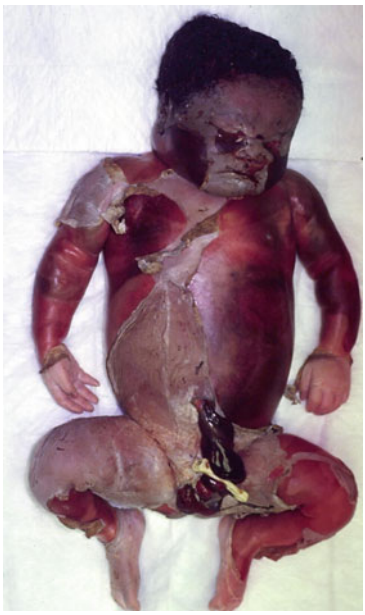

Fig. 4.6 Maceration. Skin sloughing is over the entire body. Note the brown discoloration of the umbilical cord

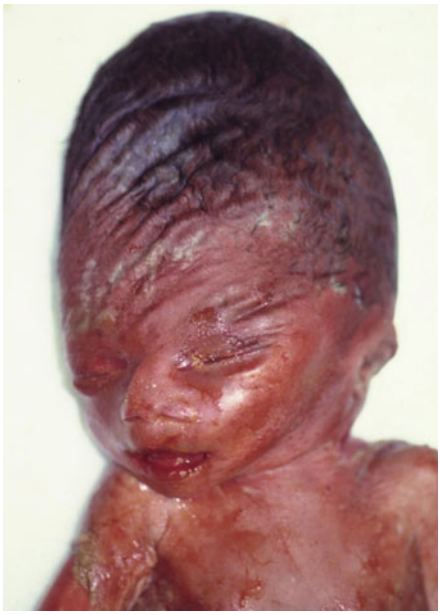

Fig. 4.7 Intrauterine fetal demise with maceration demonstrating the boggy scalp and misshapen head due to brain liquefaction and overriding skull plates

with discoloration of the underlying dermis will occur by 24 h (Fig. 4.6) (Genest and Singer 1992). The scalp will become boggy (Fig. 4.7). By 4–5 days, the skull plates separate from the dura and periosteum and will override resulting in a dysmorphic cranium (Figs. 4.7 and 4.8). Joints become hypermobile with

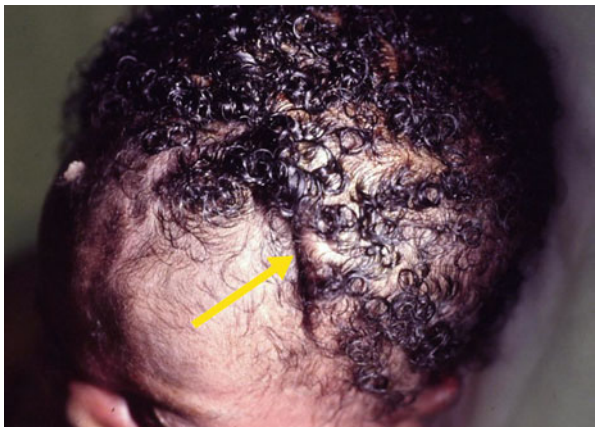

Fig. 4.8 Intrauterine fetal demise with overriding skull plates (*arrow*). This distortion has been mistaken for neonatal skull fractures

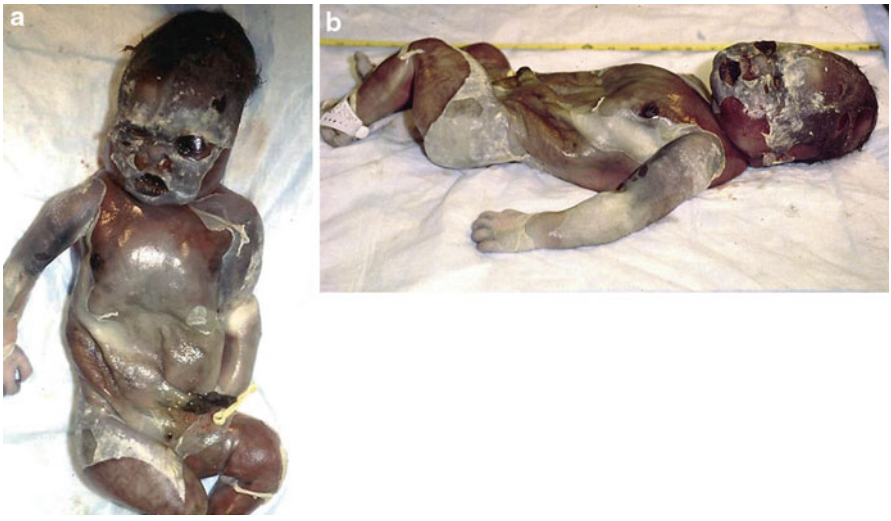

Fig. 4.9 (**a** and **b**) A 40-year-old mother reported that she did not know she was pregnant. Family members complained of an odor. With medical intervention, she delivered a partially decomposed, full-term fetus. The skin was sloughing, and the underlying dermis was green-brown. The skin of the abdomen had started to mummify (**b**)

autolysis of connective tissues. Before 48 h, little change has occurred to the internal organs aside from softening of the brain and liver. After 48 h, the internal organs turn dark red-purple due to red blood cell breakdown. Abdominal organs may become dark green-gray due to leakage of bile. By 2–7 days, serosanguinous fluid collects in serosal cavities and organs begin to liquefy. Mummification will occur 2 weeks after death (Genest and Singer 1992; Wainwright 2006) (Fig. 4.9a and b). A fetus papyraceus is a mummified fetus that died in

Table 4.4 Histological changes consisting of cellular nuclear basophilia loss in certain organs can also be used to estimate postmortem interval (Genest et al. 1992; Wainwright 2006)

Loss of nuclear basophilia, individual cells	**Death-to-delivery interval**
Renal cortical tubules	4 h
Liver	24 h
Inner half of myocardium	24 h
Outer half of myocardium	48 h
Bronchial epithelium	96 h
Tracheal cartilage	1 week
Loss of nuclear basophilia, all cells	**Death-to-delivery interval**
Liver	96 h
Gastrointestinal tract	1 week
Adrenal	1 week
Kidney	4 weeks

utero, usually during the second trimester. Fetus compressus is a mummified, flattened fetus of a multiple gestation that remains compressed between the uterus and the vital sibling's amniotic sac until delivery (usually when the term is completed). Often these two terms are used interchangeably.

Of note, fetal foot length is the most reliable body measurement for gestational assessment of the macerated fetus (Wainwright 2006).

Besides gross changes of maceration, histological changes in certain fetal organs have also been researched to assist in the estimation of the postmortem interval (Table 4.4).

Diagnostic Work-Up of a Fetal Death

The diagnostic work up for fetal deaths involves thorough analyses of the fetus, mother, and placenta (Table 4.5). The most valuable tests are the fetal autopsy with ancillary studies, placental examination, cytogenetic analysis, and analysis for fetomaternal hemorrhage (Varli et al. 2008; Silver 2007; Pauli 2010; Korteweg et al. 2012).

Intrapartum Death

Intrapartum death is the death of a child that occurs during labor and delivery. These are most often secondary to birth trauma or birth asphyxia. Birth trauma is covered in ▶ Chap. 6, "Birth Trauma". Birth asphyxia is an insult to the fetus or newborn due to lack of proper gas exchange or lack of perfusion to various organs during delivery resulting in hypoxia, hypercapnia, and acidosis (Lawn et al. 2005, 2006, 2010; Simunek 2008; Herrera-Marchitz et al. 2011; Majeed et al. 2007). The mother may have medical conditions that lower her oxygen levels; a placental

Table 4.5 Diagnostic work-up for fetal death

Placental examination with histology of placenta, membranes, and umbilical cord
Fetal karyotype (fascia lata, tendon, skin)
Fetal autopsy with toxicology
Fetal microbiology/viral cultures and nucleic acid tests
Fetal analysis for inborn errors of metabolism
Full-body radiographs
Maternal toxicology
Maternal glucose and hemoglobin A1c
Kleihauer-Betke test or flow cytometry to identify fetal red blood cells in maternal circulation
Indirect Coombs
Maternal viral, syphilis, and protozoan serology
Maternal lupus anticoagulant
Maternal anticardiolipin antibodies
Maternal screen for protein C, protein S, antithrombin III deficiency; thrombophilia testing

abnormality may prevent adequate circulation to and from the fetus; or the neonate may be unable to breathe at birth (Majeed et al. 2007). Immediately after delivery, mother-dependent respiration is replaced by autonomous breathing (Herrera-Marchitz et al. 2011). If delivery is delayed or prolonged, intrapartum asphyxia with a multisystem metabolic cascade can result (Herrera-Marchitz et al. 2011). The most severe consequences are neonatal encephalopathy, multiorgan failure, and death (Simunek 2008).

As with fetal death, risk factors for intrapartum death can be divided into fetal, maternal, and placental categories. Fetal factors include macrosomia, malpresentation, dystocias, post-term, congenital heart disease, diaphragmatic hernia, spina bifida, intrauterine growth restriction, and multiple gestations (Dudenhausen and Maier 2010; Milsom et al. 2002). Maternal factors are diabetes mellitus, heart disease, renal disease, hypertension, anemia, preeclampsia/eclampsia, excessive uterine contractions, maternal fever during labor >38 °C, uterine rupture, drugs, and prolonged labor, especially second stage. A prolonged labor with intrapartum metabolic acidosis can lead to multiorgan failure and encephalopathy in the neonate (Simunek 2008). Investigation into the labor and delivery records as well as the mother's past medical history is very important. Placental factors include nuchal cord, cord compression, rupture of membranes over 24 h, chorioamnionitis, abnormal vessel integrity, acute retroplacental hemorrhage, abruption, fetomaternal hemorrhage, and placenta previa.

When investigating a possible birth asphyxia death, signs of fetal intrapartum stress due to asphyxia should be evaluated (Majeed et al. 2007; Milsom et al. 2002; Singh and Archana 2008; Nishijima et al. 2005) (Table 4.6). One of these signs is the aspiration of squamous cells and elements of vernix caseosa. Vernix caseosa is a proteolipid biofilm produced by the fetus during the last trimester. It has several in utero and postnatal functions such as a thermal regulator, antimicrobial, antioxidant, moisturizer, and enhancer of wound healing (Singh and Archana 2008).

Table 4.6 Indicators of intrapartum asphyxia

Non-reassuring fetal heart tones
Passage of meconium
Low Apgar scores (<7 at 5 min)
Acidosis (cord blood pH < 7)
Seizures
Intrathoracic serosal petechiae at autopsy (pleura, epicardium, thymic cortex)
Pulmonary hemorrhage
Hepatic subcapsular hemorrhage
Squamous cells and elements of vernix caseosa in the distal airways at autopsy

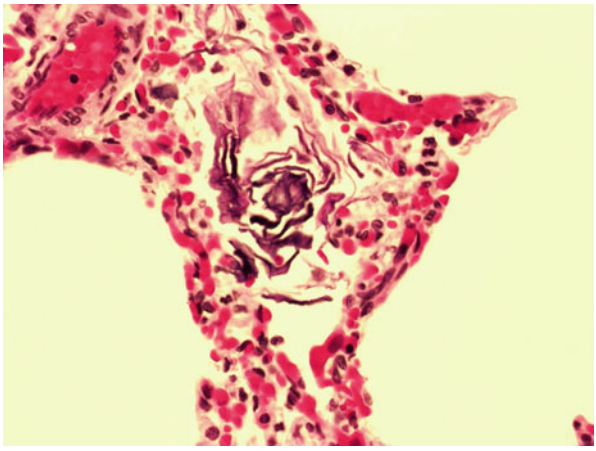

Fig. 4.10 Squamous cells and debris from vernix caseosa are in the alveolar spaces of an infant who experienced birth asphyxia (Hematoxylin and Eosin, H&E × 40)

Vernix caseosa is composed of water, lipid, and protein, in particular water-containing corneocytes embedded in a lipid matrix. Fetal distress leads to reflex gasping efforts by the fetus. Histologically, numerous stacks of flattened, desquamated squamous cells and vernix components such as mucin and lipid can be seen in the distal airways (Figs. 4.10–4.16). Such aspiration can be so massive as to lead to vernix aspiration syndrome and/or airway obstruction (Nishijima et al. 2005).

Another sign of fetal distress is the early passage of meconium (Milsom et al. 2002). Meconium is the first fecal matter passed by a neonate, a highly complex matrix composed of water, mucopolysaccharides, bile salts and acids, bile pigment, epithelial cells, intestinal enzymes, cholesterol and other lipids, as well as a residue of swallowed amniotic fluid (Gallardo and Queiroz 2008). It is generally accepted that meconium begins to form at approximately 12 weeks gestation (Gallardo and Queiroz 2008). It is excreted by the neonate several times a day for the first 1–5 days postpartum (Gallardo and Queiroz 2008). If passed in utero or during delivery, meconium is an indicator of fetal stress and asphyxia as neural stimulation

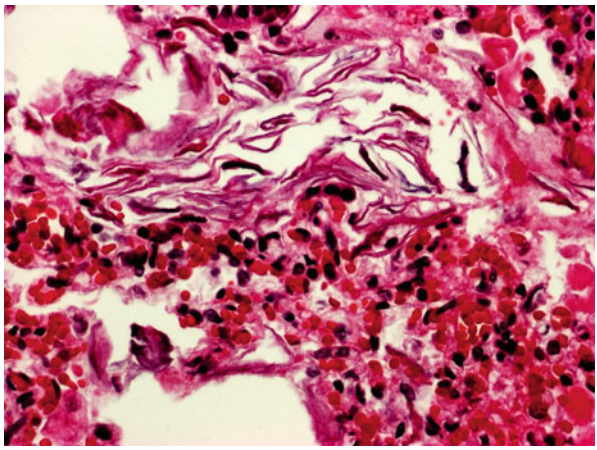

Fig. 4.11 Aspirated stacks of anucleated squamous cells from the fetal skin secondary to birth asphyxia (Hematoxylin and Eosin, H&E × 40)

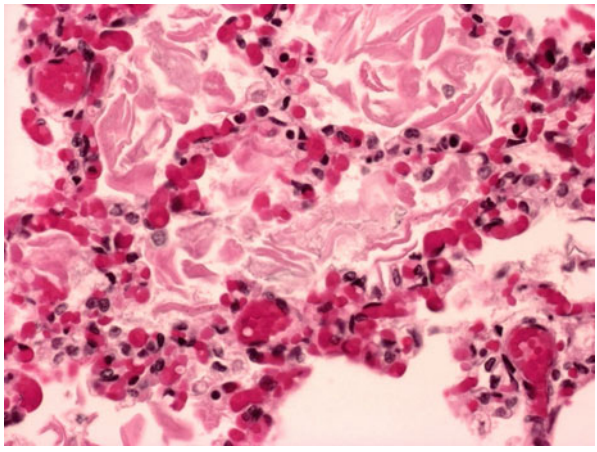

Fig. 4.12 Eosinophilic debris and squamous cells fill alveolar spaces (Hematoxylin and Eosin, H&E × 40)

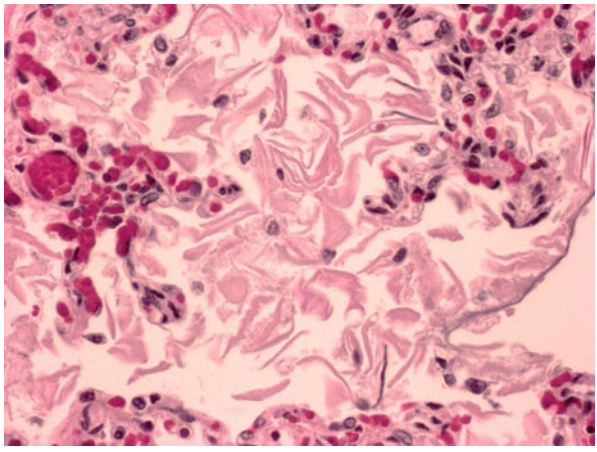

Fig. 4.13 Numerous aspirated squamous cells and debris of vernix caseosa (Hematoxylin and Eosin, H&E × 40)

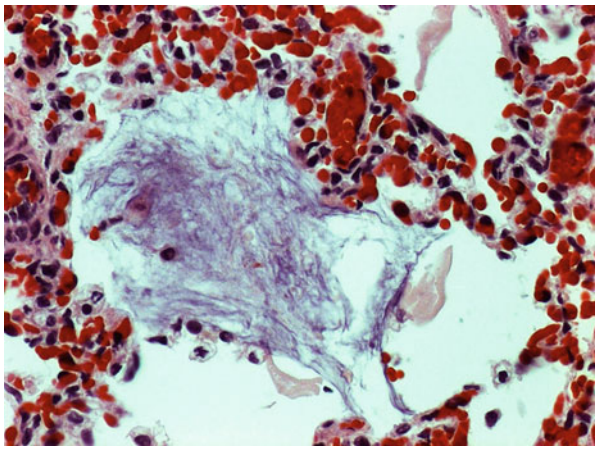

Fig. 4.14 Blue-gray mucin, proteinaceous debris, and squamous cells in the alveolar spaces (Hematoxylin and Eosin, H&E × 40)

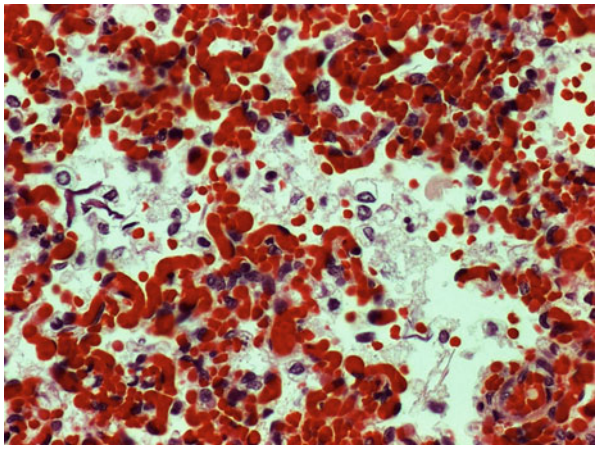

Fig. 4.15 4-day-old neonate: Numerous foamy macrophages and squamous cells in the air spaces (Hematoxylin and Eosin, H&E × 40)

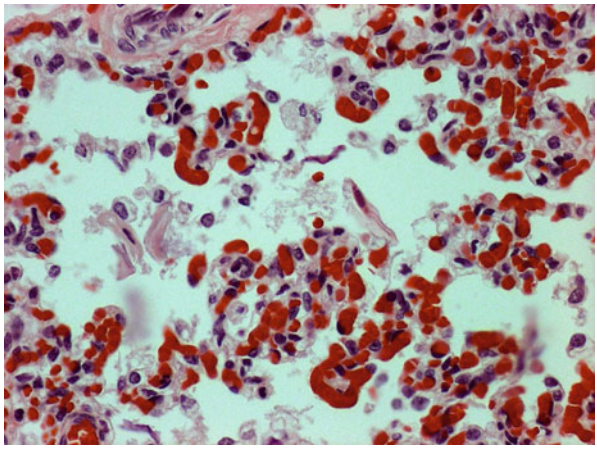

Fig. 4.16 4-day-old neonate who survived after birth asphyxia died of hypoxic ischemic encephalopathy. The air spaces contain foamy macrophages, squamous cells, and eosinophilic proteinaceous material (Hematoxylin and Eosin, H&E × 40)

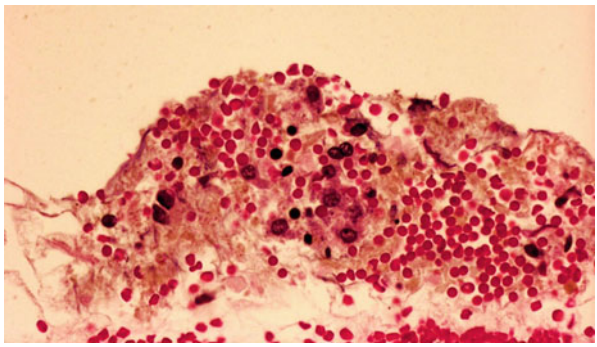

Fig. 4.17 Meconium-stained (bile pigment) placenta of a term neonate who experienced birth asphyxia and passed meconium (Hematoxylin and Eosin, H&E × 40)

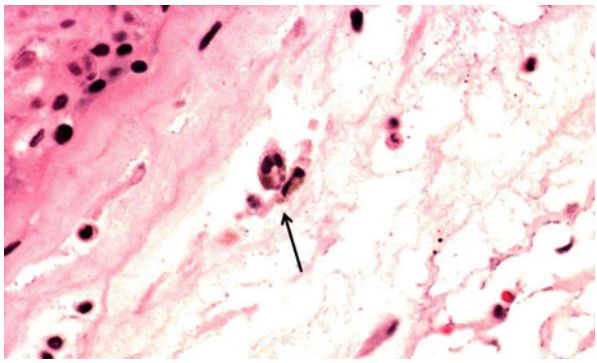

Fig. 4.18 Amniotic membrane meconium/bile pigment in macrophages (*arrow*) (Hematoxylin and Eosin, H&E × 40)

of the rectal sphincter causes relaxation and allows excretion (Milsom et al. 2002). This is evident as meconium-stained amniotic fluid, meconium-stained placenta/membranes/cord, and meconium on the fetus/neonate's skin, nails, and behind the ears (Fig. 4.17). Meconium can be identified in chorionic macrophages after 3 h (Fig. 4.18). Meconium may be aspirated (Fig. 4.19) or swallowed; meconium aspiration syndrome is described under neonatal death.

The central nervous system (CNS) is the most sensitive to intrapartum asphyxia, and the major organ injured is the brain. If the asphyxial episode is acute, resulting in rapid death, generalized edema, pale cerebral cortex, and congested white matter may be identified. Other specific areas of the brain damaged during intrapartum asphyxia are the basal ganglia, thalami, hippocampi, and corticospinal tracts around the central fissure (Rutherford 2001; Herrera-Marchitz et al. 2011). The ischemic lesions are infarctions with or without hemorrhage. In 82 % of cases, more than one organ system besides the brain are involved (Rutherford 2001; Herrera-Marchitz et al. 2011). These organs include kidney, lungs, liver, heart, and intestines. If intrapartum asphyxia does not cause death during delivery, death may occur days later during the neonatal period. Subsequent reperfusion and generation of free

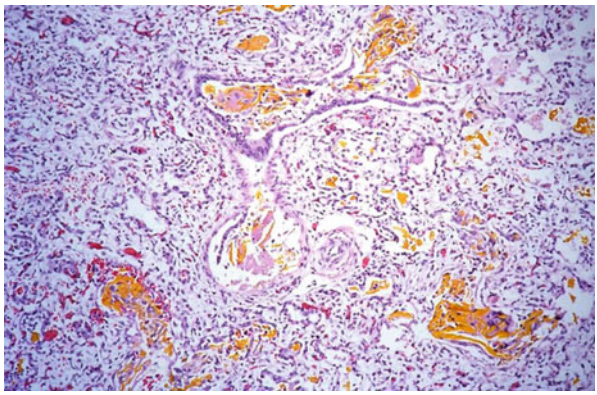

Fig. 4.19 Neonatal lung with meconium aspiration: Yellow-green bile pigment and squamous cells in distal airways and alveolar spaces (Courtesy of Patrick E. Lantz, MD) (Hematoxylin and Eosin, H&E × 40)

radicals contribute to ongoing injury. The CNS lesions will be most visible radiographically and pathologically if the child survives into the neonatal period.

Neonatal Death

A neonate is a child from birth to 1 month of age. It is estimated that each year four million children die during the neonatal period, a global average of 30 deaths per 1,000 live births (Lawn et al. 2005, 2006, 2010). Throughout the world, up to 80 % of neonatal deaths are due to infection (sepsis, pneumonia, diarrhea, tetanus), complications of birth asphyxia, and prematurity (Saugstad 2011; Lawn et al. 2010). Neonaticide is discussed in ▶ Chap. 7, "Neonaticide".

A. Infections are the single largest cause of neonatal deaths globally (Tita and Andrews 2010). Infections are usually secondary to chorioamnionitis that manifest as sepsis, pneumonia, and myocarditis both congenital and neonatal (Berardi et al. 2011; Kristof et al. 2009; Berman and Moss 2011) (Figs. 4.20–4.22). In many areas of the world, deaths are due to malaria, syphilis, and HIV. Neonates are at particularly high risk for infection because of their reduced immunity and the immature biochemical and mechanical properties of their mucosal surfaces, in either function or quantity (Bateman and Seed 2010). Early onset sepsis, which occurs from birth to 6 days, is commonly due to *Escherichia coli* and Group B streptococcus (Bateman and Seed 2010). These pathogens are generally acquired from vaginal passage during birth (Bateman and Seed 2010). Herpes simplex virus, also transmitted during vaginal delivery, is another cause of neonatal infection leading to long-term disabilities or death (Gallardo and Queiroz 2008) (Fig. 4.23a–c). Late onset sepsis, from day 7–30, is most often due to organisms acquired from the environment and/or the caregiver (Bateman and Seed 2010). The major pathogen is coagulase-negative staphylococcus comprising almost 40 % of cases (Bateman and Seed 2010). Others organisms include *Escherichia coli*, *S. aureus*, *Enterococcus* sp., *Klebsiella*, *Enterobacter* sp., *Serratia marcescens*,

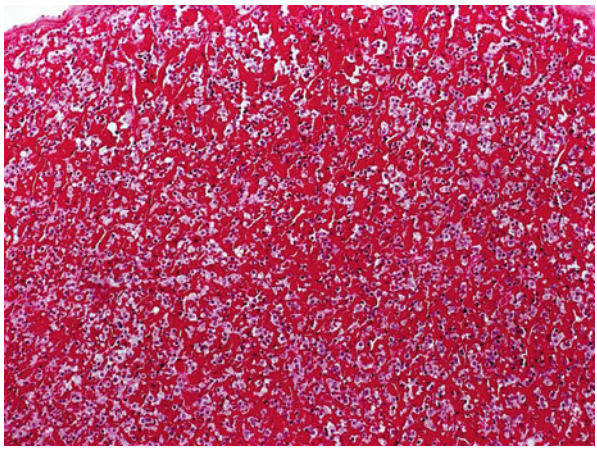

Fig. 4.20 Adrenal gland hemorrhage in a child with sepsis. Waterhouse–Friderichsen syndrome (Hematoxylin and Eosin, H&E × 40)

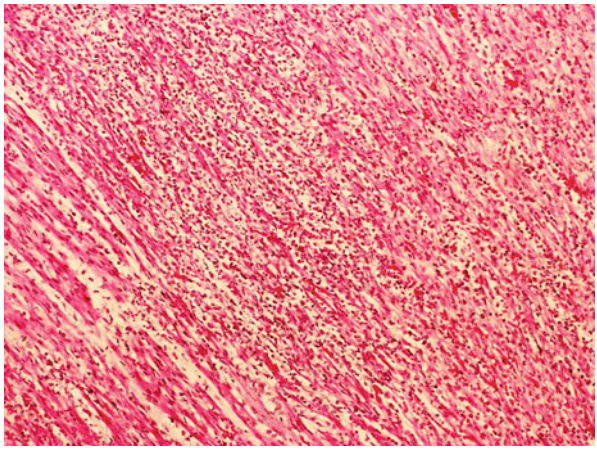

Fig. 4.21 Heart of a neonate with bacterial sepsis and acute bacterial myocarditis shows an infiltration of segmented neutrophils, edema, and myocyte necrosis (Hematoxylin and Eosin, H&E × 40)

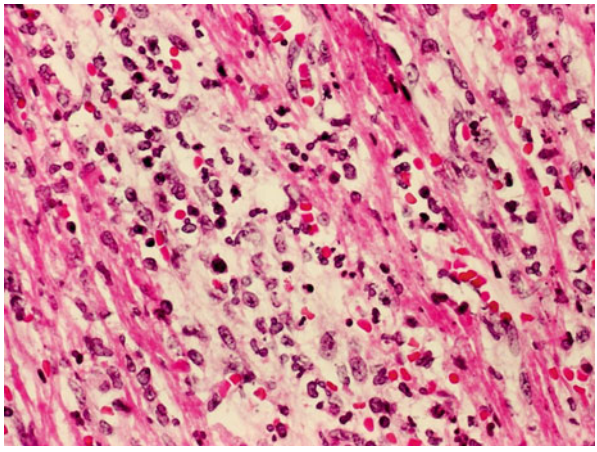

Fig. 4.22 Acute bacterial myocarditis secondary to bacterial sepsis shows segmented neutrophils, myocyte necrosis, and karyorrhexis (Hematoxylin and Eosin, H&E × 40)

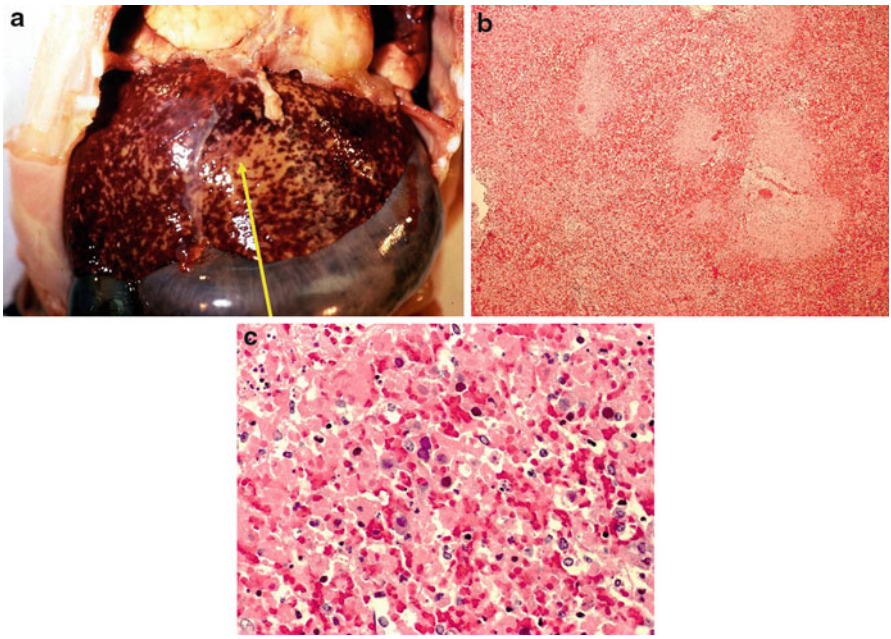

Fig. 4.23 (**a**) Gross liver in situ at autopsy with numerous yellow-tan necrotic areas (*arrow*) throughout the parenchyma. The child has herpes. (**b**) The yellow-tan areas seen grossly correspond to the focal hepatic necrosis (Hematoxylin and Eosin, H&E ×10). (**c**) Many hepatocytes have "ground-glass" nuclear inclusions. The background is hepatocellular necrosis and karyorrhectic debris (Hematoxylin and Eosin, H&E × 40)

Pseudomonas aeruginosa, and Group B *Streptococcus* (Bateman and Seed 2010). Not surprisingly, sepsis is more prevalent in premature neonates especially by Gram-negative organisms and Candida (Tita and Andrews 2010; Kristof et al. 2009).

B. Complications of birth asphyxia that can lead to death in the neonatal period include hypoxic ischemic encephalopathy, intracranial hemorrhage, cardiac papillary muscle necrosis, and meconium aspiration syndrome (Rutherford 2001; Simunek 2008). Cerebral white matter necrosis and cystic degeneration may be seen if a neonate survives 18–24 h. Cerebral infarcts may be identified in the basal ganglia, thalami, hippocampi, and corticospinal tracts around the central fissure (Rutherford 2001). Histopathological brain findings in a neonate who dies from birth asphyxia complications consist of gliosis, neuronal karyorrhexis, lipid and hemosiderin-laden macrophages, and eosinophilic neurons (Fig. 4.24a–g). Other systemic changes seen in neonatal deaths secondary to intrapartum asphyxia include renal acute tubular necrosis (Fig. 4.25a–d), renal corticomedullary hemorrhage, stress involution of the thymus, (Fig. 4.26a–c) hepatic centrilobular necrosis, hepatic microvesicular steatosis, and massive aspiration of squamous cells (Figs. 4.10–4.16).

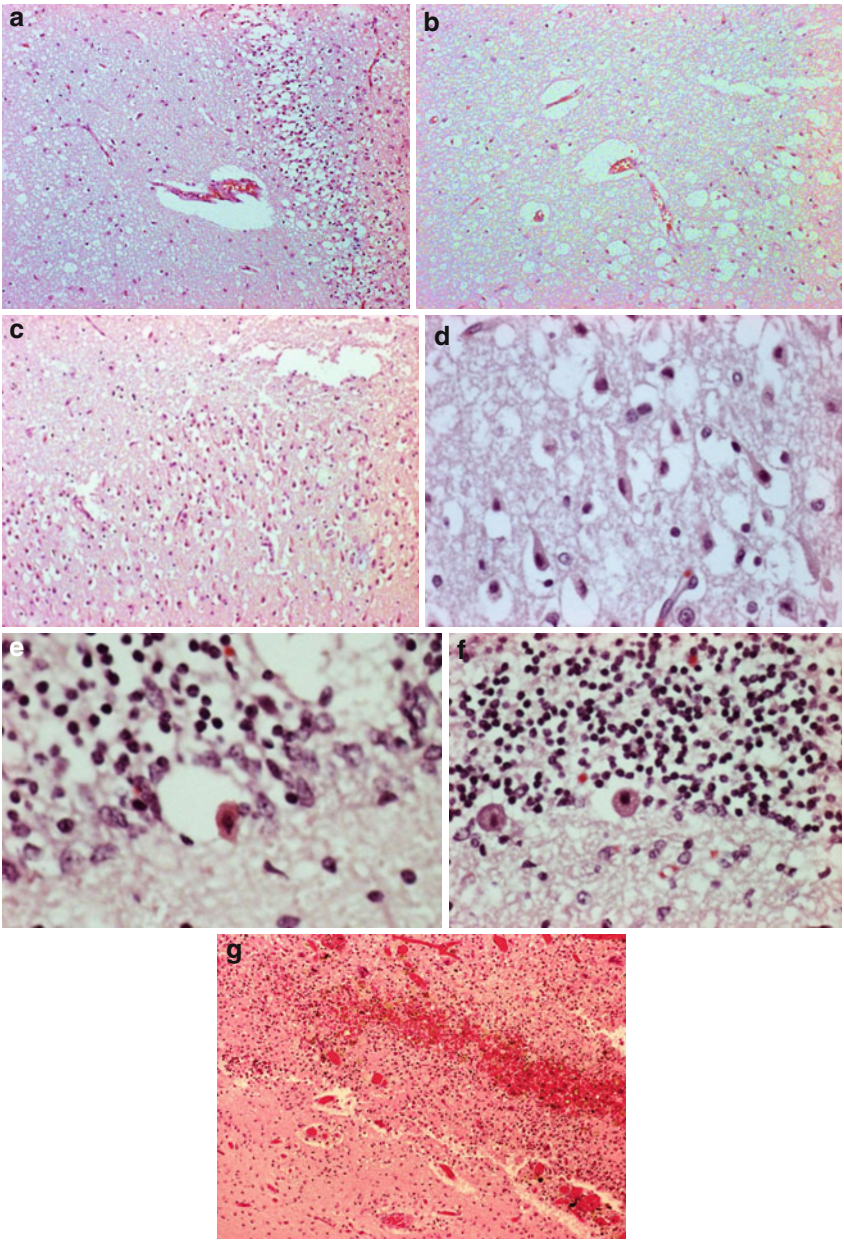

Fig. 4.24 (**a**–**f**) A four-day-old neonate suffered birth asphyxia with hypoxic ischemic encephalopathy and multiorgan failure. Sections of brain show edema, prominence of perivascular spaces, and shrunken, pyknotic neurons. (**e** and **f**) The cerebellar Purkinje cells have eosinophilic cytoplasm with dark, pyknotic nuclei. (**g**) A recent cerebral infarct showing hemorrhage, hemosiderin, edema, and karyorrhexis (Hematoxylin and Eosin, H&E; a,b,c,g × 10; d,e,f × 40)

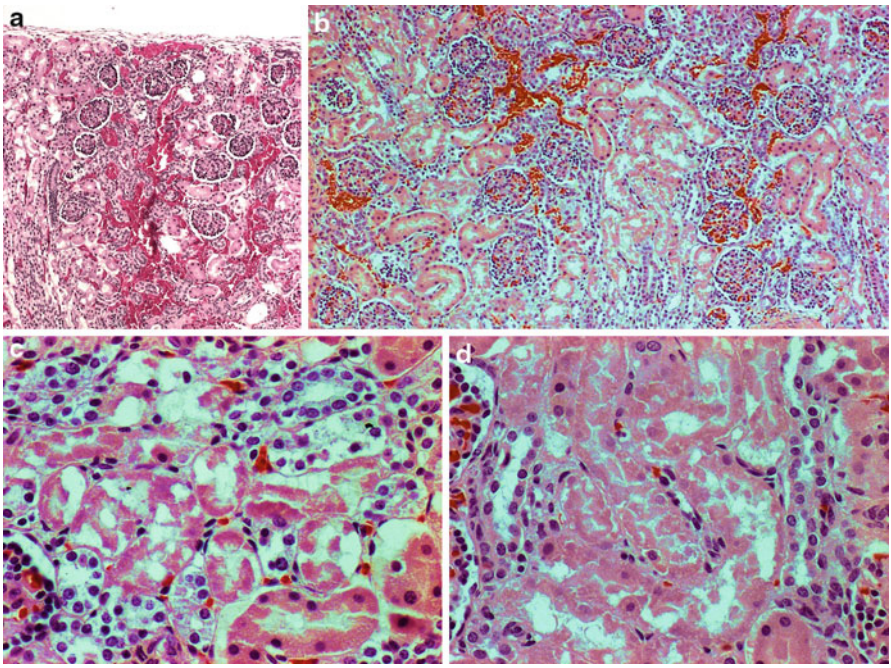

Fig. 4.25 (**a**–**d**) Acute tubular necrosis of the kidney and cortical hemorrhage in a neonate following birth asphyxia (Hematoxylin and Eosin, H&E a × 4; b × 10; c × 40; d × 40)

Meconium aspiration syndrome consists of chemical pneumonitis with hyaline membrane formation, surfactant dysfunction, mismatched ventilation–perfusion, possible airway obstruction, and possible pulmonary hypertension (Fig. 4.19). The mortality rate is as high as 20 %. Bile pigments can be absorbed by the lungs and excreted in the urine (green urine) within 24 h. Meconium may also be seen in the esophagus and stomach.

C. The worldwide prematurity rate is 9.6 %, highest in Africa (11.9 %) and North America (10.6 %). Besides sepsis, other complications of prematurity that can cause neonatal death are respiratory insufficiency and hyaline membrane disease, pneumonia, intracranial hemorrhages (especially germinal matrix and intraventricular), and in the second week of life, necrotizing enterocolitis (Dudenhausen and Maier 2010; Kristof et al. 2009; Nissen 2007; Gupta et al. 2009) (Figs. 4.27, 4.28a, and b). The greatest risk of death from pneumonia in childhood is in the neonatal period (Nissen 2007).

D. During the neonatal period, one may also see deaths from congenital malformations (most commonly congenital heart disease), metabolic disorders, and cardiac channelopathies such as prolonged QT interval (Coté 2010; Sadowski 2009) (Figs. 4.29 and 4.30). Malnutrition and diarrhea cause many

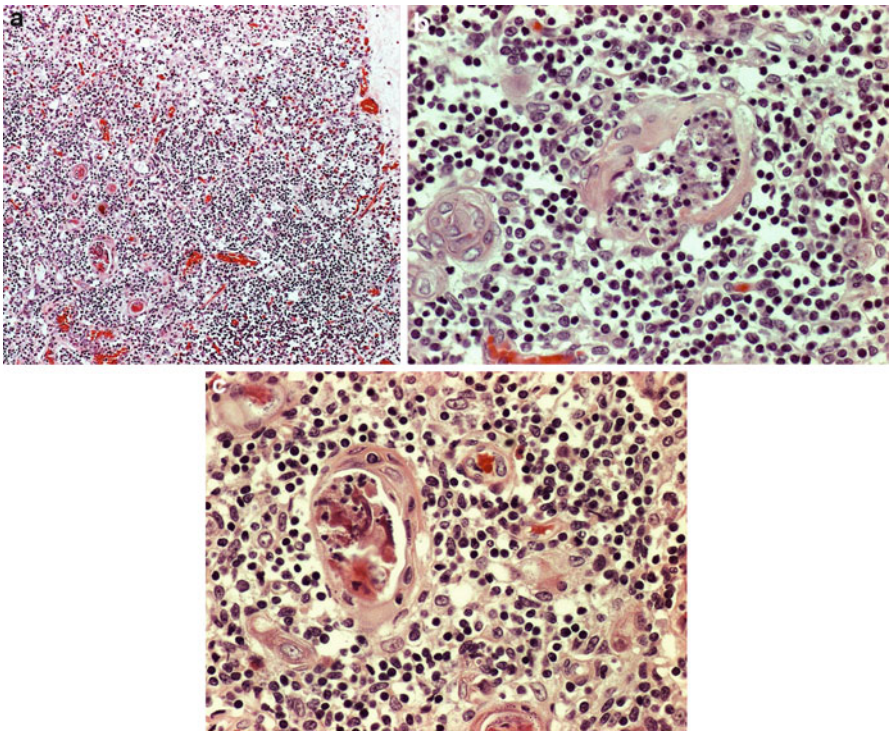

Fig. 4.26 (**a**–**c**) Thymus in a neonate who suffered birth asphyxia and died of hypoxic ischemic encephalopathy. (**a**, Hematoxylin and Eosin, H&E 10×) The thymus demonstrates acute stress involution. The cortex is poorly delineated from the medulla, there is a loss of cortical lymphocytes, Hassall corpuscles are secondarily close together, and (**b** and **c**, Hematoxylin and Eosin, H&E 40×) Hassall corpuscles have necrosis and calcifications

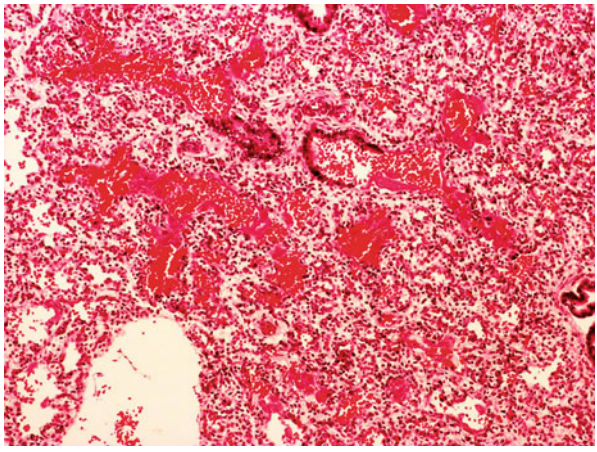

Fig. 4.27 Lung of a premature neonate with respiratory distress syndrome shows vascular congestion, hemorrhage, edema, and hyaline membrane formation (Hematoxylin and Eosin, H&E × 10)

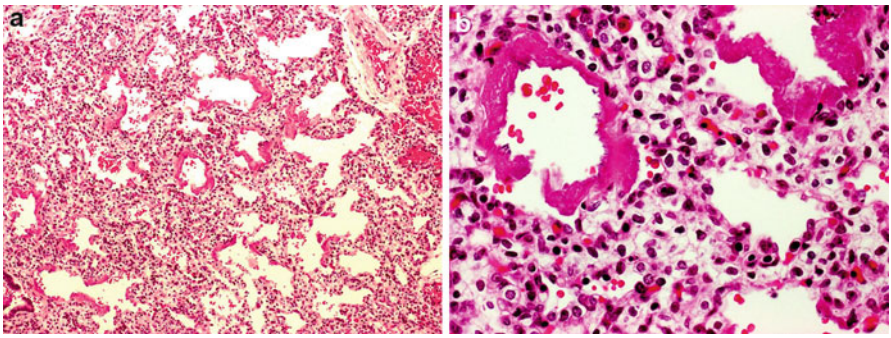

Fig. 4.28 (**a** and **b**) A neonate with respiratory distress syndrome secondary to prematurity. The lungs show hemorrhage and hyaline membranes in the respiratory bronchioles and the alveolar spaces. Of note, hyaline membranes are an indication of live birth (Hematoxylin and Eosin, H&E × 10, 40)

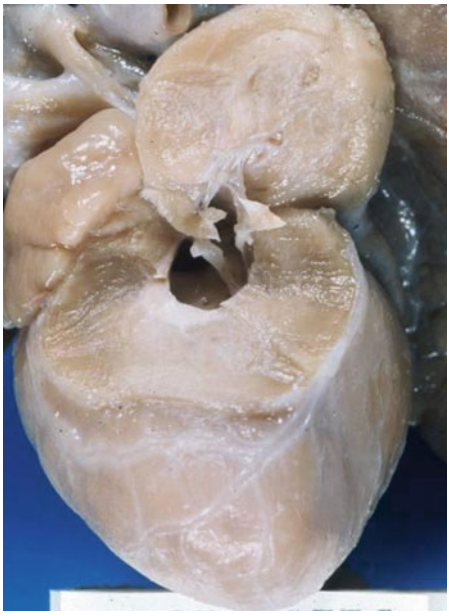

Fig. 4.29 Gross neonatal heart with hypoplastic left heart syndrome. Upward reflection of the left ventricular free wall demonstrates the very small left ventricular chamber. Most of the cardiac mass is right ventricle. Of note, often the mitral valve and aorta are abnormal

deaths throughout the world, especially in areas of poverty and underdevelopment (Bryce et al. 2005). Deaths secondary to aspiration due to dysphagia, metabolic or chromosomal disorders, or a structural abnormality such as a tracheoesophageal fistula or cleft palate also occur (Fig. 4.31a and b).

Of note, intracranial hemorrhages in the neonate have several etiologies including those listed above. The most common presentation is a seizure and many can result in neonatal death (Majeed et al. 2007). These etiologies include

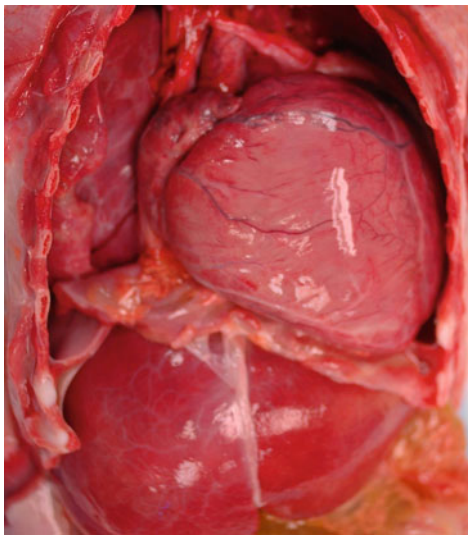

Fig. 4.30 Gross heart. Hypertrophic cardiomyopathy in situ. Cardiomegaly with protrusion of the left ventricle creates a globoid cardiac shape. Compare with the size of the liver below

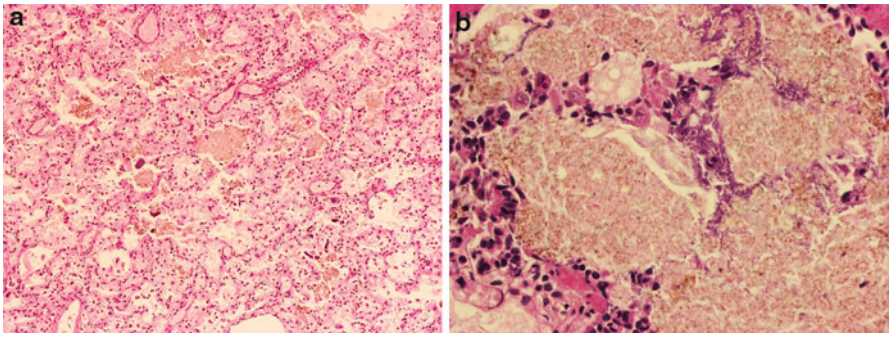

Fig. 4.31 (**a** and **b**) Lung (Hematoxylin and Eosin, H&E × 10) (**a**) and (Hematoxylin and Eosin, H&E × 40) (**b**). Acute aspiration of feeding and/or gastric contents. Granular tan-brown material partially to completely fills the alveolar spaces

intraventricular hemorrhage of prematurity, cerebral infarction, intrapartum asphyxia, birth trauma, inflicted trauma, vascular malformation, coagulopathies, disseminated intravascular coagulation, thrombocytopenia, vitamin K deficiency, hemorrhagic disease of the newborn, neoplasm, sepsis, encephalitis, and sinovenous thrombosis.

Conclusion

Death of a child from the beginning of the fetal period to the end of the neonatal period can be due to numerous causes. Some of these are unavoidable and are

inherent in the fetus. Others are preventable and/or treatable if identified in a timely manner. Most importantly, many of these deaths are associated with known risk factors. Education of healthcare providers, provision of healthcare to underserved areas, and education of the general public can reduce the number of these deaths. In order to accurately determine the cause of death and prevent future morbidity and mortality of these children, a complete autopsy with ancillary studies, examination of the placenta, and assessment of the mother is necessary in every case.

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