General Anatomical and Physiological Considerations in the Newborn and Neonates

10

Usha Saha

10.1 Introduction

Neonatal period is a very high-risk period, especially the first 24 h of life, because of the ongoing transitional changes. The anesthesiologist faces several challenges when faced with delivery of anesthesia for various surgical procedures in newborns, and term and premature neonates. The dilemmas are several, all culminating into the two goals of anesthesia: adequacy of anesthesia appropriate for the surgery and its duration, and adequacy of recovery at the end. Though they may appear simple and easy to attain, in reality, anesthesiologist is often confronted with either too less or too much of ANESTHESIA, and delayed recovery, with need for ventilatory support, prolonged duration of hospital stay, increased cost of perioperative care, and not always an optimum outcome. Their anatomical, physiological, biochemical, and organ functions are different from those in an adult or child, knowledge of which is essential for the anesthesiologist to fulfill the goals and have a good outcome [1–9].

Various parameters and methods have been used to assess this risk, gestational age (GA) at birth, and birthweight (BW) being commonly used. Worldwide, more than 1 million neonates need surgery, and nearly 6% of total live births are premature. At birth, there are incomplete organogenesis, immature physiology, and poor organ functioning. They may require surgery on day of birth itself or during the neonatal period. This number is on the rise with improvement in perinatal and neonatal care.

They are extremely prone to deleterious effects of stress and pain itself, and anesthetic and analgesic drugs further add on to these adverse effects, with very high postoperative morbidity, poor survival, apnea, proneness to RDS, IVH, ROP, hypothermia, hypoglycemia, infections, seizures, PFC, reopening of shunts, and death. Because of this, many elective operations are deferred during the neonatal

U. Saha (✉)
Department of Anesthesia, Critical Care, Pain and Palliative Care, Lady Hardinge Medical College, Smt Sucheta Kriplani and Kalawati Saran Childrens Hospitals, New Delhi, India

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period. Anesthesiologists can also apply these criteria to assess perioperative risk of anesthesia and surgery and take special precautions during administration of anesthesia. Perioperative morbidity and mortality are inversely proportional to GA and BW. The goal of anesthetic management is early recovery after anesthesia and surgery and some guidelines have been proposed for neonates undergoing intestinal surgeries [10, 11].

This chapter will discuss all these aspects and their implications in the anesthetic management.

Before advancing into the details of this topic, several queries that arise in the mind are:

1. How are newborns and neonates different? And its significance to the anesthetist.
2. What is anesthetically safe period?
3. Fetal circulation, transitional changes or adaptations at birth, and consequences of abnormal adaptation,
4. Anatomy and physiology of a newborn, neonate, and premature—growth and maturation of the body organs.
5. What are the common medical diseases likely to be encountered, and their impact on anesthesia delivery and outcome?
6. What are the conditions likely to require surgical intervention in the neonatal period, and their impact on body anatomy, physiology, biochemical and metabolic functions, and anesthetic management?
7. Perianesthetic or perioperative concerns.

10.2 Categorization (Table 10.1)

In the fetus, organogenesis occurs in the first trimester, growth and development in the second, and anatomical and functional maturation, including surfactant production in the 3rd. Mortality is inversely proportional to GA at birth. Accordingly, newborns are categorized into two: "**TERM" and "PRETERM".**

Table 10.1 Categorization and terms used for neonates

		GA (week)/age	Birth Weight (grams)
A. Categorization according to GA			
1.	**Term**	≥37 weeks (37–42) weeks	
	Early term	37 weeks 0 days to 38 weeks 6 days	
	Full term	39 weeks 0 days to 40 weeks 6 days	
	Late term	41 week 0 day to 41 week 6 day	
2.	**Newborn**	**C**	
	Neonate	0 h–28 day age	
	Infant	29 day–1 year age	
3.	**Perinatal period**	28-week GA (1 kg)—seventh day of life	
	Extended perinatal period	20-week GA (>0.5 kg) - seventh day of life	
	Prematurity	<37 weeks GA	And <2500

Table 10.1 continued

		GA (week)/age	Birth Weight (grams)
4.	**Micropremies**	ELBW	And 400–1000
	Dysmaturity (postmaturity syndrome)	>42-week GA	And cessation of weight gain (placental insufficiency)
	Post-term	>42-week GA	And no signs of dysmaturity
	Fetal macrosomia	>4000 g (8 lb 13 oz)	
	Ex premature	Premature + >38 weeks PCA	
B. Categorization according to BW			
1.	**Low birthweight (LBW)**		<2500
2.	**Very low birthweight (VLBW)**		<1500
3.	**Extremely low birthweight (ELBW)**		<1000 (2 lb 3 oz)
4.	**AGA**	37–42	And >2500
5.	**SGA**	>37	And <2500
6.	**LGA**	Any GA	>Appropriate weight

Note—(a) Neonate is from birth up to 28 days past due date. If born at 40 weeks, he is a neonate for 4 weeks, and if born at 30 weeks, it will be a neonate for 14 weeks. (10 weeks to correct to term age + subsequent 28 days). (b) Dysmaturity or postmaturity syndrome refers to the fetus whose weight gain after the due date has stopped, usually due to placental insufficiency leading to malnourishment, Marasmic appearance, desquamation of skin, loss of subcutaneous tissues, and yellow meconium staining of skin, nails, and umbilical cord. (c) Post-term includes those born after 42 weeks but with no signs of dysmaturity. They have dry, loose, peeling skin, overgrown nails, abundant scalp hair, visible palm and sole creases, minimal fat deposits, and green or brown staining of skin from passage of stools into amniotic fluid. (d) Fetal macrosomia describes a newborn who is much larger than average, with BW more than 4000 gm (8 lb 13 oz). Worldwide, incidence of fetal macrosomia is about 9% of all births

10.2.1 As Per Gestational Age (GA)

1. **TERM** babies are born at ≥37 weeks GA (37–42 weeks) and BW >2.5 kg. This is further subcategorized into **early term** (37 weeks 0 days to 38 weeks 6 days), **full term (**39 weeks 0 days to 40 weeks 6 days), and **late term (**41 weeks 0 days to 41 weeks 6 days).
2. **PREMATURE** babies are those born at <37 weeks GA and <2.5 kg BW. They are further subcategorized into

Borderline premature (near term)	36–37 GA	0% mortality
Moderately premature	31–36 GA	50% mortality
Severely premature	28–24 GA	>70% mortality
Extreme prematurity	24–28 GA	> >>>% mortality

Surgical and medical diseases and anesthesia further increase mortality.

10.2.2 As Per Birthweight (BW)

BW is an important indicator of newborn's health and well-being, and several perinatal complications are associated with it. Incidence of perioperative complications is inversely proportional to BW.

1. **Normal BW** ranges between 2500 and 3500 g. These babies are born full term, pulmonary development and surfactant amounts are adequate, and organs are mature and take over their individual functions in the extrauterine life. They have less incidence of congenital abnormalities or severe form of surgical diseases. When these newborns present for surgery, they have the best perianesthetic outcome, with nil or minimal morbidity [12].
2. **Low BW (LBW)** newborns have BW <2500 g. (India <2000 g).
3. **Very low BW (VLBW**) newborns have BW <1500 g.
4. **Extremely low BW (ELBW)** newborns have BW of 1000 g (2 lbs 3 oz) or less. These are usually born prematurely (GA <28 weeks). Though fetus is viable, organs are not fully mature and are deficient in surfactant too.
5. **AGA** (appropriate for GA) includes newborns with BW appropriate for GA.
6. **SFD** (small for date)/**SGA** (small for GA)—newborns with BW less than expected for GA, and includes those born >37 weeks but BW <2500 g, and usually have IUGR.
7. **LFD** (large for date)/**LGA** (large for GA)—are newborns with BW more than expected for GA.
8. **IUGR** (intrauterine growth retardation) or **FGR** (fetal growth restriction) is often due to placental insufficiency, and viral infection (TORCH complex—toxoplasmosis, rubella, cytomegalovirus, herpes) (Fig. 10.1).

As per the reported data of 3,952,841 births in USA in 2012, approximately 8% were LBW (<2500 g) and 1.4% VLBW (<1500 g). The incidence of low BW and related problems is more in developing countries like India. With improvement in antenatal and perinatal care (maternal steroids, surfactant replacement, and advanced neonatal care), survival of LBW, VLBW, and ELBW newborns has improved remarkably. Currently, accepted minimal age of viability is 23 weeks, a decline

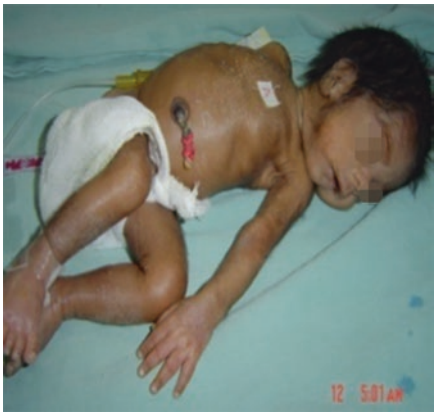

Fig. 10.1 LBW newborn (BW 1500 g)

from old figure of 28 weeks. Neonatal anesthesiologists are likely to face challenges when managing these babies presenting for surgery, especially during their neonatal period. ELBW survival has improved with the widespread use of exogenous surfactant agents, maternal steroids, and advancements in neonatal technologies. Current minimum age of viability is 23 weeks' gestation, with scattered reports of survivors at 21–22 weeks too.

10.2.3 The Ballard Maturational Assessment

The Ballard Maturational Assessment (**Ballard Score**) introduced in 1979 is a reliable tool for assessing fetal maturation and gestational age. A score is assigned to various physical and neurological criteria, and sum total is extrapolated to estimate the GA in the range of 26–44 weeks [13]. The New Ballard Score includes extremely preterm babies (20 weeks) [14].

10.2.4 APGAR Score

APGAR Score [15] was developed by an anesthesiologist Virginia Apgar in 1952 to assess the status of the newborn after birth. It gives an estimate of how well the newborn is adapting to extrauterine environment. It gives numerical scores (0–2) to 5 parameters (Appearance, Pulse, Grimace, Activity and Respiration APGAR), assessed at 1, 5, and 10 min. 1-min score reflects the status at delivery and is low in almost all newborns. 5- and 10-min score is an estimate of how well a newborn has adapted. Low score at 10 min is associated with poor survival or survival with severe disability. Maximum score is 10, but score of 7–10 is accepted normal at both 5 and 10 min, 3 as critically low, and 4–6 as fairly low. (Table 10.2) Normal values of vital parameters at birth are RR 60–80/min, HR 120–160/min, and Temp 36.3–37.2 °C

Factors that influence Apgar score include maternal conditions (drugs, infections, high-risk pregnancy), labor and delivery (complicated labor and delivery, trauma, resuscitative measures, operative delivery), and fetal factors (GA, BW, congenital anomalies, hypoxia, hypovolemia, and cardiopulmonary and neurologic dysfunction) (Table 10.3).

Table 10.2 Apgar score

Criteria	0	1	2
Appearance	Entire body pale or blue	Good color with bluish hands or feet	Good color all over
Pulse (HR)	Absent	<100	>100
Respiration (breathing)	Absent	Slow irregular	Good rate and effort with strong crying
Grimace (reflexes)	No response to stimulation	Facial grimace during stimulation	Pulls away, cries vigorously, or sneezes on stimulation
Activity (muscle tone)	Absent, limp, floppy loose muscles	Some muscle tone, some flexing of arms and legs	Active spontaneous motion, flexed arms and legs that resist extension

Table 10.3 Major problems in ELBW neonates

System	Pathology
Respiratory	Apnea, Resp failure, RDS, CLD (chronic lung disease)
CVS	PDA (patent ductus arteriosus)
CNS	IVH, PVL (periventricular leak), seizures
Renal	Electrolyte imbalance, acid-base disturbances, renal failure
Ophthalmologic	ROP, strabismus, myopia
GI & Nutritional	Feeding intolerance, NEC, inguinal hernia, cholestatic jaundice
Immunologic	Poor defense mechanism, infections (perinatal, nosocomial)

Table 10.4 Anesthesia Risk

GA at birth	Critical period—44-week postconception	Safe period—60-week postconception
28 (severe premature)	16 (4 months age)	32 (8 months age)
32 (mod premature)	12 (3 months age)	28 (7 months age)
36 (borderline, near term)	8 (2 months age)	24 (6 months age)
40 (full term)	4 (1 months age)	20 weeks (5 months age)
44 (post-term)	0 (0 months age)	16 weeks (4 months age)

10.2.5 Anesthesia Risk

Anesthetists can use 10-min score to estimate the risk to the neonate and take appropriate care during anesthetic management. Newborns with low score are at a greater risk of anesthesia and related complications because of their immaturity. (Table 10.4).

10.3 Anatomical and Physiological Considerations

All body systems each and every system is different. We will consider each system separately along with its anesthetic implications—respiratory system, airway and apnea, cardiovascular system, central nervous system, thermoregulation endocrinology, metabolic, hepatic and metabolic, renal, body H2O distribution, hemopoiesis and coagulation, NM transmission, pharmacokinetic, pain, feeding and intestine physiology, immune system, ophthalmic considerations, and skin physiology.

Box 10.1 General Features at Birth

(a) Head is large, nearly one-third of body length—Great heat loss. Molding of skull bones for delivery causes a prominent crown and neck flexion and airway obstruction.
(b) Copious secretions may be present for hours after delivery.
(c) Term newborns have brown fat stores as internal heat source; they do not have the ability to shiver.
(d) Respiration may be irregular and erratic, and heart rate is high 120–160 min.
(e) Mild jitteriness, uncoordinated, and acrocyanosis are normal.
(f) Reflexes present—Grasp, sucking, rooting, and startle reflex.

10.3.1 General Features at Birth

General features at birth are listed in Box 10.1.

10.3.2 Common Medical and Conditions

The medical and surgical derangements seen in the neonatal age are different from those in children and adults. (Boxes 10.2 and 10.3) They are only seen in this age and, if not treated or managed, can have adverse outcomes or long-term sequelae.

Not all of these conditions are necessarily life-threatening. Incidence of congenital anomalies is 3% of all live births, and its presence may convert a simple condition to that with higher perioperative risk:

(a) **Life threatening—**related to the airway, cardiac anomalies, facial anomalies, open lesions of the spinal cord, abdominal wall defects, and from birth trauma, while.
(b) **Non-life threatening** includes birth marks, extra fingers or toes, and club foot.

Box 10.2 List of Common Medical Conditions in the Neonatal Period

1. Prematurity
2. Problems of transition—PFC, PPHN, RDS
3. Resp system—Apneic spells, RDS, BPD, MAS, HMD, air lock (emphysema, pneumothorax, pneumomediastinum), pulmonary hemorrhage, lung cysts, pneumatoceles, congenital lobar emphysema, lung hypoplasia, vascular rings, TEF, micrognathia, glossoptosis.
4. Nonpulmonary causes of respiratory disease—ICH/IVH, CHD, hemolytic, and NM ds.
5. Anemia, polycythemia, hematological disorders, hemolytic ds of newborn
6. Inborn errors of metabolism
7. CVS—Congenital birth defects
8. CNS—ICH/IVH, seizures
9. Hepatic—Jaundice, hyperbilirubinemia, kernicterus
10. Metabolic—Hypoglycemia, hypocalcemia, hyponatremia
11. Immune system—Infections, sepsis
12. Eye—ROP, RLF
13. GI related—Feeding problems, diarrhea, acute abdomen, vomiting, dehydration
14. Congenital anomalies, genetic syndromes
15. Endocrine—Thyroid disorders, insulinoma (nesidioblastoma)
16. NM diseases, muscular dystrophy
17. Vertebral defects—Spina bifida

10.3.3 Common Surgical Conditions

Box 10.3 List of Common Surgical Conditions in the Neonatal Period

1. CDH, eventration of the diaphragm
2. Tef
3. Abdominal wall defects—Omphalocele/gastroschisis
4. Thoracic/pulmonary—Lobar emphysema/BPD, lung cyst, abscess, lobar/pulmonary agenesis, congenital pneumothorax
5. Airway related—Tracheal webs, narrowing, stenosis, tracheomalacia, laryngomalacia, choanal atresia
6. Congenital cardiac defects—PFO/VSD/PDA, TAPVD, TOF, ASVR (anomalous systemic venous drainage), persistent LSVC (left superior vena cava), cardiac failure
7. GIT—NEC/bowel perforation and peritonitis, PVID (patent vitello intestinal duct), obstruction, malrotation, intussusception, Hirschsprung's disease, IHPS (idiopathic hypertrophic pyloric stenosis), umbilical hernia, inguinal hernia. GI atresia (duodenal, jejunal, ileal), ARM (anorectal formation), imperforate anus, cloacal anomalies
8. Genitourinary—PUV, ectopia vesicae, Wilm's tumor, nephrectomy, congenital hydronephrosis, obstructive uropathy, exstrophy bladder, undescended/torsion testis, hypo-epispadias, hydrocele
9. Vertebral defects and neural tube defects—Meningomyelocele, meningocele, encephalocele
10. CNS—Congenital hydrocephalus, craniosynostosis, craniopharyngiomas
11. Cystic hygroma, teratomas—Cervical, sacrococcygeal
12. Hepatic—Biliary atresia,
13. Eye—RD (laser, cryosurgery), vitrectomy
14. Birth and neonatal care injuries [16],
15. Orthopedic—CTEV, hip dislocation, shoulder dislocation.

10.4 The Airway Anatomy and Respiratory Physiology in Newborns

Respiratory system in the newborn baby is still in a developing phase and respiratory mechanics are immature (Box 10.4). The central control and responses to hypoxemia and hypercarbia are also not fully functional. The alveoli are small, have little elastin, are stiff, and are poorly compliant. Vasomotor tone is not developed and pulmonary capillaries have high resistance [17–19]. Of the autonomic nervous system components, parasympathetic is most predominant.

Box 10.4 Respiratory System—Development

- 17–28 weeks GA—Alveolar formation
- 8–36 weeks GA—Pulmonary capillary formation
- 24 weeks GA—Surfactant production starts
- 36 weeks GA—Marked surge in synthesis of surfactant
- 20 million alveoli at birth and 300 million 8 months age
- Full maturation only by 36 weeks GA.

10.4.1 Airway Anatomy

Airway anatomy is different not only in dimensions, but also in its functionality. Clinical assessment is nearly impossible unless the anesthesiologist is familiar with the anatomy and physiology of the pulmonary system and airways. **Neonatal airway is described as a difficult airway.** All aspects of airway difficulty are present due to the unique anatomy of the head and trachea (Box 10.5, Fig. 10.2): mask holding, laryngoscopy, intubation, and ventilation.

The differences in anatomy are related to the **large head size** and prominent occipital bone. Laryngoscopy and intubation require the head in sniffing position. In older children and adults, a small pillow placed under the head extends the neck and provides correct position, but placing a small pillow under the occiput in a neonate will flex the head on the neck instead of extending it, with potential airway obstruction, difficult laryngoscopy and its view, and difficult intubation. Hence, it is preferable to place a small pad under the neck and shoulders, with a large ring under the head to accommodate the occiput (and stabilize the head) for induction, laryngoscopy, and intubation. **Improper mask size** and forceful grip on the jaw and surrounding soft tissue will also obstruct the upper airway. Hence, mask holding should be gentle, using a C or E technique. **Nares are narrow** and any nasal instrumentation must be avoided to prevent trauma to nasal mucosa and postoperative problems in breathing after tracheal extubation. **Larynx is high** (C3–4) and more **anteriorly placed**, cricoid cartilage (subglottic) is the narrowest part of the airway (debatable), and even small edema will have a greater narrowing effect, and **short tracheal length** puts them at risk of endobronchial intubation and accidental extubation even with minimal head manipulations. They are **obligate nose breathers** and relatively large tongue and more complaint pharyngeal tissue, makes them liable to obstruction during sleep and periods of relaxation (as at anesthetic induction).

Box 10.5 Neonatal Airway—Difficult Mask Holding, Laryngoscopy, Intubation, Ventilation

1. Large unstable head
2. Small jaw, short neck—No chin lift, avoid pressure over soft tissues of neck and jaw
3. Macroglossia—Use oropharyngeal airway to keep oropharyngeal airway patent
4. Obligate nasal breathers, small nares—Prone to obstruction
5. Narrow nares—No nasal instrumentation
6. Larynx—High C 2–3 and anterior—(external manipulation, BURP)
7. Epiglottis—Long floppy, omega shaped, 45° to the tongue
8. Straight blade laryngoscope preferred and epiglottis lifted at laryngoscopy
9. Cricoid—Narrowest, conical/cylindrical—Selection of ET tube
10. Face mask or supraglottic device or definitive airway
11. Angle of tracheal bifurcation (45°)—Equal chance of right or left endobronchial intubation

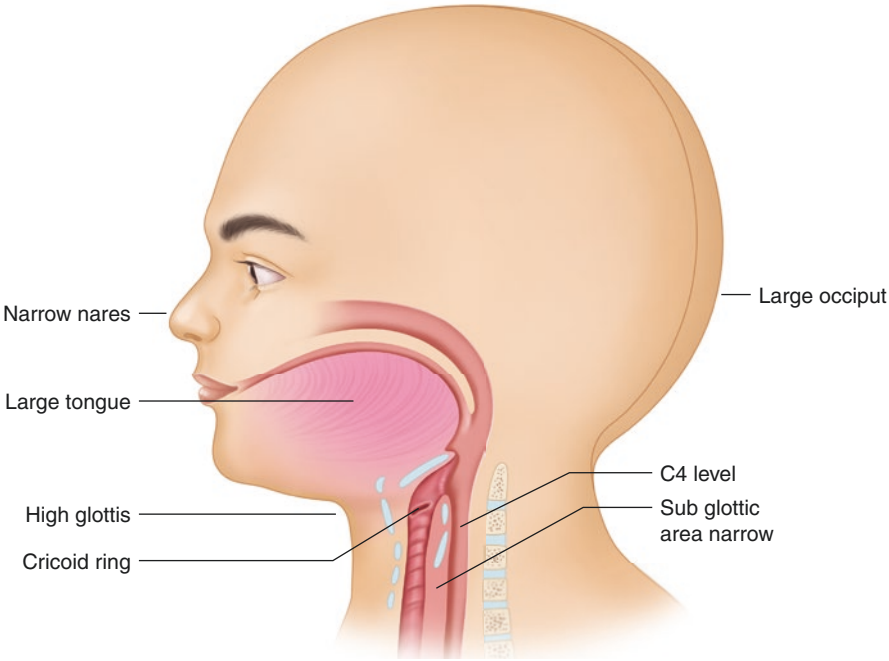

Fig. 10.2 Airway anatomy—unique features

10.4.2 Respiratory Physiology

Unique features of the neonatal **respiratory physiology** arise from the fact that their metabolic demand of O_2 is high to cater to the ongoing growth and maturation after birth. Important aspects of significance to the anesthesiologist are as follows:

(i) **Airways are narrower**, are **poorly supported by the surrounding structures** and can easily give in and collapse, causing further narrowing, and obstruction to flow of air or O_2, and **increased work of breathing and O_2 demand**.

(ii) **Chest wall is highly compliant** and ribs provide little or no support to the lungs. The negative intra thoracic pressure is poorly maintained, which essential for generation of inspiration, hence decreased lung volumes and capacities.

(iii) The **lung volumes and capacities** are small but appropriate for weight and age. (Note—Vt in a 3 kg baby is just 15–20 mL) (Table 10.5) **FRC** is low and CV and CC are high. They have poor O_2 reserves.

(iv) Basal **respiratory rate** is high (60–70/min at birth) which decreases over the period of 4 weeks to 30–50/min. This increases the demand of O_2 by the respiratory muscles. Work of breathing is three times and O_2 consumption is twice that in adults (5–6 mL/kg/min vs 2–3 mL/kg/min).

(v) The **respiratory muscles** are immature. The fatigue-resistant type I muscle fibers are deficient in neonates. Adult fiber configuration is reached only by 2 years of age [20].

(vi) The **ribs are more horizontally** placed. **Chest wall** lacks the **bucket handle movement** that allows increase in Tv by increasing the transverse diameter of the chest in adults.

(vii) **Diaphragm**, the chief muscle of respiration, is deficient in the proportion of high oxidative contractile fibers type 1. Adults have 55%, term newborns have 25%, and premature (at 30 weeks gestation) have 10%. Diaphragm easily tires, **with high risk of apnea.**

(viii) **Early fatigue and tachypnea cause further reduction in Vt and increase in O_2 demand.**

(ix) The **respiratory pattern** is also different. There is no pause between inspiration and expiration; i.e., no expiratory or inspiratory pauses and the respiratory movements are **see-saw like**. During the **inspiratory pause,** air gets redistributed from the fast to the slow alveoli, allowing their expansion through alveolar recruitment. Extruded alveolar fluid drains via the venous and lymphatic systems, thereby further improving gas exchange. During the **expiratory pause**, intrathoracic pressure is low, which allows better venous return to the heart, improved cardiac filling, and improved CO and better peripheral perfusion. **With the see-saw like pattern, the advantage of the inspiratory and expiratory pauses is LOST.**

(x) There are **two types of alveoli—fast and slow**. Fast alveoli have low resistance and are very compliant and fill and expand quickly, and slow alveoli have high resistance and slow compliance and fill slowly and are unable to expand fully. In the newborns, especially the premature, **alveoli are slow** (stiff or collapsed and have residual fluid).

(xi) During periods of complete relaxation, as at induction and during anesthesia, use of muscle relaxants, FRC decreases further (to 10–15% of TLC), nearing CC, leading to Atelectasis, V: Q mismatch, and Hb desaturation.

(xii) Increase in O_2 supply can only be met with by increasing the RR (as they cannot increase their Vt). Minute ventilation is high (>200 mL/kg/min) compared to 100 mL/kg/min in adults.

(xiii) **Poor cough reflex**

(xiv) **Response to hypoxia** is different, and an initial brief increase in ventilation is followed by sustained depression. Immature central respiratory center is prone to greater depression after anesthetic drugs.

(xv) **Oxygen dissociation curve** in neonates is placed more leftward, an indication of high affinity of Hb F to O_2 and reduced release at tissue level. Both presence of Hb F and poor medullary response make neonates prone to hypoxia and apnea.

(xvi) **CO2 response curve** is shifted to left.

(xvii) **Pulmonary circulation** is high resistance system in neonates. Asphyxia, acidosis, and hypercarbia cause pulmonary vasoconstriction and increased pulmonary arterial pressure. Splanchnic, renal, skeletal muscular, and cutaneous arterioles are vasoconstricted allowing redistribution of flow to the vital organs.

(xviii) **Prolonged asphyxia** causes further myocardial depression and decrease in cardiac output and poor peripheral perfusion.

All these factors contribute to early respiratory fatigue, O_2 deficiency, CO_2 retention, respiratory failure, and APNEA in neonates.

Table 10.5 Pulmonary Parameters

Pulmonary Indices	Term	Premature	Adult
O2 consumption mL/kg/min	6.4	7	3.5
Alveolar ventilation mL/kg/min	130	120–130	60
CO2 production mL/kg/min	6	5–6	3
VT mL/kg	6	4–5	6
RR/min	35	50–60	12–16
VC mL/kg	35	<35	70
FRC mL/kg	30	<30	35
Closing capacity mL/kg	35	>35	23
Tracheal length cm	5.5	Less	12
PaO_2 on air mmHg	65–85	60–70	95–97
$PaCO_2$ mm hg	30–36	30–36	36–44
pH	7.34–7.4	7.3–7.35	7.36–7.44
SpO_2%	85–95	80–90	95–100

Table 10.6 ETT size and length

Body Weight kg	ID mm	Length cm (at angle of mouth)
1	2–2.5	7
1.5	2.5–3	7.5
2	2.5–3	8
3 preterm	3	8–9
3 term	3.5	10

Guide—1, 2, 3, 4 kg = 7, 8, 9, 10 cm length

10.4.3 Airway Management

With the airway anatomy and respiratory physiology in the newborn and neonate, it is preferred to secure and maintain the airway by endotracheal intubation, and assisted or controlled respiration, during surgery under anesthesia, size appropriate (Table 10.6). Uncuffed ETT is preferred; however, special microcuff ETT are now available for use in neonates.

10.5 Respiratory Abnormalities at Birth

Most of transitional changes occur within a few hours of birth. They are functional changes and permanent changes occur earliest by 4 weeks. Several factors can interfere with normal transition at birth and cause pulmonary-related problems [21], chiefly;

1. Apnea of the newborn.
2. TTN—transient tachypnea of the newborn.
3. Respiratory distress syndrome (RDS)—BPD, MAS, HMD.

10.5.1 Apnea of the Newborn

Apnea is one of the very common causes of neonatal death. The compensatory responses to hypoxemia and hypercarbia are weak in the newborn because of immature medullary respiratory centers, contributing to the high mortality following apnea in these babies [22–24].

Periodic breathing, short episodes (about 3 s) of shallow breathing or apnea, followed by periods of regular breathing lasting 10–15 s, is normal in neonates. Irregular breathing is of common occurrence in late premature or near-term newborns. The incidence of apnea varies from 25 to 85%, more in LBW and premature babies.

Apnea in neonate is defined as cessation of breathing for 20 s or more, or cessation of breathing of less than 20 s accompanied with bradycardia (decrease of 30 beats/min or of more than 20% from baseline), or cessation of breathing (of any duration) accompanied with cyanosis, pallor, or hypotonia. Heart rate may remain normal. Apnea may be primary or secondary.

Primary Apnea—Failure of newborn to breathe at birth (no alveolar expansion, alveoli remain fluid filled), or initial breathing followed by apnea, leading to hypoxia. Normal response to hypoxia is respiratory stimulation. If the newborn fails to respond, hypoxia will lead to further inhibition of breathing (apnea) and bradycardia. This must be managed as soon as it is identified, by tactile stimulation and high FiO_2 (40–50%) via face mask. If apnea persists, management is as for secondary apnea.

Secondary Apnea—Unresolved primary apnea or neonatal apnea, and there is further fall in heart rate, blood pressure, and PaO_2 (bradycardia, hypotension, hypoxemia). Management includes -

(a) High FiO_2 (50–60%),
(b) Check for any obstruction to respiration—use oropharyngeal/nasopharyngeal airway,
(c) Respiratory support—in a baby who has spontaneous efforts, CPAP should be tried through oropharyngeal or nasopharyngeal route. Tracheal intubation and mechanical ventilatory support are reserved for newborns with no respiratory effort or who do not respond to initial measures.
(d) Provide care in a thermoneutral environment.

Once stabilized, additional avoidable causes of apnea must be looked for and managed.

The consequences of apnea are grave because of hypotension, bradycardia, hypoxemia followed by death, and needs urgent intervention. Early O_2 therapy and IPPV are advised to prevent hypoxic ischemic injury to the brain.

10.5.1.1 Risk Factors for Apnea in Neonates

- **Maternal related—**elderly age >35 years, diabetes mellitus, hypertension, cardiac disease, respiratory disease, severe anemia, infections, alcohol, and/or drug abuse,
- **Pregnancy related—**APH, toxemia of pregnancy, multiple births,
- **Delivery related—**Abnormal presentations, prolonged or difficult labor, cord prolapse, fetal distress, narcotic or MgSO4 administration, malpresentation, instrumental/operative delivery.
- **Fetal factors**—prematurity, congenital malformations, birth trauma, fetal distress.

Diagnosis is made by exclusion of treatable causes.

Etiologically, apnea is of three types—central—due to immature medullary centers, **obstructive**—nasal, pharyngeal, laryngeal pathology, and **mixed—**is the most common, combination of both central and obstructive types.

Monitoring includes vitals (HR, RR), SpO_2, temperature, and ECG.

Management depends on the cause, frequency, and severity of apneic episodes. All premature babies should be monitored for apnea in the NICU settings in O_2 tent in a thermal controlled environment.

1. Nonpharmacological measures include elimination of treatable **causes of apnea** (Table 10.7), monitoring, tactile stimulation, repositioning to lateral or semi lateral position, and clearing of nasal and oral cavities.

Table 10.7 Factors that affect respiration

Stimulate respiration/tachypnea	Depress respiration/apnea
Mild acidosis	Severe acidosis
Hypercarbia	CNS damage
Hypoxia	Hypoxia
Sensations—Pain, cold, touch, noise	Drugs—Magnesium, alcohol, opioid, barbiturates

2. Maintenance of Hb saturation by O_2 therapy, high FiO_2 (50–60%), bag mask ventilation, noninvasive CPAP, or tracheal intubation and assisted ventilation, and extracorporeal membrane oxygenator (ECMO).
3. Drug therapy—Three drugs used with varying success rates, either alone or in combination, are caffeine, theophylline, and doxapram.
   (a) **Caffeine citrate** is a central medullary stimulant and improves the response to hypoxia and hypercarbia by diaphragmatic contractility, and increase in minute ventilation and metabolic rate. It can be given IV in a dose of 5–10 mg/kg, and if administered preoperatively, it can reduce the incidence of postoperative apnea in risky neonates.
   (b) **Theophylline** is administered IV in a dose of 5 mg/kg, followed by a maintenance dose of 2 mg/kg two to three times a day. Risks associated are tachycardia, arrhythmias, and seizures.
   (c) **Doxapram** can be administered IV in a dose of 1–2 mg/kg. Its side effects are hypertension and seizures (because of additive benzyl alcohol).

10.5.1.2 Neonatal Apnea and the Anesthesiologist

Postoperative apnea is of grave concern to the anesthesiologist, critical period being the first 12 h, but the risk persists up to 72 h, especially after general anesthesia. Hence, all neonates should be kept admitted in the hospital for observation for minimum of 24 h postoperatively. Risk factors for postoperative apnea include **patient factors** (prematurity (<35 weeks GA), anemia, H/o birth apnea, CNS/lung disease), and **iatrogenic factors** (hypoxia, hypercapnia, hypoglycemia, anemia, hypothermia, ICH, sepsis, heart failure, drugs).

10.5.1.3 Premature Neonates are at Extreme Risk of Perioperative Hypoxemia, Due to

- Greater central immaturity and lack of compensatory responses
- Weak muscles of respiration and diaphragm
- High incidence of birth apnea
- High metabolic rate and O_2 requirement
- Low FRC (less than CC) and poor respiratory reserve

10.5.1.4 Care During Anesthesia Management to Prevent Hypoxemia

- Avoid nasal instrumentation as far as possible.
- Avoid 100% O_2, and if required, use for the shortest duration (risk of developing ROP, BPD).
- Use of minimal FiO_2 to maintain target SpO_2 (88–92%).

- Use low PEEP to prevent basal collapse.
- NO crash induction/RSI, as they cannot tolerate even short periods of apnea.
- General care—prevention of hypothermia, maintaining heart rate, rhythm, and volume status.
- Avoidance of anemia and maintaining Hct.
- Thorough asepsis in handling them and during procedures and drug administration.
- Always assist ventilation. No spontaneous ventilation during aesthesia.
- Adequate analgesia and muscle relaxation
- Provision for postoperative ventilatory support.

10.5.2 Transient Tachypnea of the Newborn (TTN)

TTN is the mildest and transient complication of incomplete clearance of fetal lung fluid. It is more frequent in preterm and male babies and presents as tachypnea (RR >60/min), lung crackles, crepitations on auscultation, tachycardia, flow murmur, and acrocyanosis.

Contributing factors are decreased Na^+ transport and low surfactant. If surfactant deficiency is severe, features of RDS become evident. Babies at risk are those who have problem with clearing of lung fluid at birth (operative deliveries, diabetic or asthmatic mothers, and multiple pregnancies).

Management includes O_2 by mask to maintain SpO_2. Other care includes care of nutrition and antibiotic cover. Outcome—as the name implies, it is transient and usually resolves within 48 h. If it persists, it is known as malignant TTN, which is a precursor of RDS.

10.5.3 Respiratory Distress Syndrome (RDS)

RDS is the most common cause of morbidity and mortality worldwide, with preponderance in male and preterm neonates, and can be because of BPD (bronchopulmonary dysplasia, arrest of lung development, evolving chronic lung disease, neonatal chronic lung disease, respiratory insufficiency), MAS (meconium aspiration syndrome), HMD (hyaline membrane disease).

10.5.3.1 Pathophysiology

Surfactant production starts in the second trimester (24 weeks) and continues up to 32 weeks, with a surge at 36 weeks, in preparation for the birth of the baby. Babies born prematurely have deficiency of surfactant and may develop BPD, HMD, and RDS. Prematurity (<30 weeks GA) and LBW (<2 lbs) are risk factors for BPD, and risk factors for HMD include (high risk—prematurity, asphyxia, maternal diabetes

and hemorrhage, operative delivery, and multiple births, and low risk—IUGR, maternal hypertension, steroid therapy, placental insufficiency, and heroin addiction). MAS, hypoxia, acidosis, hypotension and shock, and pulmonary hemorrhage all cause endothelial damage and affect surfactant production (refer to the chapter on transitional changes at birth).

Pathological changes in the lung are alveolar collapse, alveolar and interstitial edema, diffuse hyaline membrane in the distorted small airways, reduced pulmonary and alveolar compliance and lung distensibility, stiff alveoli, poor alveolar stability, increased airway resistance (rigid bronchioles), reduced FRC, right-to-left shunt, reduced effective pulmonary blood flow, inefficient gas exchange, hypoxemia, and pulmonary hypertension.

10.5.3.2 Presentation—Clinical Features Appear Soon After Birth

- At birth—apnea, cyanosis, grunting, stridor, tachypnea, intercostal and subcostal retraction, hypotension.
- Chest radiology—ground glass appearance because of alveolar collapse, and signs of inflammation.
- ABG—low PaO_2, elevated $PaCO_2$, acidosis.
- ECHO—to rule out cardiac defects as cause of pulmonary hypertension.
- Autopsy finding—alveolar collapse, alveolar and interstitial edema, and diffuse hyaline membrane in the distorted small airways.

10.5.3.3 Management—Aims at Improving Oxygenation and Correcting Hypoxemia. Preventive/Prophylactic

Goal—PaO_2 of >55 mmHg, with normal $PaCO_2$ (40–60 mmHg).

(a) High FiO_2 and airway pressures.
(b) Noninvasive CPAP of 4–6 cm H_2O using face mask, in a spontaneously breathing neonate.
(c) If the baby is apneic with severe hypoxemia, or acidosis (pH <7.20)—immediate tracheal intubation and ventilation must be instituted.
(d) Premature and VLBW newborns—O_2 supplementation, ventilatory support—CPAP, IPPV with PEEP may be necessary for prolonged period.
(e) Drug therapy—bronchodilators, steroids, diuretics, antibiotics.

Special Care

- These babies are at risk of barotrauma and BPD during IPPV and high FiO_2.
- Use lowest peak inspiratory pressures and lowest FiO_2 to maintain PaO_2 and pH.
- Increase in minute ventilation can be achieved by increase in RR.
- O_2 requirement is increased, but even with 100% FiO_2, gas exchange and tissue oxygenation may not improve.
- Avoid use of 100% O_2 (high FiO_2 may inflame the lining of the lungs, injure the airways, and slow lung development in premature newborns).

Supportive care includes maintenance of body temperature, intravascular volume and electrolyte status, nutritional support (100–120 calories/kg/day), higher in LBW, correction of metabolic acidosis (base deficit (mEq) = base excess × 0.6 × body weight (kg)), oral feeds started once the baby is stable to provide 100–120 calories/kg/day, and vigorous monitoring of intake/output, body weight, electrolytes, acid-base, blood gases, serum and urine osmolality, and X-ray chest. **Advanced measures** include surfactant replacement therapy, ECMO, whole lung lavage, and lung transplantation [25–30].

10.6 Cardiovascular System (CVS)

The heart undergoes marked adaptation at birth. In utero it behaves as a conduit between right and left side of the heart. After birth, there is a change in the available energy substrate, its utilization, and in the cardiac metabolic activity, with shift from CHO to fatty acid utilization. In O_2 lack situations, neonatal heart can undergo anaerobic energy production and still maintain cardiac function. The load on the newborn heart is huge as it must take over the complete function. How efficiently it works depends on adequacy of pulmonary gas exchange, coronary blood flow, and nutrient intake [31].

Neonatal cardiac myocytes are poorly contractile. Both, the intracellular contractile protein- and calcium-dependent sarcoplasmic reticulum, are immature and cellular mass is less. Myocardium has more connective or non-contractile tissue. Both ventricles are equal unlike in adults where LV is predominant. Starling law is not applicable. Poor myocardial contractility and poor ventricular compliance prevent both early and late diastolic filling, with decrease in stroke volume and cardiac output.

Cardiac output (SV x HR) in the neonate is high, almost 200 mL/kg/min. Myocardial force of contraction and hence, stroke volume, cannot increase, so CO is HR dependent; such that if HR decreases, CO also decreases. Starling's law does not apply. With increase in HR, CO increases, but excessive tachycardia is also detrimental by limiting diastolic filling and SV, and while there is no increase in CO, but myocardial O_2 demand becomes excessive, with risk of myocardial damage. Net result is that both bradycardia and excessive tachycardia reduce CO and blood pressure markedly.

Heart rate in a newborn is 120–180/min, and by 1 month of age, it should not exceed 160/min in term neonate. **It is utmost important to maintain HR in within a range of 120–180/min.**

Vasomotor tone—Parasympathetic innervation of the neonatal heart is more developed compared to sympathetic innervation. Baroreflex mechanism is also weak. Catecholamine stores are small and inadequate, and all stress responses are blunted. Thus, the initial response to any stimulation or stress is bradycardia (parasympathetic), unlike tachycardia in older children and adults. Premature heart is extremely susceptible to bradycardia and hypotension. Vasoconstrictive responses to volume change are weak and hypotension is poorly compensated. Besides,

volume changes as in hypovolemia, hypotension, and hemorrhage, are not accompanied by increase in HR. They cannot tolerate fluid and blood loss.

Systemic blood pressure (SBP) varies with GA and normalizes by 36 h of life. In a term neonate, it is >90/65 mmHg and >80/45 mmHg in a preterm neonate. MAP ranges between 45 and 50 mmHg and DBP between 30 and 35 mm Hg. Table 10.8 shows mean circulatory values with BW.

MAP should not be allowed to drop below 20% of baseline or below an absolute value of 30 mm Hg. A rough guide for the lowest acceptable MAP is a value equal to the GA of the neonate in weeks. **ECG**—unlike a mature heart, newborn heart has right predominance. ECG shows right axis deviation (tall R, (right lead), deep S (left lead).

Patent ductus arteriosus (PDA) more common in premature infants; normally closes 10 days to 2 weeks after birth. It is associated with increased pulmonary flow and pulmonary congestion, and low DBP. These neonates are prone to NEC, IVH, BPD. May reopen whenever pulmonary arterial pressure rises (hypoxemia, hypercarbia, acidosis, or respiratory distress syndrome), causing **shunt reversal**. Therapeutic strategies include administration of O_2, prostacyclin and/or indomethacin, nitric oxide, or surgical ablation. **PFC** occurs due hypoxia, hypercarbia, and acidosis, all that cause pulmonary vasoconstriction and high PVR (Table 10.9).

Care during anesthetic management must be taken to prevent increase in PVR and decrease in SVR, so as to prevent reversal of shunt, meticulous fluid management (Table 10.2), avoidance of bradycardia, arrhythmias, undue tachycardia.

Table 10.8 Mean circulatory values and birthweight

BW kg	0.75	1	2	3	>3
SBP	44	49	54	62	66
MAP	33	34	41	46	50
HR	160–180	160–180	120	120	

Table 10.9 Ductus arteriosus and foramen ovale closure

	Functional closure	Anatomical closure	Initiation of closure	Reopening risks/shunt reversal
Ductus arteriosus	10–15 h	2–3 weeks	↑ PaO_2	Hypoxia, acidosis (CDH, MAS, RDS), Hypothermia, Excessive airway pressure—Crying
Foramen Ovale	At birth (within 24 h)	3 mth-1 yr.	↑ LAP	

10.7 Central Nervous System

The central nervous system is immature and incompletely developed at birth, cerebral cortex is poorly developed, and myelination is incomplete. Newborn brain has high water content. As cerebral maturation occurs, water content decreases steadily, and myelin and protein concentration increase.

10.7.1 Anatomy

A newborn brain weighs 350–400 g (nearly 1/fourth the size of adult brain). Rapid growth and maturation occur after birth, and its weight doubles by the end of first year. By 5 years of age, brain weighs 90% of the adult size, which is reached by teenage.

Major bones that compose the skull of a newborn include 2 frontal bones, 2 parietal bones, and 1 occipital bone, held together by fibrous sutures. Sutures allow the bones to move during the vaginal birth process. They are like expansion joints that allow the bone to enlarge evenly as brain grows and the skull expands into a symmetrical shaped head. (Fig. 10.3) **Important sutures are**

- **Metopic or frontal suture**, from the top of the head down the middle of the forehead, toward the nose, between 2 frontal bone plates.
- **Coronal suture** extends from ear to ear, between each frontal and parietal bone plates.
- **Sagittal suture** extends from the front of the head to the back, down the middle of the top of the head, between the 2 parietal bone plates.
- **Lambdoid suture**, across the back of the head, between each parietal and occipital bone plates.

Fontanelles are spaces where the sutures intersect and are present in the newborns and infants. There are 2 fontanelles which are covered by tough membrane that protects the underlying brain tissue:

- **Anterior fontanelle or the soft spot** is diamond shaped membrane, at the junction of the 2 frontal and 2 parietal bones. It remains soft until about 18 months to 2 years of age and is normally flush with the outer skull. Any fullness is indicative of raised ICP.

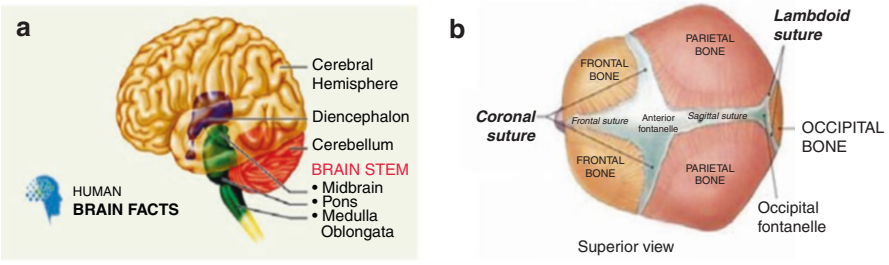

Fig. 10.3 (**a**) Newborn brain and (**b**) Newborn skull

- **Posterior fontanelle** is at the junction of the 2 parietal and the occipital bone. It usually closes earlier, during the first few months of life.

10.7.2 Blood–Brain Barrier (BBB)

Blood–brain barrier (BBB) is immature at birth, but matures soon after. It is permeable to many large lipid soluble molecules, such as volatile anesthetic agents and bilirubin. The partition coefficient of inhalational anesthetic agents is high, with a rapid wash in and wash out, and the clinical effect is achieved at lower concentrations and more rapidly. This also increases the susceptibility of the developing brain to anesthesia neurotoxicity. Permeability to bilirubin makes the newborn, especially the premature, at high risk of developing kernicterus.

10.7.3 Cerebral Blood Flow (CBF)

Brain receives almost 15% of cardiac output, 30–40 mL/100 g brain tissue. Newborn brain has a high metabolic activity. Higher CBF takes care of the O_2 and nutritional demand and for removal of CO2 and metabolic waste. CBF or cerebral perfusion pressure (CPP) is a factor of mean arterial pressure (MAP) and intracranial pressure (ICP). Any decrease in MAP of more than 20% from the baseline or increase in ICP above 15 mmHg reduces CPP. Cerebral venous drainage occurs through the 3 sinuses, which drain into the jugular veins—superior sagittal sinus, 2 transverse sinuses, and sigmoid sinus. In infants with open fontanelles, CPP varies in accordance with arterial blood pressure. Immaturity of the central nervous system also contributes to the development of ROP, where retinal vascular narrowing and obliteration are followed by neovascularization, hemorrhage, and in retinal detachment in severe cases [32].

10.7.4 Neonatal Brain Is Protected from Hypoxic Insults by Four Mechanisms

1. **Dual blood supply**—The anterior part is supplied by the two internal carotid arteries, branches of the arch of aorta, and posterior part by the two vertebral arteries which arise from the subclavian arteries. These two circulations communicate with each other at the Circle of Willis and provide backup and cerebral protection in case one gets blocked.
2. **Autoregulation**—The cerebral vessels respond to chemical (hypoxia, hypercarbia), metabolic (hypoglycemia, acidosis), pressure (MAP, ICP), and neural changes, so that a constant blood flow is maintained over a wide range of adverse conditions. However, in neonates, the range of blood pressure over which autoregulation occurs is very narrow, nearing the perfusion pressure itself. Asphyxia itself compromises autoregulation further. The lower limit of autoregulation in age more than 6 months is not reached till blood pressure

decreases by 40% from baseline, but in those under 6 months of age and neonates, it occurs when MAP decreases 20% from baseline. Low cerebral autoregulatory reserve is a risk of both IVH and inadequate cerebral perfusion during periods of hypotension. The period immediately after anesthetic induction, prior to surgical stimulus, is particularly vulnerable.

3. **Cerebrospinal fluid (CSF) buffer**—In newborns, 40–150 mL of CSF is synthesized per day. It contains leukocytes, lymphocytes, protein, electrolytes, and other substances. CSF is incompressible and protects the brain from injury by acting as a buffer. It maintains the water–electrolyte equilibrium of the fluid bathing the intracranial contents, maintaining ICP. Any increase in production or problem in its drainage can alter this equilibrium with rise in ICP, reduction in CPP, cerebral ischemia, and risk of HIE, convulsions, and coma.
4. **Metabolic protection—**Neonates' brain is unique in that in adverse circumstances, it can undergo anerobic metabolism for its energy needs, without undergoing permanent damage.

10.7.5 Intraventricular Hemorrhage (IVH)

The incidence of IVH is up to 50% in LBW and VLBW neonates, due to rupture of fragile capillaries within the germinal matrix, especially within 72 h of birth. This leads to ventricular dilatation, hydrocephalus, parenchymal infarcts, periventricular leukomalacia, cerebral palsy, and permanent CNS deficiency. **Risk factors for IVH include** hypoxia, hypotension, sepsis, toxic injury, RDS, aggressive resuscitation with hypertonic IV fluids, and mechanical ventilation. Presence of PDA also increases the risk of intracerebral bleed. Wide fluctuations in systemic blood pressure may be a contributing factor.

10.7.6 Spine and Spinal Cord

The spinal cord ends at L 3–4 and dura at S 3–4, in neonates. Care should be taken when giving spinal and caudal anesthesia in these neonates. They are at risk of injury to the spinal cord. Intrathecal puncture should be made below L3 and above S3 (Fig. 10.4). Sacrum does not fuse posteriorly until late teens. Sacral hiatus is relatively larger and higher placed. Epidural space has less fat and fibrous tissue.

Pain and pain pathways—Neural mechanisms for pain are present in the fetus by 6 weeks of gestation. The pain pathways are integrated with somatic, neuroendocrine, and autonomic changes early in gestation, and hormonal responses to pain and stress may be exaggerated in newborns.

Anesthetic implications—Brain of a neonate is extremely vulnerable to any hypoxic insult. Maintaining of MAP, CPP, PaO_2 and minimizing O_2 consumption should be the primary goal during anesthesia management. While both hyper- and hypocapnia are not wanted, controlled permissive hypocapnia may be beneficial. Rise in ICP may not be evident because of open fontanelle, hence due

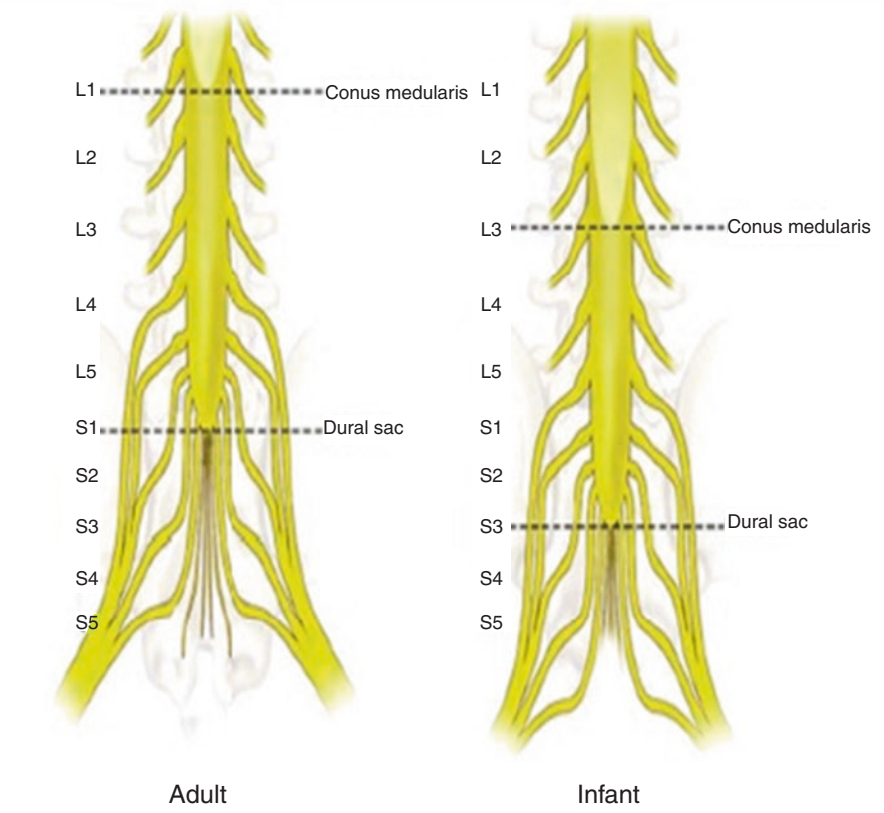

Fig. 10.4 Anatomy of the spine and spinal cord in an infant and adult

precautions must be taken in the perianesthetic care. They are prone to cerebral edema, convulsions, altered requirement of inhalational anesthetics (due to rapid wash in and rapid wash out, higher MAC), and risk of anesthesia neurotoxicity. It is important to maintain MAP within the limits of cerebral autoregulation for cerebral protection.

Special concern is in premature neonates who are very prone to cerebral edema and convulsions, anesthesia neurotoxicity, and greater muscular hypotonia. However, despite their CNS and NM immaturity, premature neonates have a normal response to stress and pain that needs attention during anesthesia and surgery, as in term neonates.

10.8 Thermoregulation, Endocrine, and Metabolic Functions

Newborn babies are prone to various metabolic and endocrinal disturbances. The hypophysial pituitary adrenal axis is immature, and this in turn affects brown fat thermogenesis and temperature control, with risk of hypothermia, and

affects hormone releases, response to stress, and glucose and lipid metabolism [33].

Common metabolic disturbances seen in the neonatal period are related to glucose, calcium, magnesium metabolism, and endocrinal disorders (growth hormone, gonadotrophin, thyroid, ACTH, cortisol).

Adverse Effects of Metabolic Immaturity Can Have Long-Term Consequences Because of

- Immature BBB with risk to cerebral edema, raised ICP, and convulsions.
- Acid-base disturbances, because of abnormalities in transition process at birth expose the immature brain of the newborn to early, severe, and extensive hypoxic damage.
- These effects are compounded by the adverse effect of drugs received by the mother in the antenatal or perinatal period, including narcotics, sedatives, anesthetic drugs, maternal drug, and alcohol abuse.
- Additionally, effects of anesthetic drugs and techniques used during operative delivery, complications of anesthesia (airway or hemodynamic related), and indication of Cesarian section itself will add to the newborn risks.

10.8.1 Thermoregulation

A growing fetus produces twice as much heat as an adult, and small amounts dissipate through into amniotic fluid and uterine wall. Core temperature of the fetus is 0.5 °C above the maternal temperature. Fetus does not expend energy to maintain body temperature, and glucose supplied to it is converted to glycogen in the liver and stored for later use. The temperature (axillary) of a newborn is 36.5–37.4 °C, but heat loss starts soon after birth from exposure to external environment. Cutaneous receptors signal the brain to initiate heat production by brown fat metabolism. The newborn utilizes fetal glycogen stores as energy substrate to maintain body temperature and other organ functions.

Thermoneutral temperature is the external temperature at which there is a balance between heat loss and heat gain, while **critical temperature** is that external temperature below which one cannot maintain core body temperature (Table 10.10).

Table 10.10 Thermoneutral and critical temperature °C

	Thermoneutral temperature	Critical temperature
Preterm neonate	34–35	28
Term neonate	32–34	23
Adult	25–28	1

Ideal OT temperature >28 °C
Birth to 1 week age—32 °C and for premature—35 °C

Providing controlled thermal environment improves the chance of survival and quality of outcome, particularly in small (BW <1000 G), premature, and critically ill neonates, by minimizing their O_2 and metabolic demands, and stress responses to cold or overheating. Neonates weighing >1500 g and without respiratory distress or hemodynamic instability can be cared for at 30–32 °C.

10.8.2 Brown Fat Metabolism and Thermogenesis

Hormone surge (cortisol, catecholamines, and thyroid) at birth activates brown fat thermogenesis, alternative to the white fat in adults. Brown fat is about 5% of body weight of a newborn and is abundant around the kidneys, intrascapular, and nuchal areas. It is highly vascular, has higher O_2 consumption, and is rich in iron-containing mitochondria and unmyelinated nerves, providing sympathetic stimulation to the fat cells. It generates heat by uncoupling of oxidative phosphorylation in the mitochondria. When lipid reserves of brown fat are depleted, as on prolonged exposure to cold, it gets darker in color.

Newborns are extremely prone to temperature instability especially in the first few days of life. Both hypothermia and hyperthermia are harmful and should be prevented.

10.8.3 Hypothermia - Causes

1. **Greater heat loss**—Relatively larger body surface-to-body weight ratio.
2. **Poor heat conservation**—Poorly developed thin subcutaneous tissue, and limited fat reserves.
3. **Minimal motor activity**—Inability to generate heat.
4. **Inability to shiver.**
5. **Central thermoregulation**—is immature and there is poor response to hypothermia.
6. **Higher energy utilization** for maintaining body functions.
7. **Anesthesia effects**—Both volatile and intravenous anesthetics depress nonshivering thermogenesis. This contributes to the increased risk of hypothermia in the perioperative period, while heat loss continues with reduced thermogenesis and poor thermal compensation.

Methods by Which Term Neonate Maintains Core Body Temperature:

(a) **Brown fat metabolism** (nonshivering thermogenesis) that produce twice the amount of heat as compared to white fat metabolism.
(b) **Shivering thermogenesis** (from physical activity of kicking and crying)—minor role in heat production, and.
(c) **Peripheral vasoconstriction** secondary to exposure to cold and decreased heat loss from skin surface.

Preterm neonates—While all newborns are at danger of hypothermia, premature and small for date babies are at a greater risk, more so in winters and cold environment, because:

They are poikilothermic—Human beings are homeothermic, i.e., they have the ability to control body temperature independent of ambient temperature, but premature babies lack this feature and they adopt the ambient environment temperature.

(a) They have **less brown fat** as compared to term neonates, so less heat production.
(b) Their BSA:BW:: ↑↑, which allows greater loss of heat from the exposed skin surface.
(c) Their skin is poorly keratinized, thin with less subcutaneous fat, thus poor heat conservation.
(d) Shivering is an important mechanism for production of heat in cold environment in older children and adults. This is absent in premature neonates, so they are unable to generate activity-related heat.

Adverse Effects of Hypothermia— Cold Injury

All newborns, especially premature and small for date neonates, are at risk of hypothermia and its adverse effects. Hypothermia is one of the main causes of neonatal mortality, and special measures must be taken to reduce this risk.

1. **Increase in carbohydrate (CHO) metabolism and glucose utilization,** in an attempt to maintain body temperature. This leads to depletion of already poor glucose stores, increasing the risk of further hypoglycemia.
2. **Cold induces depression of enzymatic and metabolic activity** is proportional to the duration and degree of hypothermia and inversely proportional to the gestational age. Thus, hepatic metabolism of drugs is reduced, with prolongation of their duration of action and effect. Polypharmacy, inherent to general anesthesia, is a cause of concern in babies already suffering from the ill effects of the surgical disease, and slow emergence from anesthesia.
3. **Dosages of anesthetic drugs—**since their ECF volume is more, the Vd of drugs is higher. Initial dose need not be reduced. The serum concentration may be lower but brain and other organ systems being still immature; adequate effect can still be achieved. But care must be exercised with top-up dosages, which must be reduced and have more spacing in-between two.
4. Increase in **cardiovascular stress** because of the stimulation of still immature compensatory mechanisms.
5. **Activation of brown fat thermogenesis** produces twice the amount of heat then from white fat. This consumes more O_2, increasing the metabolic O_2 demand. During hypothermia, neonates need higher FiO2. They are at risk of hypoxemia and metabolic acidosis.
6. **Pulmonary and Intracranial hemorrhages.**
7. Increased risk of **Infections and sepsis** because of immune suppression.
8. **Reduced Bilirubin conjugation and metabolism, causing** hyperbilirubinemia (unconjugated bilirubin), which can easily cross the immature BBB, with occurrence of kernicterus.

9. Hypothermia has a **depressant effect** on medullary respiratory centers and on responses to hypoxia and hypercarbia, with risk of **apnea** or apneic episodes.

Management is preventive and corrective. Prevention and treatment go hand in hand. One need not wait for hypothermia to occur before adopting corrective measures. It is important to maintain thermoneutral environment and prevent reaching critical temperature range in any care setting (ward, NICU, perioperative period, and in the operation room). Measures that must be adopted are:

1. Vigilant monitoring
2. Reduce O_2 consumption—avoid stress, pain, environment temperature fluctuations, hypoxia, respiratory, and hemodynamic disturbances.
3. Reduce heat loss—Maintaining environmental (OT, ward, incubator) temperature to thermoneutral range or at least more than >28 °C (table above), protective wrapping, heat shields, reflective foils, head cover.
4. Provide external heat—use of overhead radiant warmers, forced air heating units, heating mattresses, and blankets. Servo-controlled heat humidifiers are very effective.
5. Avoid transfusing cold intravenous fluids, blood, and blood products. They should be warmed before infusion.
6. Use of warm humidified gases during anesthesia.
7. Use of warm irrigating fluids during surgery.
8. Avoid wide fluctuations in the external temperatures.
9. IV glucose supplement (as a substrate for metabolism).
10. Higher FiO_2, respiratory support, and CPAP.
11. Avoid spontaneous ventilation during anesthesia, except for short procedures. Preferable to use CPAP by mask or secure the airway and use controlled ventilation.
12. Vit K injection (0.25 mg) intravenous, to reduce the risk of spontaneous hemorrhages.
13. Avoid IM and SC injections.

10.8.4 Hyperthermia

Hyperthermia (axillary temperature >37.4 °C or rectal temperature >37.5 °C) can be due to pathological condition (infection, sepsis, septicemia), iatrogenic, or environmental factors.

Effects of hyperthermia are consequent to vasodilatation and increased insensible losses, dehydration, hypovolemia, hypotension, and shock-like state, risk of risk of hypothermia, and secondary cold injury.

Management

(a) Must not lower axillary temperature to normal.
(b) Record skin, axillary, and air or incubator temperature.

(c) Environmental hyperthermia—reduce environmental heating temperature and thermal insulation (blankets or clothing).
(d) Avoid rebound hypothermia.
(e) Maintain volume status, renal perfusion, and urine output, and.
(f) Maintain electrolyte and acid-base balance.

Important Points to Remember

1. Heat production is an active process needing O_2 and glucose—a newborn should be allowed to breathe O_2-rich air for a few hours after birth.
2. Both hypothermia and hyperthermia are dangerous in the neonatal period and should be avoided.
3. Persistent hypothermia will result in metabolic acidosis, hypoglycemia, and decreased surfactant production, hemorrhages—newborn should be kept in a warm environment.
4. Hormonal surge at birth mobilizes glycogen, still glucose levels decline to a lowest point at 1 h of age. Newborns should be routinely given dextrose water orally or IV until initiation of regular feeds.
5. Care during anesthetic management and in the perioperative period.

10.9 Endocrine Physiology

Endocrine processes are actively involved in normal fetal growth and development. Endocrinal physiology is an interplay of several complex processes and disturbances in these can affect fetal growth depending on the stage of development at which exposure occurs. Clinical manifestations may not be apparent at birth but predispose the baby for disease at later age. Transient endocrine disorders (adrenal insufficiency, hypothyroidism) are frequent in the newborn period, but are of not much physiological consequences in a healthy term newborn. To evaluate suspected endocrine pathology in a newborn, knowledge of the normal, dynamics, changes, and maturation of the hormonal function is essential. Special attention must be paid to thyroid and adrenal gland function, glucose and calcium metabolism, and the mechanism of switching in energy substrate from CHO to fatty acid oxidation. Endocrine maturation occurs by 6–12 months of age, but adult hormonal values are reached by adolescence.

Physiological endocrinal disturbances at birth—These are mostly related to the withdrawal from maternal hormones (estrogen, progesterone, and prolactin), presenting mildly as vaginal discharge or bleeding lasting for 1–2 days in females, and enlargement of the mammary glands and secretion, in both sexes, by third day of life, which subsides in 2–3 weeks [34, 35].

10.9.1 Hypothalamic–Pituitary Axis

Hypothalamus arises from neuroblast proliferation in the intermediate zone of the fore brain, and supraoptic and periventricular nuclei and differentiates into anterior and posterior pituitary glands. Neurohypophyseal tract is formed by the nerve fibers

between hypothalamus and posterior pituitary. Hypothalamus secretes both stimulatory and inhibitory hormones and regulates the pituitary gland, which becomes functional after 12th week of gestation. Growth hormone-releasing hormone (GHRH), thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH), and gonadotropin-releasing hormone (GnRH) from the hypophysis stimulate anterior pituitary gland to secrete growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The main inhibitory hormones are somatostatin and prolactin inhibitory factor. Somatostatin inhibits GH release and prolactin inhibitory factor inhibits prolactin release. The posterior pituitary secretes vasopressin (ADH) and oxytocin.

Most disorders of the hypothalamic-pituitary axis in the neonate are from insufficient hormone secretion due to genetically inherited disorders, malformations, trauma, and infection.

Anterior pituitary dysfunction is difficult to detect at birth.

1. Presence of malformation (cleft lip and palate, optic nerve atrophy, transsphenoidal encephalocele, holoprosencephaly, anencephaly) is suggestive.
2. Tumors that suggest anterior hyposecretion include hypothalamic hamartoblastoma, Rathke pouch cyst, craniopharyngioma, and glioblastoma.
3. Syndrome of septo-optic dysplasia (SOD) comprises of hypopituitarism, optic nerve hypoplasia, absent septum pellucidum, wandering Nystagmus, and blindness at birth.
4. Hypoglycemia, micropenis, and cholestatic jaundice are indicative. Hypoglycemia is usually severe, and glycemic response to glucagon is brisk, which creates further confusion in diagnosis. Jaundice, initially unconjugated, but later predominantly conjugated, often resolves after hormone replacement therapy.
5. There may be **combined deficiency of multiple pituitary hormones** or **isolated deficiency** of a single hormone.

Posterior pituitary hypofunction (partial to complete panhypopituitarism) includes diabetes insipidus (DI) and SIADH (syndrome of inappropriate secretion of ADH).

10.9.2 Growth Hormone

Growth hormone is important for normal growth in the IU life, but in the early postnatal life, thyroid hormone, insulin, and nutrition are more important growth determinants.

- GH is tonically elevated in the first few days of life and normal serum levels are >10 ng/mL.
- Deficiency of GH (value <10 ng/mL) presents as hypoglycemia and micropenis (stretched penile length <2.5 cm in term infant). GH provocative test with increase in GH value to >25 ng/mL is normal.

- Congenital deficiency of GH—there is no IUGR nor effect on linear growth until 6–9 months.

Family history of short stature indicates familial autosomal dominant GH deficiency.

10.9.3 Gonadotrophins and Gonads

At 5–6 weeks of gestation, there is no sex differentiation of the embryos, and both male and female reproductive components are present. Wilms tumor suppressor gene (WT1) and steroidogenic factor 1 (SF-1) play important role in gonadal development and sex determination. Mutations in these are associated with gonadal dysgenesis. Sexual differentiation is complete by 12 weeks when testes descend into the scrotum and testosterone production increases under pituitary gonadotropin stimulus. At birth, gonadotrophin deficiency may be suspected by micropenis in a male baby, but in female baby, it is not identified until puberty.

10.9.4 ACTH and Adrenocortical Hormone Function

Adrenocorticotropic (ACTH) hormone deficiency rarely presents as acute adrenal crisis. ACTH deficiency causing adrenal insufficiency is unlikely if cortisol level is >20 μg/dL. Cortisol insufficiency is usually mild, with hypoglycemia or hyponatremia, normokalemia, and occasionally hyperbilirubinemia. Combined GH and ACTH deficiency may cause severe hypoketotic hypoglycemia. Isolated ACTH deficiency is extremely rare and is usually in association with multiple pituitary hormone deficiencies. **Adrenal hypoplasia congenita (AHC)** is life threatening. Early diagnosis and treatment with corticosteroid and mineralocorticoid replacement can be lifesaving.

Role of Cortisol at Birth and in Neonates

Adrenocortical hormones and cortisol play an important role in the transitional changes at birth by influencing cardiopulmonary changes, metabolism, and hormonal release. Fetal cortisol synthesis and release are under fetal hypothalamic control; levels are low and increase with the period of gestation (Table 10.11). Fetal adrenal cortex atrophies soon after birth creating a relative cortisol deficiency, and abnormality in transitional process, with persistence of fetal circulation (PFC) and persistent pulmonary hypertension of the newborn (PPHN).

Table 10.11 Cortisol levels

Gestational age	Fetal cortisol levels
30 weeks	5–10 μg/mL
36 weeks	20 μg/mL
40 weeks (prelabor)	45 μg/mL
Few hours postdelivery	200 μg/mL

At birth, normal serum cortisol levels are 2.6–10 μg/dL with no diurnal variation. "Cortisol surge" influences the cardiopulmonary, metabolic adaptations, and hormonal release at birth. Cortisol is responsible for lung maturation and for surfactant production, clearance of lung fluid, for normal transition at birth, thyroid hormone secretion, hepatic gluconeogenesis, catecholamine secretion, production of digestive enzymes, and for temperature regulation. (Box 10.6).

Box 10.6 Role of Cortisol in Newborn

1.	Surfactant production in the fetal lungs
2.	Increase in β-receptor density in the heart and lungs, near term and at birth.
3.	Catecholamine release in response to stress at birth (poor in SFD babies).
4.	Maturation of the thyroid axis and in conversion of T_4 to T_3.
5.	Metabolic and energy substrate metabolism in the liver.
6.	Gut maturation and its digestive capacity.

10.9.5 Catecholamines and Other Vasoactive Substances

Catecholamines and other vasoactive substances (norepinephrine, epinephrine, dopamine, angiotensin II, renin)—In response to stress at birth, there is increase in release of catecholamines. In Cesarean-born babies, catecholamine levels are lower than following labor and vaginal delivery. In premature newborns, catecholamine levels are higher because (1) organs are immature and less responsive, and (2) higher concentration is required to illicit similar response. However, stress response is normal in preterm babies. Catecholamines play a role in adaptation at birth by inducing peripheral vasoconstriction, increasing SVR, closure of extrapulmonary shunts, increase in glucose and fat metabolism after birth, and in brown fat thermogenesis, temperature control, and prevention of hypothermia in newborns.

10.9.6 Thyroid Hormones

There is increase in serum levels of T_3 and T_4 in response to cortisol surge, cord clamping, and cold stimulus at birth. Levels only normalize by the age of 10 years.

Role of Thyroid Hormones in Neonate

(i) Clearance of fetal lung fluid (by activating Na^+, K^+, ATPase).
(ii) Congenital hypothyroidism—no abnormality or signs at birth or in neonatal period. Usually presents after 2–3 months of age.
(iii) Very preterm babies—responses at birth (increase in T_3 and T_4) are blunted with depressed adaptive behavior.

Thyroid-Stimulating Hormone (TSH) deficiency is asymptomatic in the newborn and is usually associated with other pituitary deficiencies. Hormonal screening shows low T_4 concentration with normal TSH value, which can be misinterpreted as euthyroid sick syndrome. In a neonate with any CNS abnormality, secondary hypothyroidism should always be ruled out.

10.10 Metabolism

10.10.1 Carbohydrate Metabolism

Fetal energy needs are met with transplacental transfer of glucose and fetal liver acts as a store for glycogen, fat, and other substrates. The microsomal enzyme system is immature at birth until 3 months of age. In early hours of birth, plasma glucose falls. Catecholamine release, cortisol surge, and decrease in insulin levels help maintain normal levels of plasma glucose and free fatty acids. The normal blood/plasma sugar in a newborn is 50–100 mg% (not on glucose supplement), and caloric requirement is at least 100 kcal/kg/day. A 2.5 kg baby should receive 10% dextrose @ 9–10 mL/h (90–100 mL/kg/day) [5, 6].

Fetal heart is a mere conduit and not much energy is consumed by its myocardial activity. At birth, it assumes its role in maintaining cardiac output and peripheral circulation and tissue perfusion, which are high energy consuming. Availability of substrate for metabolism in the newborn depends on:

(a) Pulmonary gas exchange,
(b) Coronary blood flow,
(c) Nutritional intake, and.
(d) Efficiency in shifting from CHO to fatty acid utilization as substrate.

Neonatal myocardium is capable of anaerobic energy production and can maintain cardiac function even at low PaO_2, protecting the myocardium from ischemic injury. However, persistent hypoxia or asphyxia adversely affects transitional changes much before myocardial effects become apparent.

Important Points that to be Kept in Mind During the Perioperative Period in Neonates Are

1. They have high BMR and glucose utilization.
2. Gluconeogenesis is not active.
3. Glycogen stores from IU period are low and suffice for only 10–12 h of birth,
4. This makes neonates extremely prone to hypoglycemia (blood sugar <40 mg%) even with short periods of starvation. Hence, they should not be kept fasting for long.
5. During fasting or NPO interval, glucose must be supplemented to maintain blood sugar >40 mg% (>2.6 mmol/L) with 0.5–1 mg/kg of dextrose infused @ 5–6 mg/kg/min.
6. AVOID hypoglycemia, hyperglycemia, hypovolemia, and dehydration.

Preterm babies have abnormal response to cortisol and catecholamines. Serum levels are higher and catecholamine release is increased. Their glycogen, fat, and substrate stores are small, which creates difficulty in adaptation at birth. They often need glucose infusion, as substrate for metabolism and energy production, to prevent hypoglycemia, hypothermia and allow normal transitional.

Babies born to diabetic mothers behave differently from those born to non-diabetic mothers:

1. They have lower blood glucose levels.
2. Congenital anomalies—incidence of congenital heart disease (CHD) and CNS anomalies (anencephaly, spina bifida, microcephaly, caudal regression syndrome) is significantly higher.
3. They are at a greater risk for RDS than other newborns of comparable gestational age.
4. Hypoglycemia incidence is high and is proportional to cord plasma glucose value.

Both hypoglycemia and hyperglycemia can have adverse short- and long-term consequences and should be avoided.

Hypoglycemia

Hypoglycemia is defined as plasma glucose of <40 mg% (term and preterm newborns). Maternal, fetal, and postnatal factors can cause hypoglycemia in the newborn baby (Table 10.12).

Diagnosis—The newborn cannot complain hence no symptoms, and diagnosis is based on observation, clinical signs, and laboratory investigations. **Signs** are usually non-specific and include tremulousness, twitching, jitteriness, irritability, exaggerated Moro reflex, high pitched cry, prolonged seizures, apnea, limpness, poor feeding, cyanosis, temperature instability, cerebral damage, and coma. **Screening** for plasma glucose is advised at 1, 2, 4, 8, and 24 h in at-risk newborns, not receiving glucose containing IV fluids, or when exhibiting clinical signs. Newborn hypoglycemia is classified as:

- **Mild**—Plasma sugar levels 20–40 mg% and
- **Severe**—plasma sugar levels <20 mg%

Aim of management (Table 10.4) is to achieve plasma glucose of >40 mg% (2.6 mmol/L) (50–100 mg%), while avoiding over transfusion, using D10% instead of D5%, and maintaining Hct <65%.

(i) **Preventive measures**—during fasting, baby should receive IV glucose (0.5–1.0 mg/kg) @ 5–6 mg/kg/min.

Table 10.12 Newborns at risk of hypoglycemia

Maternal factors	Fetal factors	Postnatal factors
IUGR<10%ile>, Diabetic mothers, Gestational diabetes, On oral hypoglycemics, Glucose overload prebirth	SGA (<10%ie), LGA) (>90%ile), Premature, Postmature.	Postasphyxia, 5 min APGAR <5, Polycythemia, immune hemolytic ds, Suspected sepsis, Hypothermia, Congenital anomalies

(ii) **Mild hypoglycemia** (40–50 mg %, asymptomatic)—can be managed with oral feeds and glucose water. If the neonate is NPO, as in the perioperative period, IV glucose can be supplemented as described above.
(iii) **Moderate hypoglycemia** (<40 mg%)—baby should receive 4–8 mg/kg/min dextrose as D10 (plain or in 0.2 NS) @ 100 mL/kg/day or 10 g/kg/day or 7 mg/kg/min.
(iv) **Severe hypoglycemia** (<20 mg%, symptomatic)—D10 bolus (2 mL/kg = 0.2 g/kg) over 1–2 min.
(v) **Continuous infusion:** 90–120 mL/kg/day = (6–8 mg/kg/min) as D10.

Monitoring of plasma glucose (capillary blood from the heel) is done every 2 h after starting treatment, and every 30 min if symptomatic. Infusion is adjusted to maintain plasma glucose >40 mg% (if <40 mg%—increase infusion rate to 10 mg/kg/min). Once normal levels stabilize for 24 h, IV infusion can be tapered off over next 24 h, and oral feeds continued.

While Infusing 10% Dextrose, Care Must Be Taken

- Never give with blood or products in the same line as glucose,
  - Risk of fluid and solute overload, so avoid using D5, and RL solutions, because babies are already in congested states and are at risk of peripheral and pulmonary edema,
  - Volume load causes dilutional hyponatremia, hypokalemia, and hypocalcemia,
  - Hyperglycemia and serum hyperosmolality and intracranial hemorrhage (ICH) especially in VLBW newborns.

Hyperglycemia is defined as plasma glucose >200 mg% in the first few hours to days of life and is usually iatrogenic following IV glucose administration. **Adverse effects** of hyperglycemia are increased risk of IVH, ROP, NEC, BPD, prolonged hospital stay, bacterial and fungal infections, and death. **Neonates at risk** include LBW, VLBW, on IV glucose infusion, and congenital diabetes mellitus. Sudden onset polyuria (plasma glucose >250 mg%) is a sure sign. Abrupt increase in plasma glucose levels (rapid infusion of 25% or 50% dextrose), or unmonitored glucose infusion can result in ICH. **Management** (Table 10.13) is preventive (timely care in

Table 10.13 Plasma glucose levels in newborns and management of hypoglycemia/hyperglycemia

	Plasma Glucose	Management	Screening-capillary sample
Normoglycemia	50–100 mg%	Normal feeds	Once at 2 h
Mild hypoglycemia	20–40 mg%	Enteral glucose	2–4 h until normal for 24 h
Severe hypoglycemia	<20 mg%	Bolus IV D10–2 mL/kg (0.2 g/kg) Infusion at 4–8 mg g/kg/min(90–120 mL/kg/D)	Every 30 min
Hyperglycemia	>200 mg%	Stop IV glucose, IV insulin 0.1 U/kg/h	Every 4 h until normal for 24 h

newborns at-risk and vigilant monitoring) and corrective (plasma glucose >200 mg%), by reducing infusion rate, addition of IV insulin 0.1 U/kg/h, and blood sugar monitoring every 1–4 h until normal for 24 h.

10.10.2 Protein Metabolism

(a) Protein production is slow at birth and normalizes by 1 year of age.
(b) High risk of hypoproteinemia, hypoalbuminemia, fluid overload, peripheral, cerebral, and pulmonary edema.
(c) Reduced drug binding and more of free (active) drug in circulation.
(d) Enzyme system is immature, and different systems mature at different rates.
(e) Drug metabolism is slow—prolonged duration of action of drugs.
(f) They are at risk of adverse drug effects.

Hence, great care must be taken during administration of fluids and electrolytes. It is preferable to use 5% albumin than crystalloids in treatment of hypovolemia and dehydration, avoiding high sodium containing fluids, as well as reducing the doses of drugs administered.

10.10.3 Calcium Metabolism, Neonatal Hypocalcemia, and Osteopenia of Prematurity

A fetus starts to accumulate calcium during the third trimester of pregnancy, and this continues to a peak in early adulthood. Thereafter it begins to decline at a rate of 1% per year. These variations are due to continual remodeling of bone, excess of bone formation during growth spurt in early adulthood, and breakdown in late adulthood. In the newborn, serum calcium levels are low (1.9–2.8 mmol/L), **but become normal by the age of 1 y.** Hypocalcemia is diagnosed when plasma ionized calcium concentration is <0.75 mmol/L (3 mg%). **Neonates at risk** of hypocalcemia include premature, babies born to diabetic mothers, postbirth asphyxia, and congenital, genetic, and hormonal disorders [36].

Categorization of Hypocalcemia by Age of Onset

1. **Early-onset hypocalcemia** is usually iatrogenic. It occurs in preterm newborns who receive sodium bicarbonate for treatment of metabolic acidosis. Risk is greatest at 12–24 h of age. In most asymptomatic babies, it normalizes within 72 h without treatment.
2. **Late-onset hypocalcemia** is seen after 7 days of life in those on formula milk low in calcium and high in phosphorus content. This is not common.
3. **Very late-onset hypocalcemia** (osteopenia or rickets of prematurity) is a relatively frequent in preterm neonates. Large amounts of calcium and phosphorus are transferred from the mother during the third trimester. Hence, in premature newborns, both calcium and phosphorus are reduced. Osteopenia causes weak and brittle bones and often remains silent until signs of rickets or fractures occur at a later age.

Symptoms of hypocalcemia usually occur later in infancy and are nonspecific-jitteriness, seizures, apnea, bleeding, and decreased myocardial contractility. **Management** in symptomatic neonates or hypocalcemia in laboratory report should be instituted immediately. There is no benefit of empirical calcium supplements in all neonates without evidence of hypocalcemia. **Treatment** consists of 10% calcium gluconate administration, starting with 100–200 mg/kg (1–2 mL/kg) as slow IV "push" over 30 min, followed by continuous infusion @ 400 mg/kg/day, or 100 mg/kg every 6 h slowly over 30 min. **Care during calcium infusion** calcium gluconate is preferred and can be given via peripheral line. Do not given with sodium bicarbonate, dioxin, or antibiotics in the same infusion due to risk of precipitation. **Monitoring** of plasma ionized calcium level should be done every 12–24 h. Once calcium level remains normal for 24 h, the infusion is reduced by 50% and discontinues after another 24 h if calcium level is normal and baby is asymptomatic. In neonates on oral feeds, oral calcium supplement is added. To prevent occurrence of late osteopenia, commonly in sickest and least mature premature neonates, long-term enteral and parenteral calcium support must be continued.

10.10.4 Magnesium Metabolism

Magnesium is a trace element, and second most abundant intracellular cation, essential for life [37].

Congenital hypomagnesemia may occur in premature neonates, IUGR, and babies born to Mg-deficient mothers. **Management** is replacement therapy using 50% $MgSO_4$ (0.2 mmol or 0.4 mEq/kg/day = IV 0.1 mL/kg/day) for 5 dose days or oral 1.0 mL of 10% magnesium chloride (0.5 mmol/kg/day Mg).

Hypermagnesemia is more common in newborns, usually from Mg overdose in mother or inadequate renal function in eclamptic mothers. No active **management** is required and Mg normalizes by 48 h. In obtunded and depressed neonates, IV calcium and glucose saline infusion are given. Rarely, dialysis may be needed.

To summarize, metabolic immaturity and imbalance can have greater and long-term adverse effects because of immature BBB and increased risk of cerebral edema, raised ICP, convulsions, and extensive hypoxic damage. Hyperbilirubinemia is common in newborns, but kernicterus occurs at lower bilirubin levels (12–13 mg%); for this reason, exchange transfusion is indicated at serum levels of 15–20 mg% in preterm and at >20 mg% in term neonates. These effects are compounded by the adverse effect of drugs received by the mother in the antenatal or perinatal period, e.g., narcotics, sedatives, anesthetic drugs, maternal drug addictions, and drug and alcohol abuse. Additionally, effects of anesthetic drugs and techniques used during operative delivery, complications of anesthesia (airway or hemodynamic related), and indication of Cesarean section itself will add to the immature newborns' risks.

10.11 Hepatic Anatomy and Physiology

10.11.1 Anatomy

Liver is the biggest gland in the body, with endocrine (secretion of Insulin-like growth factors, angiotensinogen, and thrombopoietin), exocrine (production of Bile), synthetic (protein, carbohydrates, lipids, clotting factors, lymph), metabolic (urea production, drug detoxification), storage, and excretory (bile and products of metabolism) functions. Adult liver is 2.5–3.5% of body weight (1.4–1.6 kg (3.1–3.5 lb). At birth, liver is very small, weighing 120 g (4 oz), but it is 4% of body weight.

10.11.2 Functions of Liver-Fetal Liver Has Two Important Roles Besides Other Functions, Mainly Cardiovascular and Hemopoietic [38–40]

Embryologically, liver appears as a hepatic diverticulum extending out from the foregut at third week of gestation and grows rapidly from fifth to the tenth week. The cells proliferate into hepatocytes and are a rich source of stem cells. As the liver grows, liver sinusoids and bile canaliculi appear. A branch from the diverticulum grows into the gall bladder.

(a) **Cardiovascular (CVS) Function**—Liver occupies major portion of the abdominal cavity of the fetus. It is supplied by the umbilical veins, with Hb saturation of 80%. It acts a conduit between the placental vessels and heart. Blood bypasses the liver via the ductus venosus (shunt between left portal and left hepatic veins) into the IVC, thereby to RA, and to the left side of the heart via Foramen Ovale and Ductus Arteriosus (refer to chapter on fetal circulation and adaptation).

(b) **Haemopoietic function**—Primitive erythropoiesis starts in the yolk sac at around seventh week, and by midterm, liver is the main erythropoietic tissue, producing RBCs before the bone marrow can take over. Hematopoietic stem cells are pluripotent and form all the hematopoietic cells (RBC, WBC, B and T lymphocytes, and platelets). Fetal liver releases blood stem cells that migrate to the fetal thymus, creating T lymphocytes, and by 13th week T lymphocyte production starts in the thymus. By 15th week, erythroid and myelo-lymphoid production moves to spleen and to bone marrow by 16th week. By 32 weeks, bone marrow completely takes over the erythropoiesis. Thrombopoietin, produced in the liver, regulates production of platelets by the bone marrow. The switch mechanism from fetal to adult hemoglobin (Hb) also takes place in the liver. Three hormones play a role at different periods of gestation in production of hemoglobin, **testosterone** (between 10 and 13 weeks), **β-adrenergic stimulation** (between 8–11 weeks), and **erythropoietin** (by late second trimester).

Other activities taking place in the fetal liver are **bile production** (by 12th week), **glycogen storage** (by 30th week) and gradually increase thereafter, and **drug clearance** via P 450 iso-enzymes (reaches 85% of adult levels by 44 weeks and adult levels by 6 months of postnatal age). Within 2–5 days of birth, umbilical vein gets obliterated into round ligament of the liver, while ductus venosus get obliterated into ligamentum venosum. In cirrhosis and portal hypertension, the umbilical vein can reopen. At birth, liver is not mature enough to take over all the functions fully, and special care must be taken in the perioperative period.

(c) **Carbohydrate metabolism—**The microsomal enzyme system matures only by 3 months of age. At birth and during the neonatal period, the basal metabolic rate (BMR) is high and so is glucose utilization:
   (i) Gluconeogenesis is not active. Fetal glycogen stores are low and last only up to 10–12 h. Thus, neonates are prone to becoming hypoglycemic (normal range of blood sugar = 40–60 mg%).
   (ii) They are susceptible to periods of starvation—so minimal duration of fasting in the preoperative period and otherwise.
   (iii) During fasting period, glucose must be supplemented to maintain blood sugar >40 mg% (>2.6 mmol/L) using dextrose infusion of 0.5–1 mg/kg @ 5–6 mg/kg/min.
   (iv) Always avoid hypoglycemia, hyperglycemia, hypovolemia, and dehydration.

(d) **Protein Metabolism—**Protein production is low and becomes normal by the age of 1 year, hence:
   (a) Low drug binding to proteins, and more of free (active) form of in circulation.
   (b) Decreased drug metabolism and prolonged duration of action of drugs.
   (c) Hence, dosages of IV drugs must be reduced, and intervals between supplements prolonged.

(e) **Bilirubin metabolism**—At birth, serum bilirubin is high (17–20 mg%), which normalizes by 1 month of age. This is due to:
   - Deficiency of Vit K-dependent clotting factors (II, VII, IX, X), and 20–60% prolongation in prothrombin time. Hence, all neonates should receive parenteral Vit K for 3 days preoperatively.
   - Liver is unable to conjugate bilirubin. Unconjugated bilirubin can cross the BBB; hence, kernicterus can occur at lower serum bilirubin levels (12–13 mg%).

(f) **Biotransformation of drugs—**The enzyme system is immature, and different systems mature at different rates. Drug metabolism is slow and they are at risk of adverse drug effects. Besides, there is danger of hepatotoxicity of the immature liver by various drugs.

10.12 Neonatal Renal Physiology and Excretory Function

When trying to understand the development and functioning of the renal and the excretory system, it should be done in relation to total body water (TBW), its distribution, expected fluid and electrolyte shifts, and functional capacity of the kidneys. Neonates are already in a delicate state of fluid balance, and these changes become quite relevant in the presence of medical or surgical pathology, and during surgery under general anesthesia [41–43].

Renal system plays a tremendous role in growth and development of a fetus, in maturation and well-being after birth. It maintains body homeostasis and regulates body water, electrolytes, acid-base balance, removal of waste, metabolites, and clearing of drugs from the body. During this time, there is little margin for error especially in the premature and VLBW neonates. Significant risks for all neonates include overhydration, dehydration, electrolyte imbalances, oliguria, and acidosis.

Renal efficacy is a function of GA, total renal mass, renal blood flow, and hemodynamic stability. Abnormal renal functioning in the neonatal period is a predictor of CVS and renal disease risks, though acute renal failure (ARF) may occur in up to 24% of sick neonates in NICU.

Urine formation consists of four processes—glomerular filtration, tubular reabsorption, tubular secretion, and urinary excretion. Fetal kidneys produce urine by late first trimester. Each kidney has about a million nephrons and 60% of nephrogenesis occurs after 20th week, up to 36th week of gestation. At birth, kidneys also undergo transitional changes. Being immature at birth, the excretory system continues to mature over a period of 3 months, attaining full maturity by 2 years of age. The preterm newborns (<36 weeks GA) are especially vulnerable to renal dysmaturity, with prolonged postnatal maturation, up to 7–8 years of age.

Renal blood flow (RBF), glomerular filtration rate (GFR)—Kidneys weigh less than 0.5% of body weight, but they are highly vascular. RBF is 5% of CO at birth, increases to 20% by 1 month, and reaches adult value of 25% by 2–3 years. Effective plasma flow (EPF) is low, 83 mL/min/1.73 m^2 at term, increasing to 650 mL/min/1.73 m^2 by 2 years. At 25 weeks' gestation, GFR is only 10% of adult values, 35% birth, and doubles by second week of life, and continues to increase up to 3 months. (Table 10.14) Various factors affect GFR, such as IUGR, maternal steroids, postnatal high FiO_2, nephrotoxic drugs, stress and sympathetic stimulation, and hypoxic ischemic injury to brain. Clinical conditions associated with renal dysfunction include need for vasopressors in the first week of life, IVH, PDA, NEC, sepsis, and high-frequency ventilation (HFV).

Tubular function is also immature at birth. Renal tubules are insensitive to antidiuretic hormone (ADH), and levels of ADH are high in newborns. **Neonates** are **obligate salt losers**. They have less ability to excrete sodium load and to concentrate or dilute urine. Their daily requirement of sodium is 2 mmol/kg, and 1 mmol/kg of potassium and calcium, each. They cannot also conserve bicarbonate and are extremely prone to developing metabolic acidosis.

Table 10.14 RBF/EPF, GFR, and urine osmolality in neonates

Age	RBF/EPF	GFR mL/min/1.73 m^2	Urine Osmolality (mOsm)
TERM			
Newborn	5% of CO/83 mL/min/1.73 m^2	20–25	525
2–4 weeks	20% of CO	40–60	950 (28 days)
Adult values (by 2 years in term NB),8 years in ELBW)	25% of CO/650 mL/min/1.73 m^2	100–130	1400
PRETERM			
25 weeks GA		2	
27–31 weeks GA to 7 days age		8–29	
27–31 weeks GA to 21 days age		13–35	

A newborn usually passes hypo-osmolar urine within first 24 h of birth (525 mOsm), which increases to 950 mOsm by 28 days, and 1400 mOsm by 1 year. N**ormal urine output is 0.5 mL/day**. They **cannot deal with major volume changes such as overload, dehydration, or solute load.**

Body weight **gain i**n the first week of life is due to sodium retention, and once sodium excretion begins, weight gain decreases, rather there may be weight loss, which recovers by 1 month of age. Sodium containing fluids should be avoided in the first week, but need to be given if weight loss is more than 7% of BW.

Hormonal control is inefficient and less effective including renin–angiotensin aldosterone system (RAAS), atrial natriuretic peptides (ANP), vasopressin, and catecholamine system. RAAS plays a role in regulating blood pressure, intrarenal blood flow, and fluid and electrolyte balance.

Sodium balance—Sodium is easily filtered at the glomerulus. Nearly all is reabsorbed (70% in proximal convoluted tubules (pct), 15–20% in ascending loop of Henle, 5% each in the distal convoluted tubules (dct) and collecting tubules), and urine finally formed is hypotonic, very low in sodium content. In premature, sodium losses are high as the immature renal tubules cannot reabsorb. After first week of life, term neonates have a positive sodium balance. Premature neonates are prone to hyponatremia and dilute urine in the first week and later to hypernatremia and increased urinary sodium losses. They require 3–5 meq/kg/d of sodium replacement in the first week of life. Hypoxia, diuretics, jaundice, high fluid load, or salt intake increase sodium excretion and should be avoided.

Potassium balance—Potassium is secreted in the dct. Immaturity of the dct and reduced sensitivity of collecting tubules to aldosterone reduce excretion of potassium in term neonate, with hyperkalemia. In premature neonates, potassium shifts out of the intracellular compartment. With use of diuretics, there is increased loss of potassium. This gradually returns to normal by 2–3 weeks. It is important that

Table 10.15 Acid–base balance

Age	pH	HCO3 mmol/L	PaCO2 mmHg
Birth	7.14–7.34	14–26	29–69
Neonate	7.18–7.5	17–24	27–40
Infant	7.2–7.5	19–24	27–41
Adult	7.37–7.41	20–28	37–45

during perioperative period, meticulous care is taken in fluid and electrolyte therapy, avoid or manage changes in volume status and electrolytes, and prevent acidosis and further deterioration in the already compromised renal function.

Calcium balance—Calcium levels fall soon after birth to about 8 mg% and lower in premature (7 mg%). This usually corrects by 2–3 weeks of age.

Acid-base balance (Table 10.15)—Neonates have poor capacity to conserve bicarbonate. The respiratory buffer has a limited capacity, renal buffer is immature, and remaining buffers (bicarb carbonic acid, oxy Hb, protein, PO4 buffer) are in less quantity. At birth, blood pH is slightly acidic and remains so throughout the neonatal period.

Creatinine is a reliable indicator of renal function. A product of muscle metabolism is secreted into the blood at a steady rate and freely filtered at the glomerulus. It is not affected by weight, gender, or age, but varies with hydration and clinical status.

Serum creatinine (SCr) and GFR are inversely related. High SCr indicates poor renal function. With decline in GFR, creatinine takes 7–10 days to stabilize and hence is a better indicator of chronic renal dysfunction. Higher levels at birth reflect maternal levels (1.1 mg%). Normal values are 0.2–1 mg% on day 1–3 and 0.2–0.5 mg% by 1 year. In VLBW and premature neonates, levels peak by 2–3 days and decrease by 4–5 days, because of tubular reabsorption and leaky renal tubules, which improves by the first week of life.

Accurate measurement of GFR is problematic due to the unavailability of the gold standard inulin for neonates. The traditional use of creatinine to estimate GFR is unreliable in preterm due to its tubular reabsorption and its dependence on muscle mass as an endogenous marker. Alternatively, cystatin C and beta trace protein (BTP) are used. Cystatin C is filtered across capillaries and completely reabsorbed by pct and is a better measure of GFR.

Blood urea nitrogen (BUN) represents urine-concentrating capacity. Urea is formed in the liver from amino acids and ammonia and is filtered in the glomerulus. If GFR decreases, BUN increases. BUN has a wide variation in range, 6–43 mg% (mean 20.9 mg%) on day 1, 8–110 mg% (mean 36 mg %) on day 7, 5–17 mg% at 3 years of age, and 7–20 mg% in adults. It is affected by age, protein intake, and low GFR (dehydration, hypotension) and is not the first choice for estimating renal function in neonates.

Medications and drug clearance—reduced RBF and GFR, and immature tubular function, interferes with clearance of drugs from the body with resultant prolonged action. This also implies that the time interval between two doses of drugs

given repeatedly during general anesthesia, such as muscle relaxants and narcotics, is longer.

Drug metabolism is slower in neonates, more so in prematures. Special care is needed in the dosing and monitoring of renal functions when administering drugs that may be nephrotoxic to the developing kidneys, such as antibiotics (aminoglycosides, glycopeptides, amikacin, vancomycin, gentamicin), analgesics (ibuprofen, indomethacin). Ibuprofen, as prophylaxis or treatment of PDA during the neonatal period, reduces GFR significantly, persisting through 1 month of age.

Diuretics are commonly used in a sick neonate, such as lasix, aldactone, and thiazides. Each is associated with several side effects and toxic effects. Furosemide (lasix) inhibits chloride reabsorption in the ascending limb of the loop of Henle, inhibits tubular sodium transport, and leads to increased sodium, potassium, and calcium loss, with severe dyselectrolytemia, ototoxicity, metabolic alkalosis, and renal calcinosis especially in the premature. Lasix dose 1–2 mg/kg once in 12 h in term and once in 24 h in premature. Spironolactone (Aldactone) and aldosterone antagonist (1–3 mg/kg/d in 12 h) is associated with hyperkalemia, lethargy, and GI disturbance in neonates. Chlorothiazide (decreases sodium reabsorption in dct) is associated with dehydration, electrolyte imbalance, metabolic alkalosis, hypercalcemia, hyperglycemia, hyperuricemia, especially in newborns with liver or renal disease. Keeping a check on dosages and intervals in between, aiming to use the least effective dose, at maximum interval, and least number of doses, will help contain these side effects.

10.13 Total Body Water, Body Water Distribution, and Blood Volume

Total body water (TBW) is higher in neonates compared to adults and children. In a full-term neonate, TBW is 80% of body weight and is distributed equally into the intracellular (ICF) and extracellular (ECF) compartments. In preterm neonates, TBW is >80% of body weight, and more than 60% is in the ECF compartment. Adult figures are attained by the age of 4 years, when TBW is 60% body weight, and proportion of ICF volume increases to two times ECF volume (40% is ICF and 20% is ECF) (Table 10.1).

Blood volume is also higher in neonates, 85 mL/kg body weight at term, and 90–100 mL/kg body weight in premature, compared to 60 mL/kg in adults (Table 10.16).

Hemoglobin (Hb) ranges between 16–20 g% in term neonates while it is lower in preterms, with higher hematocrit (Hct) (50–55%). Blood transfusion trigger is

Table 10.16 TBW, distribution, and blood volume

Category	TBW and its distribution (ICF:ECF)	Blood volume
Neonates	TBW 80–85% of body weight	85–100 mL/kg
Full term	80 mL/kg—ICF:ECF::1/1	85 mL/kg
Premature	90 mL/kg—ICF:ECF::1:3.	90–100 mL/kg
4 years	60% of body weight—ICF:ECF::2:1	60–70 mL/kg
Adults	60% of body weight—ICF:ECF::2:1	60 mL/kg

lower in neonates and, more so in the preterm, goal being to maintain the higher Hct except in congenital heart disease, where Hct is kept low.

Two important Anesthetic Implications are relating to:

1. TBW, drug distribution, elimination, and duration of action, and
2. Increased losses and hypovolemia.
    1. Drug distribution, elimination, and duration of action
        (i) Higher TBW and proportion of ECF increase the apparent volume of distribution (Vd) of drugs.
        (ii) Increased Vd acts as a double-edged sword
            a. It will cause greater dilution of drugs given intravenously (induction agents, muscle relaxants, and narcotics), lower serum concentrations and possible inadequate effect, and
            b. Necessitating higher doses for the desired effect, with consequent prolonged duration of action and delayed recovery from anesthesia.
        (iii) Drug dosages administered as per body weight will result in lower plasma concentration, while dosages based on body surface area will result in higher serum concentration.
        (iv) But because of hypoproteinemia and hypoalbuminemia, there is reduced binding of drugs to albumin and α acid-glycoprotein and increased free drug concentration.
        (v) Enzyme systems are immature—poor drug metabolism, impaired renal excretion, and potential hypothermia further slow drug metabolism and excretion.
        (vi) Net effect—increase in elimination half-life, prolonged duration of action, and delayed recovery from anesthesia.

Caution—Care must be taken during drug administration, titrating to the desired effect.

Increased Losses and Risk of Hypovolemia

Larger BSA makes neonates prone to greater loss of water and at risk of developing hypovolemia. Their insensible fluid losses are high (65 mL/kg/day—20 mL by evaporation, 10 mL via GIT, 35 mL by kidneys). Factors that increase losses are as follows:

1. Larger BSA, and thin and less keratinized skin.
2. Higher metabolic (0.2 MJ/kg/day) and respiratory rates, with greater water turnover.
3. Greater ambient temperature and use of radiant warmers.
4. Use of dry inspired O_2 and gases during anesthesia and increased insensible losses.
5. Excretory system is immature at birth and is still in developing phase in the neonates. Glomerular and tubular functions are immature. They have
    (a) Reduced glomerular filtration rate (GFR) at birth. It doubles by second week and reaches adult values by 2 years of age.
    (b) Limited ability to concentrate urine.
    (c) Limited ability to excrete large water load.
    (d) Poor hormonal control—less effective renin–angiotensin mechanism, alpha natriuretic peptide, vasopressin, and catecholamine system.

Table 10.17 Fluid requirements in neonates

Age in days	Fluid requirement mL/kg/day
1	60
2	80
3	100
4	120
5–28	150

Table 10.18 Intraoperative fluid requirement

	Maintenance Fluid	Replacement Fluid
Term neonate	70–80 mL/kg/day	
Preterm neonate	100 mL/kg/day	
Minor loss surgery	4 mL/kg/h	2 mL/kg/h
Moderate loss surgery	4 mL/kg/h	4 mL/kg/day
Extensive loss surgery	4 mL/kg/h	6–8 mL/kg/day

Caution—Meticulous fluid therapy

Hence, neonates are more prone to dehydration and hypovolemia, water and solute overload, and acidosis.

Fluid requirement is high in the newborns and neonates, especially in the first few days of life (Table 10.17), and then remains stable at 150 mL/kg/day throughout the remaining neonatal period.

Intraoperative fluid therapy is provided as 5% or 10% dextrose (D5 or D10) in either Ringer lactate (RL) or normal saline (NS), or as isolyte P. Intraoperative requirement can be calculated as maintenance and replacement fluids. Since neonates requiring surgery are already on IV fluid therapy during fasting, deficit is usually not calculated. The fluid requirement as per the type of surgery is described in Table 10.18.

10.14 Hematopoiesis and Coagulation

10.14.1 Hematopoietic System

RBC production begins in the first week of gestation and proceeds through three phases: mesoblastic (yolk sac), hepatic, and myeloid (bone marrow). **Mesoblastic** (embryonic, primitive) red cells are extremely large, have a short life span, and are insensitive to erythropoietin. They do not mature into RBCs but can differentiate into other cell types. Fetal liver is the major store for iron and main erythropoietic site at midterm **(hepatic phase)**. After 24 weeks, major erythropoiesis shifts to the bone marrow **(myeloid phase)**, but by 36 weeks, bone marrow is the only site.

Three hormonal influences are **testosterone** (in first trimester), **beta-adrenergic activity** (10–13 weeks), and **erythropoietin** (in second trimester) [40, 44].

Hematopoietic system also undergoes transitional changes at birth, namely via circulation and oxygenation. At birth, bone marrow is fully active and only site for hemopoiesis. Postnatal extramedullary hematopoiesis is abnormal, except in premature neonates where a few foci may be seen in the liver, spleen, lymph nodes, or thymus.

10.14.2 Hemoglobin

Hemoglobin types—Abnormalities in embryonic hemoglobin (Hb ε) can lead to a delay in switching from Hb F to Hb A. **Hb F (α2 λ2)** has 2 alpha and 2 gamma globin chains and is the major Hb in fetal life. Synthesis of adult Hb (Hb A α2β2) starts at ninth week and by 21 weeks 14% of total Hb is Hb A. After 34 week, Hb A rises, while Hb F decreases, but even at birth, more than 60% is Hb F. It decreases to less than 2% by 6 months. The switch from Hb F to Hb A is genetically controlled and takes place in the liver. The Hb concentration fluctuates in the early weeks and months after birth and is affected by factors, such as: -

(a) Gestational age (GA) and birthweight (BW),
(b) Time of cord clamping,
(c) Hypoxic stress,
(d) Crying,
(e) Sampling site—Capillary vs venous (higher in capillary sample), warm vs cold limb,
(f) Race—African American—0.5 g% lower than white NN,
(g) Mode of delivery, and.
(h) Genetic defects—Trisomy 13.

The **average Hb** in term newborn is 18–20 g%. Nearly 60% is Hb F with high O_2 affinity, but high blood volume and CO compensate for the decreased release of O_2 from fetal Hb. Hb A levels are achieved by 6 months of age. In preterms, the proportion of Hb F is higher (70–80%) and total Hb is lower (13–15 g%), making them more prone to hypoxemia. By the age of 1 month, Hb decreases to about 14 g% and to 10 g% by 3 months.

Average **Hct** at birth is 55% (45–65%), and more than 65% is abnormal (hyperviscosity). Hct increases by 5% during the first 48 h of life. By 2–4 months, it falls to a mean of 40%.

The total **blood volume** is 85–90 mL/kg for term and 90–100 mL/kg for premature newborn. Adult value of 65 mL/kg is achieved by 4 months of age. Newborns have polycythemia (high RBC count) in the first 24 h due to in utero hypoxia, which triggers erythropoietin production and slowly declines after 2 weeks.

RBCs are macrocytic in the first week of life, whereafter they become normocytic normochromic. In term neonates, 43% RBCs are biconcave disks compared to 78% in adults, 3–5% being dysmorphic (fragments, target cells, distorted).

Table 10.19 Blood cell counts at birth and in neonates

	Newborn	1 Week	4 weeks
BW < 1200 g			
Hb g%	15–16	16–18	11–12
Platelets	1.5–1.6 L	1.5–1.6 L	1.3–1.4 L
TLC	13,000–15,000	12,000–13,000	13,000–14,000
BW 1200–1500 g			
Hb g %	20	18	12
Platelets	1.5 L	1.3–1.4 L	1.7–1.9 L
TLC	10,000–11,000	8000–9000	10,000–12,000
BW >2000–3500 g			
Hb g%	16–20	14–18	12–16 (14)
Hct	45–65 (55)	35–60 (45)	25–45 (40)
TLC	3500–6000	3500–5000	7000–10,000

Reticulocyte count at birth is high (4–6%) and falls to less than 1% by sixth day. Counts are higher and fall is slower in premature. **Leukocytes** (WBC) appear by ninth week and megakaryocytes (platelet precursors) by sixth week of gestation. **Platelet** counts range from 150–400 × 109/L, comparable to adult values. Thrombocytopenia (<100 × 10^9 platelets/L) is associated with birth trauma and high-risk neonates (sepsis, RDS). Normal Hb and cell counts are listed in Table 10.19.

10.14.3 Oxygen Dissociation Curve (ODC)

O2 affinity of Hb F is greater than that of Hb A. Levels of 2,3-DPG (diphosphoglycerate) are lower in newborn, HB F has lower affinity for 2–3 DPG, and ODC is shifted to the left. P50 of Hb F (mean PaO2 at which Hb is 50% saturated) is 19 mmHg compared to 26 mmHg of Hb A. Low P50 (and shift of ODC to left) means greater binding of O2 to Hb F. At PaO2 25 mm Hg, 80% O2 is bound to Hb F (Fig. 10.5). Thus, there is decreased O2 release at tissue level. As PaO2 falls <90 mm Hg, 3.0 mL of O2 is released in a newborn, while 4.5 mL is released in an adult, per 100 mL blood (because of higher affinity of Hb F for O2). Adverse effects of leftward shift of ODC in the neonate are offset by high Hb concentration, high Hct, and high cardiac output. Adult values are reached by the age of 1 year.

After birth, the ODC gradually shifts to the right, reaching adult curve morphology by 6 months. In a premature, 2–3 DPG levels are even less than in term neonates, and leftward shift of ODC is more pronounced, requiring greater fall in PaO2 to release equivalent amount of O2. After birth, the rightward shift is also slower. It is important for the neonatal anesthesiologists to be aware of and take special care during peri anesthetic management to avoid factors that may further shift ODC to left, such as hyperventilation, hypocarbia, hypothermia, and alkalosis.

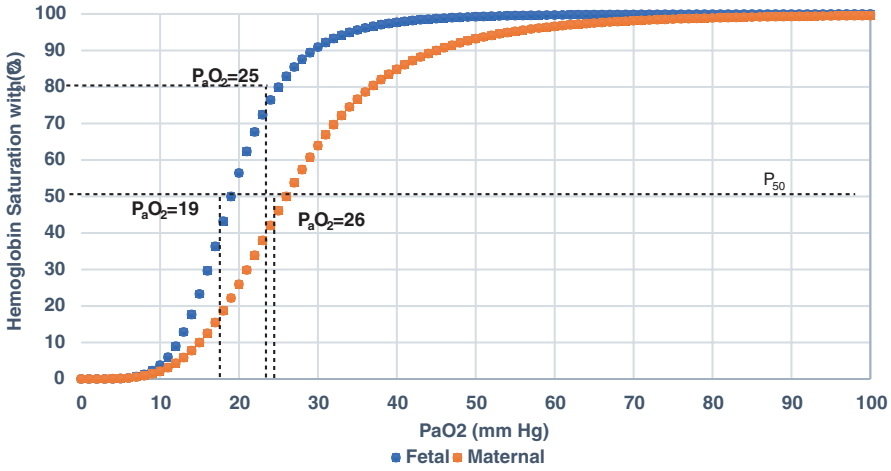

Fig. 10.5 ODC—Oxygen dissociation curve—showing maternal and fetal curves

10.14.4 Physiologic Anemia

Erythropoietin, the primary regulator of erythropoiesis, is present in cord blood and falls to undetectable levels after birth. RBC, Hb, and Hct values decrease slightly in first week, but more rapidly in the second month (physiological anemia) [40].

Causes of Physiological Anemia are:

(a) Changes at birth—increase in PaO2 and decrease in erythropoietin production,
(b) Decrease in Hb production and fall in hematocrit,
(c) Shorter life span of fetal RBC (60–70 days in term, 35–50 days in premature neonates), compared to 120 days in adults, and.
(d) Transmembrane potassium influx is significantly less in neonatal RBC and they are more sensitive to osmotic hemolysis and oxidant injury.

Anemia diagnosis in neonates is difficult because they cannot communicate their symptoms, and clinical signs are non-specific, as they are indicators of other medical conditions also, such as sepsis, apnea, seizures, and growth failure. Hb, Hct, and clinical condition is the only guideline for diagnosis. Hb of less than 13 g% and or Hct of less than 40% is diagnostic of anemia in a neonate.

Perioperative Care in Anemic Neonates –

1. Minimizing losses
   (a) Avoid repeated venous and arterial punctures
   (b) Avoid unnecessary bruising of the skin or hematomas

(c) Proper stabilization and dressing of indwelling catheters to avoid accidental disconnections or dislodgments.
(d) Closure of all injection and sampling ports
2. Reducing surgical blood losses,
3. Accurate assessment of blood losses
4. Replacement of losses—Preferably packed red blood cells (PRBC) should be used.
5. Whole blood transfusion is associated with risk of overhydration and early onset of massive blood transfusion problems.
6. Transfusion goal is to maintain high Hct (>45%), or up to 15 mL/kg of PRBC.
7. Rule of thumb—each 1 mL/kg body weight of PRBC transfused, expected rise in Hct is 1%. Hence, to reach the goal of 45% Hct in a newborn with pretransfusion Hb of 10 G% (Hct 30%), will need 15 mL of PRBC/kg. Hence calculate accurately and transfuse appropriately. PRBC has a Hct of 80–90%.
8. Transfuse PRBC Screened for viral pathogens (HIV, hepatitis B, and C, HTLV I/II, and CMV).
9. Extra care in babies who are anemic, congenital heart disease, major surgeries, marked acid-base disturbances, and premature.

10.14.5 Neonatal Homeostasis

Levels of most pro- and anticoagulant proteins are low in the fetus with prolonged PT, TT, APTT. **At birth,** the vitamin K-dependent coagulation factors (II, VII, IX, X) are low (30% of adult values) until 6 months of age. Factors XI and XII are 50% of adult values. Fibrinogen, factor VIII, and von Willebrand factors are normal. There is 30–40% deficiency of physiologic anticoagulants (protein C, protein S, antithrombin) at birth. Fibrinolytics (plasminogen and α2-antiplasmin) are same as in adults. Tissue plasminogen activator (TPa) are low and plasminogen activator inhibitor are increased. Healthy premature neonates over 30 weeks' gestation have slightly lower levels of coagulation factors and longer coagulation tests compared with term neonates. Neonates have a wide "normal" range and the physiological prolongation observed does not indicate a bleeding tendency/need to correct. Low levels of procoagulants are balanced with lower levels of inhibitors and lower activity of the fibrinolytic system.

Overall, there is no coagulation or bleeding problem in healthy term neonate. But in acutely sick or premature neonates, there is a risk of bleeding diathesis, in the form of pulmonary and intracranial hemorrhages, because of:

(a) Vit K-dependent factor deficiency is more and prolongation in PT, PTT, and aPTT.
(b) Thrombocytopenia is more, and.
(c) Increased capillary fragility and prolonged BT.

High risk and premature newborns must receive 3 doses of vitamin K, as a precaution, especially if these neonates are to undergo surgery.

10.14.6 Anesthetic implications

The aim is to minimize surgical and other blood loss, maintain Hct of 45%, maintain blood volume and CO, by early transfusion. Transfusion trigger is reached early. In neonates with CHD, lower Hct is targeted (35–40%) [45]. Avoidance of hyperventilation, hypothermia, and alkalosis is of paramount significance. Surgical neonates and preterms are at greater risk of bleeding due to low levels of procoagulants and need routine administration of Vit K.

10.15 Neuromuscular System

In the embryonic life, the muscle spindle, NM endplate (NM junction—NMJ), and neural development all complement and facilitate each other, and development occurs as follows:

- 8 weeks—acetylcholine (ACh) receptors appear over the muscle fibers.
- 9–16 weeks—primitive motor-end plates appear.
- 16–24 weeks—transition from polyneuronal to mononeuronal innervation takes place, and
- 24–31 weeks—NMJ matures,
- Growth continues until 1 year postnatal age.

Earlier to 36 weeks of gestation, the fetus is in a state of hypotonia. As maturation progresses, the fetus assumes passive flexor tone which develops in a centripetal direction, i.e., lower limbs earlier than upper limbs, such that, at term the baby is in a flexed posture, while a preterm newborn is in an extended posture. With improving tone, the wrists, hips, and knee joints become more flexible and resistant to extensor stretch.

To assess the maturation of the NM system at birth, Philadelphia Children's Hospital, formulated a method using six evaluations during physical assessment. A score is assigned to each assessment, and all are totalled. Higher score indicates more neurologically maturity. Scores are very low in premature babies. The areas of assessment include **posture** (how does the baby hold his or her arms and legs), **square window** (how far the baby's hands can be flexed toward the wrist. In term baby, the wrists make an acuter angle to the forearm, compared to more flattening in preterm), **arm recoil** (how much the baby's arms "spring back" to a flexed position), and **popliteal angle** (how far the baby's knees extend following gentle extension of the leg and release. Resistance to extension lacks in the preterm newborn, with more obtuse popliteal angle), **scarf sign** (how far the elbows can be moved across the baby's chest), and **heel to ear** (how close the baby's feet can be moved to the ears). By adding the physical assessment and NM scores, one can estimate the gestational age of the baby.

10.15.1 NM Transmission

Two molecules of ACh combine, opening the central pore on the NM end plate, allowing sodium (Na) ions to enter. In the fetus, the pore open time is longer, allowing more Na to enter, thereby generate a larger action potential. This is evident as increased sensitivity to ACh and resistance to d tubocurarine in the newborn baby. There is deficiency of NM transmitters, but increased receptor sensitivity to ACh compensates for this deficiency in the immature nerve endings and facilitates spontaneous fetal movements essential for normal NM development [46, 47].

Fetal receptors are not seen after 31 weeks of gestation, but they may reappear in pathological states with prolonged inactivity (e.g., burns, denervation injury, and prolonged muscle paralysis) at extra junctional sites later in life, with the typical response (hypersensitivity to scoline and resistance to NDMR). Maturation of the myotubules into mature muscle fibers continues for several weeks after birth. Diaphragm and intercostal muscles mature from the initial slow contracting to rapid contracting muscles, with increased force of contraction.

NM transmission is immature at birth. There is less available ACh and increase in sensitivity to NDMR. Maturation of the muscle spindle, NMJ, and NM transmission is slower and delayed in preterm and low birth weight babies.

10.15.2 Features of NM Transmission (NMT) in Neonates

1. Newborns have less NM reserve (less Ach), and muscles are resistant to decamethonium (depolarizing drug), producing nondepolarizing or dual block like features (PTF, improvement after neostigmine).
2. They behave like myasthenics. **Neonatal myasthenia gravis** is a transient disease, due to inherited failure of development of motor-end plates. Clinical implication is that if a baby, after single dose of scoline, does not breathe adequately after a long surgery, reversal with anticholinesterase can improve recovery from dual block.
3. Tetanic stimulation at 50 Hz is poorly tolerated, and following a tetanic stimulation of 15–20 s, there is no fade in twitch height at 1–2 Hz, but significant fade at 20 Hz.
4. In premature newborns, duration of post-tetanic exhaustion (PTE) is longer (15–20 min).
5. Train of four (TOF), degree of PTF (post-tetanic facilitation), and tetanus twitch (TT) ratio improve with age.
6. High CO and faster circulation allow rapid transfer of NM blocking drugs, to and away from the NMJ (faster onset and faster wash out).
7. Larger ECF fraction increases the volume of distribution and dose requirement.

Clinical Implications—Neonates behave like Myasthenics up to 10 days of life (sensitive NDMR and resistant to DMR) [48–50].

10.15.3 Depolarizing Block and Muscle Relaxants (DMR)

Succinyl choline is the only depolarizing drug approved for clinical use. Newborns are resistant to DMR, arising from the fact that

- They have higher ECF volume and greater volume of distribution,
- Immature NMJ,
- Less Ach stores and less release on stimulation,
- Deficiency of pseudocholinesterase (50% of adult concentration), and
- Persistence of fetal-like NM transmission or desensitization of the motor-end plate.

Features of Depolarizing Block (Scoline) in Neonates

- Rapid onset of action and short duration (6–8 min),
  - Elimination by enzyme hydrolysis (butyrylcholinesterase or pseudocholinesterase),
  - Vagal preponderance and increased risk of bradycardia and arrythmias, especially with second dose. Premedication with atropine (0.1 mg, IV) is advised,
  - No fasciculations or increase in potassium (K) and intragastric pressure (IGP),
  - Rise in intraocular pressure (IOP),
  - They tolerate higher doses (3–4 mg/kg), or 5 mg/kg IM (on body weight basis, calculated dose is higher, but on basis of BSA, the dose is same as in adults),
  - Scoline infusion—Tachyphylaxis occurs before phase 2 block.
  - Phase 2 block is seen with higher dose (4.1 mg/kg) during halothane N2O narcotic anesthesia.

Side effects and disadvantages of DMR are profound bradycardia and arrhythmia, phase 2 block, myoglobinuria, malignant hyperthermia (especially with halothane induction), pulmonary edema, and pulmonary hemorrhage.

10.15.4 Nondepolarizing Block and Drugs (NMB/NDMR)

Increased sensitivity of NMJ to NDMR is due to reduced release of ACh from immature motor nerves. Most studies are using tubocurarine (dTc), but the inferences can be applied to other NDMR keeping each drug's unique properties in mind (authors experience).

10.15.5 Features of NMB in Newborns

- Increased sensitivity to NDMR hence there is need to reduce the dose.
- But because of higher ECF volume and greater volume of distribution—no change in initial loading dose.
- The interval between repeat doses is longer.

- Respiratory depression and NM block both occur at the same time, unlike in adults, where block precedes RESPIRATORY DEPRESSION.
- Mean dTc dose to produce 95% twitch depression, and time to 75% or 50% recovery is same in neonates, children, and adults.
- Reduction in the dose in premature babies, acidosis, hypothermia, concurrent antibiotic therapy, and high concentration of anesthetic drugs in tissues.

NDMR drugs, besides causing muscle relaxation, have other actions that must be kept in mind when evaluating these babies -

(i) Histamine release (e.g., tubocurarine, atracurium, and some with pancuronium),
(ii) Vagolytic effect and tachycardia (e.g., with gallamine),
(iii) Risk of bradycardia during intubation in unpremedicated neonates.

Ganglion blocking action and hypotension (d tubocurarine) [50].

Fortified with the knowledge of the effects and side effects of various NM blocking drugs, one can safely use them in neonates, if due precautions are taken regarding the dosages, interval between two doses, avoidance of possible factors which may delay recovery by prolonging their action and having facilities for monitoring and ventilation.

10.15.6 Advantages of Using Muscle Relaxants in Neonates

1. Effective control of ventilation.
2. Relaxed patient for surgical facilitation—a good surgical field.
3. Decreasing the dose of toxic anesthetic agents because in neonates,
4. Availability of a reversal drug.

Vecuronium, Rocuronium, Atracurium, and cisatracurium are safe in all newborns and neonates including premature, low birthweight, and small-for-gestational age babies.

Rate of recovery of NM transmission is slower in neonates compared to in adults.

Elimination rate constant (Kappa) is comparable in infants and children, 0.41/min, 0.38/min respectively, and 0.15–0.17/min in adults.

10.15.7 Antagonism of NM Blocking Drugs

Residual block following NDMR administration should be antagonized by an anticholinesterase. This is especially important in neonates and small infants because of their reduced respiratory reserve. Commonly used anticholinesterases are neostigmine and edrophonium. When administering the reversal drugs, points to be remembered are

- Recovery after edrophonium is significantly faster than after neostigmine.
- Doubling the doses of the antagonists has no significant effect or benefit on recovery.

- Recovery after either antagonist is significantly faster in children than adults.
- Reversal dose in neonates—Atropine 0.03 mg/kg + 0.07 mg/kg neostigmine, or glycopyrrolate 0.01 mg//kg + 0.2 mg/kg pyridostigmine.

10.15.8 Recovery

Adequacy of reversal prior to deciding the extubate are presence of good muscle tone, ability to flex arms legs, ability to sustain tetanus at 50 Hz, and ability to produce inspiratory force of >25 cm H_2O.

Delayed recovery from general anesthesia can be due to several factors, but one most important is **prolongation of NM block.** Premature, LBW, and SGA neonates are more prone to delayed recovery. Causes of delayed recovery from prolongation of NM block are hypothermia, hypotension, acidosis, hypocalcemia, and concurrent use of antibiotics.

10.16 Pharmacology of Drugs in Neonates

Total body water (TBW) in term newborn is almost 75% of body weight and >80% in preterm newborn, with almost 60% in the ECF compartment. Total blood volume is 85 mL/kg and 90–100 mL/kg in a premature newborn. All water-soluble drugs on IV administration get distributed into the ECF volume, the volume of distribution (Vd), and this determines the effective plasma drug concentration.

Fluid requirement increases over the initial days after birth (60, 80, 100,120 mL/kg/day at day 1, 2, 3, and 4, respectively) and then remains at 150 mL/kg/day till throughout the neonatal period.

All drugs undergo metabolism and excretion by the hepatobiliary-renal and respiratory pathways. Hepatorenal function is immature at birth, and respiratory system is still undergoing changes as a part of the adaptation process. Preterm neonates bear greatest brunt of these changes. Complete maturation and normalization of the functions do not occur until the age of 1–2 years. Iso-enzymes P 450 is present at term, but even at 44 weeks, it is still 85% of adult values.

The important p**harmacokinetic variables** in neonates are volume of distribution, renal clearance, and body weight. Vd is important in relation to initial loading doses and clearance determines maintenance dosing and drug infusion rates. These parameters determine the shape of the time-concentration curve and duration of action. Body weight is usually used to calculate drug dosages in all patients including neonates.

10.16.1 Clinical Implications of Altered Pharmacokinetics in the Neonate

(i) Excess ECF volume results in higher Vd of drugs, their dilution, and hence adequacy of effect. **Thus, the initial dose of drugs needs to be higher.**

(ii) Hypoproteinemia, hypoalbuminemia, and low α-1 glycoproteins, from immature hepatic production, lead to reduced drug binding, with increased free drug concentration, risk of adverse drug effects. **Thus, the dose of the drugs needs to be reduced.**
(iii) Most anesthetic drugs are metabolized in the liver. Neonatal hepatic enzyme system, metabolism, and conjugation are immature. **This leads to prolonged effect of drugs.**
(iv) At birth, renal blood flow (RBF) is only 5% of cardiac output (CO) and increases to 20% by 1 month of age. Adult value of 25% is reached by the age of 2 years. Both GFR and tubular reabsorption are immature, leading to slow excretion of drugs, prolonged duration of action, requiring **reduction in drug dosing. In a term newborn, GFR is 35% of mature values (10% at 25 weeks GA), and even at 1 year of age, it is 90% only.** This has implications for drugs chiefly eliminated via renal route, such as aminoglycosides.
(v) Degree of maturation of lung function (alveolar ventilation, FRC, cardiac output, and blood/gas solubility) determines absorption and elimination of inhaled anesthetic agents (IAA).
(vi) Hypothermia and hypovolemia compound the hepatic and renal effects, by further affecting drug metabolism and excretion.
(vii) Their BSA to weight ratio is higher than in children and adults. Drugs doses as per body weight may have less than the desired effect.

Taking all above factors into consideration, drugs should be ideally given based on BSA. Commonly drug doses are calculated based on body weight and most often do not require any change in dosing. Special care to be taken is to avoid repeating drugs based on fixed duration or time interval. Continuous monitoring for the waning of the effect and then supplementing will be more prudent, especially for drugs that are repeated during anesthesia, such as muscle relaxants and narcotic analgesics.

10.16.2 Pharmacodynamics

The drug effect on the organs is not merely affected by the absolute dose but also on the gestational age at birth, organ function, and hepato-renal-pulmonary maturation. Effect of anesthetic drugs on the CNS depends on the permeability of BBB and on the brain sensitivity which is a function of its maturation, a function of GA and body weight. Effect on NMJ (neuromuscular junction) and cell membrane is also a function of GA and body weight or size.

Besides, the impact of the surgical condition and critical illness on the already compromised hepato-renal-pulmonary function, thereby on hepatic metabolism, renal clearance, drug effect, and duration of action, in the neonate cannot be ignored.

10.16.3 Inhaled Anesthetic Agents (IAA)

High BMR necessitates high alveolar ventilation, with consequent higher uptake of IAA in neonates as compared to children and adults. High CO also contributes to higher uptake of IAA by the vessel-rich groups, such as brain. They have a greater myocardial depression as compared to adults.

10.16.4 Minimum Alveolar Concentration (MAC)

Minimum alveolar concentration (MAC) or anesthetic vapor potency is low at birth and peaks by 1 month to 6 months age before it decreases to adult values by adolescence. However, MAC of sevoflurane is same in all age groups (3.2%) and is considered safest in neonates and preterms. Safety of IAA may get compromised by the increase in uptake by high alveolar and minute ventilation, as in mechanical or controlled ventilation during surgery, and high CO. This problem was more with the older agents (halothane).

10.16.5 Intravenous Agents (IVA)

Intravenous agents (IVA) are a significant part of modern anesthesia practice in neonates, but requires IV access. This usually does not pose much problem for the anesthetist as most surgical neonates have an already established IV line in situ. There are little data regarding dose-response relationship of drugs in neonates, and whatever knowledge we have is an extrapolation from our experience in adults.

As already stated, neonates have reduced serum proteins, which lead to higher concentration of free (unbound) drug, immature hepatic metabolism, and low renal clearance, that mandate increase in the interval between doses of drugs repeated during anesthesia, e.g., muscle relaxants, and during TIVA.

(a) **Narcotics** are more frequently used in NICU and their pharmacology and side effects are better understood. Morphine, a potent analgesic, is associated with hypotension, prolonged duration of action because of reduced hepatic metabolism and conjugation, and long elimination half-life due to low renal clearance. Morphine went into disfavor with introduction of fentanyl, which is lipophilic, binds to μ receptors with plasma brain equilibration time of 1.5 min, minimum CVS effects, shorter duration of action (terminal elimination—3.1–6.6 h), better safety, and recovery profile. Suppression of stress and reflex responses during laryngoscopy, intubation, and surgery requires higher doses of narcotics. Fentanyl, with its safety profile, suited aptly and with improved outcome too.

(b) **Barbiturates (Thiopentone)** is a time-tested drug used in adults and neonates for more than half century. It is more lipid soluble and gets redistributed into the peripheral lipid stores. Because of higher Vd, induction dose is higher than in adults (4–6 mg/kg). It can be safely used in newborns, neonates, and premature. However, several precautions must be taken when administering thiopentone in neonates, as: a. always use large vein for administration, b. always inject slowly under direct vision because of risk of extravasation, c. in case extravasation occurs, immediately stop and flush with saline, d. use 1.25–2.5% concentration, and e. risk of intra-arterial injection, hence utmost care.

(c) **Propofol** is widely used for induction and tracheal intubation in older children and adults. There is not much literature of its use and safety in neonates, especially newborns and preterm babies, but anesthetist have used it for induction in this very age group. Common unwanted effect reported is hypotension, especially in the critically ill neonate. Its delayed redistribution and clearance lead to prolonged action in neonates as compared to in adults. Chief advantage of propofol is its use as a continuous infusion for sedation, with cessation of action within minutes of stoppage, and no cumulation. Long-term propofol infusion (for hours to days) as in NICU has been associated with metabolic acidosis, organ failure, even death in children and neonates. This warrants careful dosing and duration of infusion in children, and **prohibition of its long-term use in newborns and neonates**. Table 10.20 summarizes the pharmacology of common anesthetic drugs in neonates.

(d) **Neuromuscular blockers (NMB)—**Use of NMB is the mainstay of surgical anesthesia in neonates, to facilitate tracheal intubation and to allow an ideal surgical field. **Neonatal myoneural junction is immature and behaves like myasthenics, i.e., resistant to DMR and sensitive to NDMR.**

Depolarizing NMB **(succinylcholine)** has a rapid onset and short duration of action and provides ideal conditions for laryngoscopy and intubation. It is metabolized by pseudocholinesterase in the plasma. Neonates have 50% concentration of pseudocholinesterase. Being water soluble, scoline has high Vd, and along with the resistance of myoneural junction, higher dose is required for intubation (up to 4 mg/kg), twice as in adults. Despite the large dose, its duration of action is not prolonged because of its rapid clearance. Scoline, like acetylcholine, has parasympathetic effect, and in neonates, with parasympathetic predominance, causes bradycardia. Bradycardia is more severe in combination with halothane induction and can be prevented by pretreatment with anticholinergics (atropine or glycopyrrolate). In modern practice, scoline is reserved for emergency and difficult intubation in neonates.

Non-depolarizing neuromuscular relaxants (NDMR) are more variable in their response in neonates. Being water soluble, they also have a high Vd, decreased hepatic metabolism and renal clearance. Neonatal myoneural junction is more sensitive to NDMR.

Pancuronium has vagolytic property; however, its use was limited by its prolonged duration of action in neonates. **Vecuronium** has no vagolytic property but has shorter duration. **Rocuronium,** also lacking vagolytic action, is the preferred

Table 10.20 Pharmacokinetics/pharmacology of drugs in neonates

	NN Physiology	Effect/Care
General principles	Varied Vd—↑ ECF volume, ↑Vd Hypoalbuminemia -↓Protein binding Poor peripheral Circulation ↑ free drug Conc Bilirubin displacement by drugs Immature BBB, risk of kernicterus ↓ Hepatic metabolism, oxidation, conjugation ↓Renal clearance -↓GFR, ↓tubular function	Wide variation in response ↑ dose of H2O soluble drugs (muscle relaxants) Avoid sulfonamides, salicylates Doses as per BSA esp. in first 7 days ↑ Duration of action—narcotics, theophylline, diazepam, phenytoin Delayed recovery from anesthesia
IVA	Thiopentone -↑sensitivity, safe, dose 4–6 mg/kg (1.25–2.5%) Propofol—safety??? Etomidate—no reports of use Ketamine -↑O2 consumption & ICP, NDMA receptors absent in neonates—AVOID Diazepam—venous thrombosis, long duration of action—AVOID Midazolam—safe Methohexitone 1% -1.5 mg/kg, fast induction/recovery, muscle movements, pain, respiratory depression Propanidid—anaphylactoid reaction, hypotension, cyanosis, cardiac arrest—AVOID	
IAA	↓MAC at birth—↑ MAC after 1 week ↑ BMR—↑Alveolar ventilation, Rapid Uptake & Washout—rapid induction & recovery Halothane -↑CBF/ICP, laryngospasm, hypotension, no hepatic failure despite repeated use Methoxyflurane—good analgesia, no renal toxicity, less laryngospasm Enflurane—rapid induction, respiratory irritant and depression, excitatory Isoflurane—Respiratory irritant, involuntary movements (not for induction) **sevoflurane, desflurane safe**	
Opioids	Morphine—↑sensitivity—AVOID in premature Pentazocine −0.5 mg/kg IV—risk of seizures/bronchospasm—AVOID Neurolept analgesia—no role Fentanyl—safe—lipophilic, Sufentanyl, remifentanil—safe Naloxone—keep available, dose 0.01 mg/kg	

drug because of its relative shorter duration of action. **Atracurium** that does not rely on hepatic metabolism or renal excretion is safe in all neonates. **Cis-atracurium** can produce severe hypotension and allergic reactions because of histamine release and should be avoided or used with caution.

However, in combination with IAA and narcotics, their duration of action may remain longer than 60 min in most neonates. Yet, it is beneficial to use NDMR for a good surgical field and also because the effect can be reversed using neostigmine and glycopyrrolate or atropine.

Recovery from anesthesia—The same pharmacological principles that prolong duration of action of anesthetic drugs, also are responsible for delay in recovery after surgery and anesthesia; premature, small for date, and IUGR neonates being more prone, especially for narcotics, theophylline, diazepam, and phenytoin

Other factors contributing to delayed recovery are hypothermia, hypotension, dehydration, shock-like state, acidosis, dyselectrolytemia, hypocalcemia, antibiotics (esp. aminoglycosides), combination of IAA and morphine, poor hepato-renal function, and over dosing.

10.17 Pain Pathways and Development

Pain is a sensation. It is a protective mechanism and is defined **as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage."** Half a century ago, it was believed that neonates, especially newborn and premature babies, did not feel pain, and general anesthesia for surgery in them did not include pain management. Even as late as the 90s, pain management was not always adopted by physicians, but research has proved otherwise, that a baby also feels pain after birth. Prevention of pain is important because of its potential adverse effects on the immature baby and the developing brain [51–56].

10.17.1 Reasons for Poor Pain Management in Neonates

1. Ignorance and belief that neonates do not feel pain!
2. Wrong notion that response to pain is not as much as in adults!!
3. Inadequate knowledge about drugs, their doses, effects, side effects, and safety profile.
4. Difficult to assess pain and its intensity. Crying is the only emotion in these babies whether for Hunger, Cold, Unfamiliar Faces and Surroundings, and PAIN)!
5. Basal heart rate is high (120–160/min). Tachycardia is not a reliable indicator of pain. It can be because of other factors, like effect of the surgical pathology, metabolic, biochemical, acid base and hormonal changes, and effect of anesthesia and drugs administered, anemia, and fluid and blood loss, and underlying congenital diseases.

Hence neonatal anesthesiologists must have sufficient knowledge of the basic etiopathogenesis of pain if they must prevent long-term adverse effects of pain during surgery. Some knowledge of development of pain pathways is also important as they will be faced with the challenge of anesthesia in the preterm babies too.

10.17.2 Development of Pain Pathways

By late gestation, the fetus has all the anatomic, physiological, and metabolic components for pain perception. Pain receptors are present at 20 weeks and pain pathways by 25th week. Preterm and term infants demonstrate similar or even exaggerated responses to pain. In the fetus and newborn, most fibers are unmyelinated, and nerve transmission is slower than with myelinated fibers. The threshold to

stimulation is lower and threshold for sensitization is decreased. Each trauma increases the area of sensitization and is accompanied with structural and chemical changes. The pain pathways are same as in adults:

(i) **Ascending pathway** (Afferent) sends impulses from the peripheral nociceptors in the skin, muscle, and joints via spinothalamic tract in the dorsal root ganglia, to thalamus, hypothalamus, and brainstem.

(ii) **Descending pathway** (Efferent) modulate the response to pain (sympathetic responses and withdrawal).

Density of cutaneous nerve endings is similar or even more than in adults and exposure to prolonged or severe pain may increase neonatal morbidity [56–58].

10.17.3 Anesthetic Implications

1. Even in the intrauterine period, the fetus has the capacity to sense pain and stress and responds accordingly—**fetal distress.** This led to the concept of fetal pain management during fetal surgery [57, 59].
2. **Cutaneous receptors** respond to a stimulus, be it pain, touch or tactile (handling), and temperature.
3. The **effect of pain** may be more profound and more detrimental.
4. Because of the **immaturity of the pathways,** the endogenous response (modulation) to noxious stimulus is erratic.

10.17.4 Pain Assessment in Neonates

Since babies cannot communicate, one must rely on other **indicators** of pain:

1. **Behavioral (specific distress behavior)**—Crying, facial grimaces, rigidity, changes in sleep pattern, and inconsolability.
2. **Physiological**—heart rate, saturation, respiration (rate, pattern), vagal tone, plasma cortisol or catecholamine levels.
3. **Objective indicators or scales—PIPP, CRIES, and NIPS.**
   (a) **Premature Infant Pain Profile (PIPP)**—facial actions—brow bulge, eyes squeezed shut, nasolabial furrow, and physiological indicators—heart rate, and saturation [60, 61].
   (b) **CRIES—C**rying, **R**equirement for O2 (for $Sao_2 > 95\%$), **I**ncrease in heart rate and blood pressure, facial **E**xpression and **S**leeplessness [62].
   (c) **Neonatal Infant Pain Scale (NIPS)—**facial expression, cry, breathing pattern, limb movements, and state of arousal [63, 64].

   Utility of these scales in a neonate under anesthesia (paralyzed, and with analgesia) is limited. However, CRIES physiological scale may reasonably assess pain in this situation.

   Note—A lack of behavioral responses does not indicate a lack of pain.

10.17.5 Clinical Implications During Anesthesia

- All newborns and neonates including premature babies feel pain, like children and adults.
- Surgery is a highly stressful procedure, with major physiological, hormonal, biochemical, and metabolic changes.
- In a developing baby, with added immaturity, pain and stress may affect development and have long-term adverse consequences, unforeseen.
- However, in view of the immaturity of all organ systems, care and precision in type of analgesic used, dosing, and intervals in between repeat doses, must be exercised and tailored to suit each baby depending on the gestational age and pathophysiological status.
- Only essential surgery must be undertaken to avoid adverse effects of drugs.
- Most worrisome adverse effects are on the CNS in the form of memory, and learning deficits.
- Alternative methods of pain management with fewer CNS implications can be used.
- Neonates who have experienced pain during the neonatal period respond differently to subsequent painful events [64, 65].
- Providing analgesia is not only Humane but also decreases morbidity and mortality.
- Not providing pain relief is UNETHICAL and INHUMAN.

10.18 Intestinal Physiology and Feeding

Minimal daily calorie requirement in a neonate is 100 kcal/kg/day. This need is met with by the oral nutrition in the form of breast milk feeds. The capacity of the stomach is small and each feed is of a small volume. Hence, to meet their energy requirement, they need to be fed at more frequent intervals (every 2–4 h in newborns). Larger feeds are associated with the increased risk of regurgitation and aspiration. Formula milk supplementation at very early stage is not advised because of the risk of GI problems (NEC, Sepsis) from hyperosmolarity and bulk, especially in the premature and LBW neonates. Feeding-related problems in the neonate arise from -

1. Weak muscles and poor sucking,
2. Poor swallowing reflex,
3. Early exhaustion,
4. Small gastric capacity,
5. Poorly developed cardiac sphincter and increased risk of regurgitation, and
6. Large hypertonic feeds that increase the risk of necrotizing enterocolitis (NEC)

Parenteral Feeds

Supplemental parenteral feeds must be begun in LBW babies, especially those weighing <1500 g, because these babies have the problems related to feeding, as described above. A suggested method is to start parenteral feeds and continue for

first 48 h, followed by addition of enteral feeds @ 60 mL/kg/day, and increased by 10 mL/kg/day to 100–200 mL/kg/day by 10 days, with simultaneous decrease in the quantity or prolonging the in-between interval of parenteral feeds. The goal is that by 10 days the baby should be able to take adequate enteral feeds.

The **intestine physiology** in a neonate is a complex process. It regulates the absorption of essential nutrients for growth and development. Maintenance of normal electrolyte, enzyme, and hormonal homeostasis is essential for adequate intestinal performance. GI diseases, and length and anatomic location of the resected bowel have great physiological impact after intestinal surgery. It can lead to failure of growth and development in the neonate with adverse long-term consequences [66]. When enteral nutrition or intake becomes compromised, parenteral route remains the mainstay of supplying the neonate with nutrition.

10.19 Immune System

The immune system, the network of cells, and proteins that provide defense against infections are immature in the fetus. The hematopoietic progenitor cells are the precursors of the immune system. Early in the embryonic stage, these cells divide rapidly, but with increasing gestational age the speed decreases and specialization increase. Premature newborns have more of the unspecialized progenitor cells than a term newborn. The progenitor cells travel via the blood stream to the three immune organs, liver, spleen, and thymus. By the 13th week, thymus starts producing T cells, though they do not much role in the sterile intrauterine environment. Macrophages appear in the fetal intestines by 12th week and increase rapidly up to 20th week, and B and T cells in the intestine organize into lymph nodes, the Peyer's patches.

Maternal antibodies provide defense from infections in the IU life. IgG can cross the placental barrier unlike Ig M antibodies, and fetus is less prone to infections unless there is a breach in the placental barrier.

1. **Immunity at birth (Innate Immunity)**—At birth, the immune system is still immature, and mature by 3 months of age, making the newborn more vulnerable to infections (ß streptococci, staphylococci, klebsiella, H influenza(b), meningococci, and pneumococci). Neutrophils, the first responders, are limited in quantity and cannot keep pace with overwhelming infections. Their number increases by 2–3 months of age. Newborn baby has three types of immunities:
   (a) **Passive immunity**—is temporary and starts to decrease after the first few months of life, allowing time for baby's immune system to develop.
   (b) **Via the placenta**—IgG antibodies start to cross the placenta by 13th week, but most antibodies cross during the third trimester. Because of this late transfer, premature babies have lower levels of antibodies and are more susceptible to infections than term newborns. At times, these antibodies are directed against the fetal RBC proteins, resulting in anemia and jaundice in the newborn.
   (c) **Via breast milk**—The thick yellowish milk (colostrum) produced in the first few days following birth is particularly rich in antibodies, and breastfed

babies have a longer lasting and robust immune system. Breastmilk delivers IgA antibodies (90%), macrophages, and cytokines. IgA antibodies protect intestinal mucosa from gastrointestinal viruses.

2. **Adaptive immunity at birth**

Exposure to any pathogen after birth is a new experience for the newborn and requires specific immune responses. The body responses are slow and B and T cells take longer to develop. Factors that help increase adaptive immunity are skin-to-skin contact (baby is exposed to microorganisms), sleep time (adequate sleep time routine enhances immune development), breastmilk, and vaccination at birth.

10.20 VII. Ophthalmic Effects

Immaturity of the central nervous system also contributes to the development of retinopathy of the premature (ROP). The ophthalmic vessels in the newborn baby have immature musculature and immature vasomotor tone and are extremely sensitive to hyperoxia. They respond to hypoxia and hyperoxia by severe vasospasm, retinal ischemia, and neovascularization at the junction of vascular and avascular zones. This leads to retinal scarring, fibrosis, retinal detachment, ROP, and blindness.

Retinopathy and fibrosis are predominantly seen in premature (<32 weeks gestation) and LBW (<1500 g) newborns. These babies often have low PaO2 and respiratory problems, necessitating O2 therapy with high FiO2, mechanical ventilation, and NICU stay that exposes them to the occurrence of retrolental fibroplasia (RLF) and ROP. Because of the risk of blindness, timely preventive measures must be adopted.

Hyperoxia induces a fall in enzyme superoxide dismutase, which protects against toxic effects of O2 radicals. Tocopherol/vitamin E pretreatment can partially prevent this decrease (Kittens) [67]. O2 induced vasospasm can be prevented by pretreatment with aspirin, which blocks synthesis of prostaglandins, so that retinal damage occurs only where there is inadequate vasomotor tone to protect the immature vessels. Retinal scarring may even occur without exposure to supplemental O2, possibly due to increased blood flow and raised transluminal pressure in the developing retinal vasculature (Beagles) [68].

Anesthesia concerns—During anesthesia management, especially premature, LBW, and with respiratory problems, presenting for surgery under anesthesia, extreme caution must be exerted, like

- Use of minimal FiO2 to maintain target saturation (89–92%),
- Monitoring of preductal SpO2 (ear lobe, upper limb), that reflects retinal perfusion, and postductal SpO2 (lower limb) for effect of PDA, and shunt reversal, and
- Early weaning off O2.

Infants suffering from ROP frequently require anesthetics for ocular examination and potential laser treatment for retinal hemorrhage and RD. While the etiology of

ROP is likely multifactorial, O2 toxicity (perhaps from short-term exposure during brief surgical procedures, and PaO2 >80 mmHg) may be a contributing factor.

10.21 Skin Physiology and Adaptations After Birth

Fetus lies in a bag of fluid, amniotic fluid, throughout the intrauterine period. Whole body is covered with lanugo hairs, denser on face, limbs and trunk, which is shed just before term, at 36–37 weeks of gestation. Babies born before 36 weeks' gestation still have lanugo hair covering.

A term newborn's skin is covered with Vernix Caseosa, formed after shedding of lanugo hair. It is a greasy, grayish white covering of sebaceous secretions, and decomposed epidermis. It is a natural protectant and falls off after birth. Physiological cutaneous change is observed in 100% neonates and number of lesions is more in preterms.

The body surface area-to-weight ratio (BSA:BW) is 5 times as in adults, still higher in preterms, which makes them more prone to heat and water loss, hypothermia, dehydration, electrolyte imbalance, and infections. On exposure to outside dry environment, the skin loses its moisture, becomes dry, is less acidic, nearing neutral pH. It undergoes structural and functional adaptations (moisture retention, acidification) during the first 2 weeks of life until 1 year age.

The skin of a term baby is well developed and thicker and that of a preterm baby is very thin and functionally immature. A post-term newborn skin is thin, wrinkled and has less subcutaneous fat [69, 70].

10.21.1 Functions of the Newborn Skin

Functions of the newborn skin include heat and moisture conservation, protection from light, UV radiations, and trauma, immune barrier and protection from infections, and for tactile sensation essential for baby's growth and bonding.

Premature and VLBW babies are at greater risk of skin damage as their skin is more permeable and deficient in protein and fat. Total epidermal water loss is higher compared to term newborns being 45 g/m^2/h at 26 weeks, 17 g/m^2/h at 29 weeks, and 4-6 g/m^2/h at term.

10.21.2 Physiologic Changes

Newborn skin is subject to cutaneous lesions, more in preterms. **Acrocyanosis** (peripheral cyanosis—palms, soles, around the mouth), no central cyanosis (pink tongue) is present in almost all babies at birth. Some of these are as follows:

1. **Cutis marmorata 5%**—is a bluish mottling over the trunk and extremities. It is a normal response to hypothermia and disappears on rewarming.

2. **Harlequin Color Change**—is deep red coloring on the dependent part of the body while non-dependent part is pale. This is due to poor control vasomotor control and central hypothalamic immaturity, and seen more often in premature babies.
3. **Exfoliation/Physiological scaling 21%**—occurs around the ankles and disappears within a week.
4. **Acne Neonatorum 4.5%**—is benign and self-limiting, seen only in the neonatal period.
5. **Mongolian Spots** (congenital melanocytosis) 56%—are blue–black macular self-resolving lesions over the lumbosacral area, in Asian, black, and Hispanic newborns.
6. **Erythema toxicum Neonatorum 17%**—is blotchy macular rash, over front of the chest, face and limbs, and usually fades away within 1–2 weeks.
7. Sebaceous hyperplasia (6%), Epstein pearl (5%).

10.21.3 Clinical Applications—Care and Precautions During Anesthesia and Clinical Care

Newborn skin being thin and delicate and is prone to various insults and requires care:
1. **Thermal injury/burns**, from being kept in overheated incubators or under radiant heaters or heat blowers or improperly applied cautery plate during surgery,
2. **Dehydration**, from high environmental temperature and increased evaporative water loss from the vasodilated skin,
3. **Chemical burns**, from application of strong cleansing agents and antiseptic solutions. Both alkaline and strongly acidic solutions are harmful. Solutions with neutral pH or mildly acidic should be used.
4. **Injury** from undue pressure, such as tourniquet for placing an IV line, splints, and tight restrainers.
5. **Skin abrasion**—Adhesive tapes are used for securing the vascular lines and thermal probes. At the time of removal of the tapes or of self-adhering ECG electrodes, if care is not taken, skin can easily get abraded.
6. **Ischemic injury** from tight application of a saturation probe on the finger can lead to ischemia of the distal skin.

Precautions—newborn babies should be handled gently with care. Limbs are tiny; circumference is small. When fixing lines with adhesive tape, care must be taken to never cover the entire circumference of the limb or finger. Tape should not cover more than 2/3rds of the circumference. All personnel involved in the care of the neonate should not have long fancy nail. They should remove any sharp finger rings and bangles, because of inadvertent injury to the delicate skin during handling.

10.22 Prematurity

Despite advances in neonatal care, preterm birth remains a leading cause of infant mortality, globally. Due to their LBW and organ immaturity, they may have various problems:

- Their caloric needs are high but due to the lack of sucking and swallowing reflexes, they have difficulty with oral feeding,
- Gastrointestinal immaturity impairs digestion and absorption of carbohydrates and lipids, and increased risk for necrotizing enterocolitis (NEC),
- Pulmonary immaturity makes them prone to apnea, RDS, BPD, HMD, and IRDS.
- Transitional maladaptation at birth exposes them to the risk of persistence of fetal circulation (PFC), PDA, PFO, and elevated PVR.
- Neurological immaturity contributes to the increased risk of CNS insults, which may later manifest as a poor cognitive ability, developmental delays, and other neurological sequelae.
- Visual issues like ROP have to be guarded against,
- They are at increased risk for sudden infant death syndrome (SIDS),
- Metabolic immaturity poor fat insulation, decreased glycogen stores, immature skin with increased water loss, poor vascular control, and lower maximal metabolism, narrows the range of thermal control and makes them prone to hypothermia,
- Immaturity of the immune system places them at high risk for contracting life-threatening infections, and.
- Hepatobiliary immaturity makes biliary atresia more common in them, necessitating surgery, usually by the age of 3–5 months.

Premature newborns need continuous and prolonged specialized care and must be observed for onset of anemia and jaundice and for prompt remedial measures. Round-the-clock, monitoring of blood sugar is essential since hypoglycemia is a potential danger that needs urgent attention.

World Prematurity Day is observed on November 17 each year to increase awareness of preterm birth, its risks and prevention, since 2011. Nearly 10% of all babies born worldwide are born premature (nearly 15 million babies). November is Prematurity Awareness Month. Prematurity is a major contributor to under-five mortality.

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