Section 1 Newborn and Infant Physiology for Anesthetic Management

Chapter 1

The Term Infant

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Introduction

The first moment of healthy extrauterine life is usually heralded by a deep breath followed by a cry. Within a few breaths, the color of the infant changes from a mottled dusky blue to a rosy hue and the infant is generally alert, looking around at his new environs. Once he is swaddled and brought to his mother, he may instinctively root and suck even though the mother is not yet able to nourish him. The physiologic changes that occur in the first few minutes of life are astounding. During development, the fetus develops an organ physiology that was adapted to the low-oxygen environment of the maternal circulation and then the first breath of extrauterine life initiates a process of physiologically altering his circulation and respiration. In order to care for neonates during the perioperative period, it is important to understand the physiologic changes that occur during the first few hours, days, and months of life.

Cardiac

In utero, oxygenated placental blood is divided to pass through either the liver or to the inferior vena cava via the ductus venosus. This oxygenated blood from the inferior vena cave preferentially streams across the right atrium through the foramen ovale into the left atrium. This blood passes through the left ventricle and aorta to supply the myocardium, head, and upper torso. Deoxygenated blood returns to the right atrium via the superior and inferior vena cava and is pumped out into the pulmonary arteries via the right ventricle [1]. About 11 percent of this blood is distributed to the highly resistant pulmonary vascular bed and 89 percent is distributed to the aorta via the ductus arteriosus [2]. Aortic blood then divides to supply the lower extremities and to return to the placenta via the umbilical arteries to be reoxygenated.

Immediately after delivery, with the first breath of life, the expansion of the lungs causes the pulmonary vascular resistance to drop. Concurrently, the umbilical vessels begin to narrow due to traction and the increased oxygen levels in the umbilical artery from the infant breathing the room air. Once these vessels are fully constricted or clamped during delivery, the vascular resistance of the systemic circulation is markedly increased. The result of this is less blood flow through the ductus venosus to the inferior vena cava. The decrease in pulmonary vascular resistance leads to more blood flow to the lungs and higher flows into the left atrium. Thus, the right- and left-sided cardiac pressures begin to reverse, with the left atrium developing higher pressures, which causes the foramen ovale to functionally close. The flow across the ductus arteriosus becomes left-to-right as the pulmonary artery pressure decreases and the system vascular pressure increases. Normally the combination of decreased circulating prostaglandin PGE2 and the increased oxygen levels within the duct lead to functional closure within 2–3 days in greater than 99 percent of term infants [3]. Complete closure does not occur normally until 4–8 weeks, which means that under certain circumstances the ductus arteriosus can reopen. If the vascular resistances of the pulmonary circuit become elevated during this period, it is possible for the foramen ovale to act as a right-to-left shunt, as it did during fetal life. This condition is known as persistent pulmonary hypertension of the newborn and can be exacerbated by hypoxia, acidemia, or primary structural cardiac diseases. Figures 1.1 and 1.2 offer an overview of the circulatory system.

Neonatal Heart

In a full-term infant, the neonatal cardiac output at 200 ml^{-1} kg^{-1} min^{-1} or greater is roughly double that of adults to meet the metabolic demands of

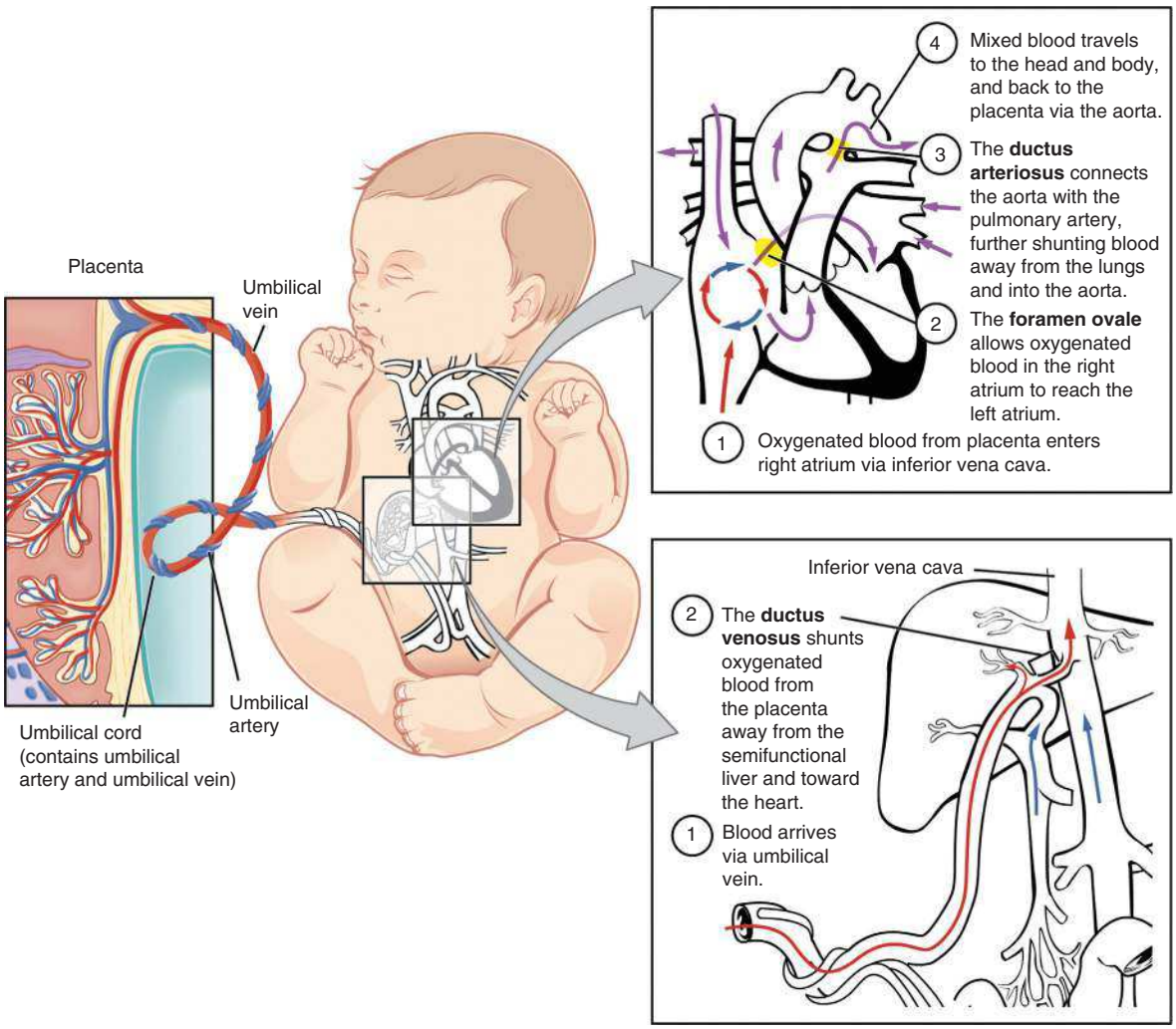

Figure 1.1 The fetal circulatory system (from Rice University's OpenStax course in Anatomy & Physiology under CCC license 4.0 http://cnx.org/content/col11496/1.6/).

eating, breathing, thermogenesis, and growing [4,5]. Because the myocardium is immature at birth, with a reduced, chaotic arrangement of myofibrils, there is limited compliance at birth [5]. Although filling pressures can increase stroke volume to a small degree, functionally the neonatal heart is primarily dependent on an increase in heart rate to increase cardiac output. At birth the ECG reflects the right-sided dominance of the fetal heart with right axis deviation and R-wave dominance in lead V1 and S-wave dominance in lead V6. After the left ventricle grows and hypertrophies, the ECG assumes the adult configuration of left-sided dominance by about six months of age [5]. Mild congestive heart failure in young infants is often heralded by sweatiness, tachycardia, tachypnea, difficulties in feeding, and may be missed during a preoperative examination. In cases of moderate to severe congestive failure there will be signs of acidosis, hypothermia, and oliguria. Management consists of diagnosing the underlying physiology, fluid restriction, diuretics, and inotropic agents.

Normal heart rates at birth at rest vary between 104 and 156 (mean 130 $\pm$ 13 mmHg). The first day of life, the mean systolic blood pressure is 70 mmHg, which rapidly increases over the next three days to 77 mmHg [6]. Mean blood pressure rises by 15 percent over the first month of life [7].

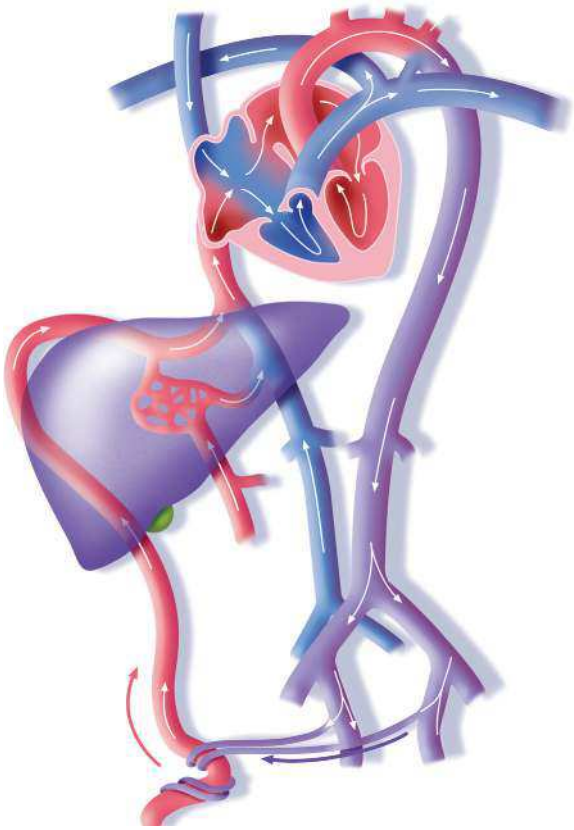

Figure 1.2 Fetal blood circulation © BSIP/UIG.

Congenital Cardiac Defects

The most common birth defect in neonates is congenital heart disease (CDH) with a prevalence of between 6 and 13 per 1000 live births [8]. It is 2–3 times more common in premature births compared with full-term births [9]. Critical CDH is defined as lesions requiring surgery or catheterizations within the first year of life, and constitute 15 percent of CDH at birth [10,11]. Approximately 30 percent of critical CDH is diagnosed after initial hospital discharge because the ductus arteriosus is still functioning, masking symptomatology [10,11]. The most common lesions involved include coarctation of the aorta, interrupted aortic arch, aortic stenosis, transposition of the great vessels, and hypoplastic left heart syndrome. Some nondependent duct lesions associated with mild cyanosis such as truncus arteriosus, Tetralogy of Fallot, and total anomalous venous return can be missed during the perinatal period. Missed critical CDH has a high mortality rate, with more than half of patients dying before surgical repair was done [12]. Presentation usually occurs when the ductus arteriosus begins to close and the infants manifest either shock or cyanosis. Careful physical examination of term newborns scheduled for surgery is important, but may not detect all infants with critical CDH. A cardiac murmur is present in many patients with CDH, but in approximately 44 percent of murmur detections in a healthy newborn there is no structural heart disease [13]. A careful physical examination along with a screening pulse oximetry test should be carried out for every preoperative patient. Attention should be paid to abnormal heart rates, precordial activity, S2 splitting, other heart sounds, murmurs, peripheral pulses, and cyanosis. In patients with cyanosis, a hyperoxia test can be done to help discern cardiac from noncardiac causes of decreased oxygen desaturation. In addition to the hyperoxia test, pulse oximeters can be placed both preductally (right hand) and postductally (left limb) to determine whether there is differential saturations. In medical centers with access to echography, a cardiac echo can rapidly determine the structural integrity of the heart.

Respiratory

The process of extrauterine breathing occurs with fluid being squeezed from the lung during vaginal delivery. The first breath is characterized by high inspiratory negative pressures to overcome the airway resistance of residual fluid in the airways, and pulmonary collapse. With alveolar expansion, the alveolar size increases and the wall tension of the alveolus decreases. Alveolar collapse between breaths is limited by a coating of surfactant that maintains surface tension within the alveolus. Type II pneumocytes are responsible for surfactant production and begin to differentiate at 24 weeks of gestation; however, surfactant synthesis for appropriate pulmonary function is not adequate until 34–36 weeks of gestation [5]. Once oxygenated blood reaches the pulmonary and central circulation, the pulmonary vascular resistance drops and facilitates the transition from fetal to adult circulation.

Neonatal lung mechanics put young infants at a disadvantage compared with older children and adults. The chest wall is exceedingly compliant and the lungs themselves relatively noncompliant; both of which can facilitate lung collapse. In fact, the closing capacity for neonates exceeds functional residual capacity.

Neonates compensate for this by producing auto positive end-expiratory pressure (auto-PEEP) by partial closure of the vocal cords and breathing through the high-resistance nasal passages. The horizontal nature of the ribs and the relatively flat diaphragm make the work of breathing inefficient and increases in minute ventilation are achieved by increasing respiratory rate. Also, infants have a relatively low functional residual capacity compared with adults. Any surgical pathology that decreases the compliance of the abdomen will necessarily affect the ability of the neonate to adequately ventilate. During the first day of life, ventilation flow mismatch accounts for up to 24 percent of cardiac output. This fraction decreases to 10 percent by one week of life [14]. In addition to the disadvantageous lung mechanics, neonates consume twice as much oxygen per kilogram as adults, thus their alveolar ventilation needs to be roughly double that of adults. Because of all these factors, modest decreases in either ventilation or fraction of inspired oxygen (FiO_2) will incline neonates to develop hypoxia.

The ventilatory centers of respiration in the brain at birth are not fully developed, and responses to hypoxia are immature in the term neonate. The peripheral chemoreceptors do not respond to hypoxia during the first 48 hours of life because they are effectively suppressed by the rise in PaO_2 following delivery and need to be reset [15]. This effect is exacerbated in infants resuscitated with 100 percent O_2 in the delivery room [16]. The feedback mechanisms by which the peripheral chemoreceptors send messages to the central centers of ventilation are also not mature, leading to unstable respiratory control mechanisms, especially in sick, unstable neonates.

Apnea and bradycardia is one of the nonspecific signs that a neonate is suffering from stress such as hypoxemia, sepsis, or hypothermia. This apnea can lead to an unstable metabolic state that further increases the risk of apnea and hypoxia. Apnea, which is generally defined as a cessation of breathing for longer than 15 seconds, can also result from airway obstruction, especially in those neonates with congenital abnormalities of the head and neck region or neonates that have been sedated with anesthetic drugs [17]. It is very common for term infants after a general anesthetic to exhibit periodic breathing, which is a breathing pattern in which the tidal volumes become shallower and shallower to the point of brief cessation, and then become deeper again. This pattern is repeated and generally does not lead to oxygen desaturations. Some studies – but not all – have shown an association between anemia and an increased risk of postoperative apnea [18].

Hematologic

At birth, 50–95 percent of the hemoglobin in an infant is fetal hemoglobin, which has an increased attraction for oxygen compared to adult hemoglobin. Fetal hemoglobin is made up of two alpha chains and two gamma chains, and is gradually replaced by hemoglobin A, which is made up of two alpha chains and two beta chains, by the time the infant is six months old. The fetus lives in a relatively hypoxic zone compared with the maternal environment and compensates for this with a much higher hemoglobin concentration of 19.3 g dl^{-1}. Within one week of birth in term infants, hemoglobin levels begin to drop and reach a nadir of about 9–11 g dl^{-1} at about 8–12 weeks of life [19]. Anemia can occur at birth as a result of blood loss before, after, or during delivery. Feto-maternal or twin–twin transfusion, placental abruption, or delayed cord clamping can cause increased blood loss. Decreased erythrocyte production can occur as a result of iron deficiency, or chronic infection. Decreased red blood cell destruction can be caused by Rh and autoimmune hemolytic disease, enzyme abnormalities such as G6 PD, membranopathies such as spherocytosis and elliptocytosis, and hemoglobinopathies such as sickle cell disease, thalassemia, and hemoglobin C disease.

Term infants can also be born with polycythemia, which can lead to a hyperviscous state and complications when the hematocrit is greater than 65 percent [20]. Maternal uterine insufficiency can lead to placental hypoxic state in which the fetus responds with increased red cell production. Postnatally polycythemia can cause decreased blood flow to vital organs including the brain, heart, and lungs, increased bilirubin production, and is associated with hypoglycemia. Treatment is a partial exchange transfusion.

The coagulation profile of neonates also differs from adults. Many of the proteins needed for coagulation are diminished in newborns, including factors II, VII, IX, X, XI, XII; others that promote fibrinolysis are increased, such as thrombomodulin, tPA, and plasminogen activator inhibitor-1 [21,22]. These probleeding tendencies are balanced by an alteration in some procoagulant proteins such as an increase in Von Willibrand factor and a decrease in antithrombin,

heparin cofactor II, alpha-2-macroglobulin, protein C, protein S, and plasminogen [22]. The end result is that neonates normally have a prolongation of their prothrombin time (PT), and activated partial thromboplastin time (aPTT), but a shortened bleeding time [21].

Newborns can be adversely affected by low vitamin K levels. Bleeding can occur because of a decrease of the vitamin K-dependent coagulation factors (II, VII, IX, X). Treatment includes prophylactic vitamin K intramuscular injections and fresh frozen plasma transfusions in infants with symptomatic bleeding.

Early thrombocytopenia in the newborn is usually related to maternal–placental factors, and late thrombocytopenia is usually caused by excessive platelet consumption, such as seen in necrotizing enterocolitis and sepsis [23]. Thrombocytopenia is a risk factor for intraventricular hemorrhage even in term infants, so many centers administer platelet transfusions to infants whose levels are below 50 000.

Thermoregulation

Regulation of body temperature depends on a balance between heat loss and heat generated. Although thermogenesis is suppressed in utero, heat production is actually greater in the fetus than the mother so the heat gradient flows from the fetus to the mother. Humans are a precocial species in regards to thermogenesis, with responses capable of generating heat within minutes of birth. Stimulation of the preoptic chiasma/anterior hypothalamic nuclei from peripheral cutaneous receptors activate non-shivering thermogenesis by sympathetic norepinephrine-secreting nerve fibers that innervate brown adipose tissue and shivering thermogenesis through the posterior hypothalamic nucleus [24].

Hepatic

During fetal development, the umbilical vein brings blood to the liver. Between 20 to 30 percent of this blood bypasses the liver and is carried directly to the inferior vena cava by way of the ductus venosus [25]. The remaining umbilical vein enters the liver, where some of it joins the portal vein. The ductus venosus typically closes by the first week of life and is then known as the ligamentum venosum.

Liver function is not fully mature until about two years postnatally. Initially, its primary role is to regulate glucose and fatty acid metabolism to maintain a supply of energy for neonates that may not be getting adequate enteral nutrition in the first days of life. It is also responsible for the production of clotting factors and serum proteins, bile synthesis, and the biotransformation of medications and other xenobiotics, as well as the endogenous metabolic byproducts.

Maturation of the many liver functions occurs at differential rates. Albumin synthesis is at adult levels at birth in term infants. The coagulation factors (all are synthesized in the liver except for factor VIII) are initially low at birth but reach adult levels by 2–3 days of life. The expression of the hepatic enzyme uridine diphosphate glucuronyl transferase is poor in the fetus, but by age 2–3 weeks postnatally it reaches adult levels. This enzyme is needed to conjugate bilirubin in order to facilitate biliary excretion into the enteric system. Some of this conjugated bilirubin is then unconjugated by intestinal B glucuronidase and then reabsorbed into the body by way of the enterohepatic circulation. It is very common for term infants to have neonatal jaundice in the first few days to weeks of life because of increased erythrocyte breakdown, deficiencies of their ability to conjugate free bilirubin, and decreased amounts of enteric organisms available to break down unconjugated bilirubin for fecal excretion [26]. Clearance of medications depends on either a drug metabolism pathway or a hepatic transport mechanism. Metabolic pathways are usually divided into phase 1 reactions that involve oxidation, reduction, hydrolysis, cyclization, and decyclization reactions, and phase 2 reactions that involve the addition (conjugation) of polar groups to phase 1 metabolites [25]. Neonates are unable to metabolize medications as rapidly as adults because the cytochrome p450 system (which oxidizes medications) does not reach adult levels until one year of age [27]. For phase 2 metabolism, infants preferentially must use sulfation rather than glucuronidation for conjugation reactions [28]. Table 1.1 summarizes the maturation of liver functions.

Renal

The kidney matures over the first two years of life. Nephrogenesis is completed by 36 weeks postconception but the nephrons are immature at birth. During fetal development the primary role of the kidney is to maintain amniotic fluid levels and renal blood flow is a very small percentage of the fetal cardiac output. For the first week of life, renal blood flow is only 10 percent

Table 1.1 Maturation of liver functions

	Oxidative enzyme activity	Glucuronide conjugation	Sulfate conjugation	Effect on drug metabolism
Premature neonates	Decreased oxidative enzyme activity (20–70 percent of adult values for cytochrome p450 activity)	Decreased glucuronide conjugation	Slightly decreased sulfate conjugation	Decreased
Neonates	Same as premature infants	Same as premature infants	Slightly decreased from adults	Decreased
Infants	Cytochrome p450 reaches adult activity by 6–12 months of age	Reaches adult levels by 24 months of age	Reaches adult levels in early infancy	Decreased

of cardiac output and does not reach the adult level of 25 percent until 24 months of life [29]. The glomerular filtration rate (GFR) is also diminished for the first two years of life. At birth it is about 40 ml kg^{-1} 1.73 m^{-2} and reaches 66 ml kg^{-1} 1.73 m^{-2} at two weeks of age, which is about one-half of the normal adult GFR [30]. The nephrons for the first few days of life are very immature and allow for some resorption of creatinine, which makes creatinine clearance a poor estimate of GFR during this period. These leaking nephrons rapidly mature and then creatinine levels drop.

One of the main functions of the kidney is to maintain fluid and electrolyte balance. At birth the extracellular volume is approximately 40 percent by body weight; this decreases to about 30 percent at six months of age and 20 percent by one year of age. Term infants generally do not have difficulty maintaining sodium balance, but excessive administration of sodium can overwhelm their kidneys, leading to peripheral edema. Likewise, the term kidney is able to maintain potassium, calcium, and phosphorus balance. Acid–base status is accomplished through ventilation, buffering capacity of serum proteins, bicarbonate-carbonic acids, hemoglobin–oxyhemoglobin and phosphorus, and the renal system. These mechanisms are all mature enough within three days of birth to handle nonrespiratory-induced acid loads.

The kidney also produces renin, which triggers the formation of angiotensin, which is converted to angiotensin II by angiotensin-converting enzyme. This enzyme increases the peripheral vascular resistance and cardiac contractility, leading to an increase in systemic blood pressure. The excretion of renin increases after birth and is higher in infants than older children. The renin angiotensin system, other humoral agents, and an increase in sympathetic activity at birth are responsible for the increase in blood pressure seen over the first weeks of life.

Neurologic

The neonatal and infancy period represents a time of dramatic brain growth, with the brain size as a neonate being 36 percent of the size of an adult brain and growing to 70 percent of its adult size by one year of age and 80 percent by two years of age [31]. During late gestation, brain development includes gray and white matter myelination, synaptogenesis, pruning, and synaptic modification. These processes continue into early infancy. Although all the cortical layers of cells are present at term and the primary cortical areas such as motor, somatosensory, visual, and auditory cortices are morphologically identifiable, the association cortices are less delineated. There is pronounced gray matter growth in the parietal and occipital areas in the first month of life. The newborn brain still exhibits a small degree of cortical neurogenesis and neuronal migration, but the dramatic brain growth is mainly due to the growth of glia and subsequent myelination during infancy. Abnormal brain growth in infancy is often a harbinger of poor neurocognitive outcomes. Microcephaly can be a result of malnutrition, and macrocephaly has been associated with autism.

MRI and autopsy studies of infants in the first year of life reveal a robust expansion of gray matter by way of elaboration of dendrites, spines, and synapses. Conversely, this is also a time of increased apoptosis or pruning. The pruning process time course begins with the primary cortices followed by the association cortices, and lastly in late childhood by pruning in the frontal lobes.

Along with synaptic pruning, there is remodeling of existing synapses and fine-tuning of neural circuits.

Synaptic remodeling is dependent on the strengthening of certain synaptic pathways and weakening of others. Some of these are time-dependent during infantile maturation, such as the development of binocular vision. Lack of input from an eye with a congenital cataract will lead to potentiation of synapses from the functioning retina and inhibition of synapses from the poorly stimulated retina. This in combination with pruning can lead to permanent visual impairment in infants who get delayed treatment for congenital cataracts.

There is a dramatic increase in the volume of glial cells postnatally, which leads to an increase in myelination during the first year of life. Myelination proceeds in a differential pattern starting with the sensory pathways, then motor and finally association pathways. It also proceeds subcortically before cortically in any given neural pathway. At birth in full-term infants, there are functional networks that include the visual, sensorimotor, and auditory processing networks.

The effects of harmful toxins, illness, and environmental deprivation may be greater in very young infants whose brains are growing rapidly in a time-dependent fashion. The long-term effects of general anesthetics on the neonatal brain have not been adequately characterized yet.

Dermatologic

The term newborn has a dermis that is 40–60 percent the depth of adult dermis, and a larger surface area to body weight ratio than adults [32]. This means that the infant is more likely to lose heat and body fluids as well as absorb any materials placed on the skin compared to an adult. The pH of adult skin is acidotic at 4.7, which is protective by decreasing the colonization of pathogenic bacteria. At term birth, the pH is 6.0 but decreases to less than 5.0 by four days of age. The skin colonization of neonates resembles adult flora after the first few weeks of life. There are differences between the skin biome of infants delivered vaginally compared with caesarian section, with 60–82 percent of neonatal methicillin-resistant staphylococcus infections occurring in surgically delivered babies [33]. The vernix caseosa is a sebaceous material made from sebum, desquamated skin, water, and lanugo that is present in term infants, which enhances the skin barrier to infection, heat, and fluid loss.

The best type of disinfective skin preparation for surgery has not been determined. Many studies have shown that chlorhexidine in *term* infants can be safely used perioperatively and decreases surgical site infections [34–36]. There is evidence that chlorhexidine absorption does occur and increases after repeated exposures. Povidine iodine is an excellent bacteriocidal agent but causes thyroid suppression secondary to iodine absorption [37]. This effect is greater in premature infants but even in infants less than three months of age, increased levels of serum iodine have been found after skin exposure. Skin rashes and burns have been seen after surgical preparations in term infants exposed to isopropyl alcohol, chlorhexidine, and povidine iodine.

There are several very common rashes seen in term babies. Erythema toxicum neonatorum affects almost 50 percent of term newborns and is heralded by an erythematous macular papular rash with pustules. It usually occurs in the first week of life and lasts a few days. Milia are pinpoint pearly white bumps seen most often on the nose, mouth, or palate which are also seen in 50 percent of neonates and generally resolve by the first month of life. Neonates often get miliaria or heat rash from overbundling. It is caused by occlusion of the sweat ducts and features 1–3 mm vesicles or papules. Treatment is to limit humid or hot environments. Neonates are also susceptible to neonatal acne [38]. This is also self-limited and resolves as circulating maternal hormones diminish.

Endocrine

There are many endocrine changes that occur perinatally. Normally neonatal blood glucose levels drop in the first few hours of birth, sometimes to levels below 30 mg dl^{-1}. A compensatory stress response involving the secretion of epinephrine and cortisol increases the plasma glucose to levels above 40 mg dl^{-1}. There are no universally agreed guidelines as to the definition of hypoglycemia in term infants, but many neonatologists consider a plasma glucose of <40 mg dl^{-1} in the first three hours of life, <45 mg dl^{-1} in the first day of life, and <60 mg dl^{-1} after three days of life to be abnormal [39]. Infants who are born of diabetic mothers, large for gestational age, or have suffered severe perinatal stress or asphyxia may have transient hyperinsulinemia. Glucose requirements in excess of 8 mg kg^{-1} min^{-1} in order to maintain normoglycemia suggests a hyperinsulinemic state. Because insulin inhibits ketone body formation, decreases glycogenolysis and gluconeogenesis, and increases peripheral

glucose uptake by cells, the brain is very vulnerable to damage such as permanent injury and seizures during hyperinsulinemia.

Thyroid homeostasis is necessary for brain development and growth, cardiac function, and energy balance. Prior to birth, the neonate is primarily dependent on maternal T3 and T4, but postnatally there is a dramatic increase (up to a 50-fold increase) in thyroid stimulating hormone (TSH) over the first 24 hours. It is important to recognize that a TSH in the first day of life in the 60–80 mU/L range is not indicative of thyroid disease [40]. One of the most common causes of abnormally low thyroid hormone levels in term infants is nonthyroidal critical illnesses, but there is no evidence that treating low levels benefits these patients [41,42]. Other causes include excessive iodine intake such as may be seen in iodinated contrast dyes or surgical preparations, and inadequate iodine intake. Congenital hypothyroidism is rare and is usually tested for at birth in the United States. Transient hyperthyroidism occasionally occurs in infants exposed to maternal hyperthyroidism.

At birth the adrenal system is mature, with adrenocorticotropic hormone (ACTH) stimulating the adrenal gland to secrete cortisol. Primary adrenal insufficiency is most often seen in infants that lack the enzyme 21 hydroxylase, which is necessary to synthesize corticosteroids and aldosterone. The symptoms include life-threatening salt wasting, hypotension, and poor growth. Affected infants also have very high levels of 17 hydroxyprogesterone and other adrenal androgens, leading to viralized infants. Female infants will have abnormal external genitalia but male infants may appear normal leading to a delayed diagnosis. Secondary adrenal insufficiency is common in extremely stressed term infants or in infants that have been treated with exogenous steroids. The mortality for infants with known adrenal insufficiency in the setting of sepsis is as high as 86 percent [43]. Treatment with glucocorticoids in infants with known adrenal insufficiency will improve blood pressure. Aldosterone is stimulated by the renin angiotensin system and thus is unaffected by low ACTH levels.

Serum calcium levels are regulated by parathyroid hormone release and special calcium-sensing receptors within the parathyroid glands. Parathyroid hormone (PTH) stimulates bone resorption to mobilize skeletal calcium and conversion of inactive vitamin D to active vitamin D to increase dietary absorption of calcium and phosphate. Transient hypoparathyroidism is seen in infants who are hypomagnesemic and infants born of mothers with diabetes mellitus and hyperparathyroidism [39]. Abnormal thyroid gland development is seen in DiGeorge's syndrome, which can lead to hypocalcemia. Hypercalcemia of the neonate is most commonly iatrogenically caused, but is also seen in patients with Williams syndrome. In this condition, the hypercalcemia usually resolves by one year of age. Infants with Williams syndrome can present with pulmonary artery stenosis and supravalvular stenosis with associated coronary artery abnormalities. Sudden death from this syndrome is rare during infancy but has occurred.

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