Chapter

19

The Premature and Ex-Premature Infant*

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Introduction

The impact of prematurity can be lifelong, and although the risk of acute complications decreases throughout infancy and early childhood, long-term morbidity remains high. Low gestational age at birth is an independent risk factor for increased mortality from respiratory, cardiovascular, endocrine and congenital disorders in childhood and early adulthood. This chapter will describe the clinical manifestations unique to the premature and ex-premature infant and specific considerations for anaesthetic management in this particularly vulnerable group.

Definitions

Definitions from the American Association of Pediatrics (AAP) are as follows:

- Gestational age: time from the first day of the last normal menstrual period to the day of delivery.
- Conceptional age: time between conception and day of delivery.
- Chronological age: time elapsed since birth.
- Postmenstrual age (PMA): gestational age + chronological age. Used to describe age during the perinatal hospital stay. For example, a baby born at 28 weeks who is now four weeks of age has a PMA of 32 weeks.
- Corrected age: chronological age reduced by the number of weeks born before 40 weeks of gestation. Used to describe the age of children who were born preterm up to the age of three years. For example, a baby born at 28 weeks who has a chronological age of 6 months has a corrected age of (26 weeks – (40–28 weeks) = 14 weeks.

Table 19.1 Terminology used for classification of preterm neonates

Terminology based on gestational age	
Full term neonate	37–42 weeks' gestation and age <1 month
Premature neonate	<37 weeks' gestation
Extreme preterm neonate	<28 weeks' gestation
Terminology based on weight	
Low birth weight (LBW)	<2,500 g
Very low birth weight (VLBW)	<1,500 g
Extremely low birth weight (ELBW)	<1,000 g

The terminology used to describe neonates and preterms is based on either gestational age or weight (Table 19.1).

Risk Factors for Premature Delivery

Risk factors for premature delivery include maternal factors, complications of pregnancy and fetal factors:

Maternal Factors

- Maternal age <17 or >35 years of age
- Lower socioeconomic status
- BMI <19 kg m^{-2} or pre-pregnancy weight <50 kg
- Previous preterm birth
- Prior cervical surgery or uterine anomalies

Pregnancy Factors

- Multiple gestation
- Vaginal bleeding
- Oligo- or polyhydramnios

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- Chorioamnionitis
- Maternal medical conditions: hypertension, diabetes, thyroid disease, asthma
- Maternal abdominal surgery during pregnancy
- Adverse behaviours: smoking, heavy alcohol consumption, cocaine, heroin

Fetal Factors

- Chromosome anomaly, structural abnormality, intrauterine growth restriction (IUGR)

Clinical Consequences of Premature Delivery

Preterm birth is relatively common, occurring in 5–18% of births worldwide. The clinical consequences of prematurity depend on the gestational age at birth and any underlying abnormalities that may have resulted in premature delivery. All bodily systems may be affected as important aspects of development are not yet complete.

Thermoregulatory Instability

Rapid heat loss can occur in preterm neonates because of their large body surface area to body weight ratio and limited heat production through brown fat metabolism. Heat loss is by increased thermal conductance, increased evaporation through non-keratinised skin, convection and radiation. Hypothermia is associated with intraventricular haemorrhage (IVH), pulmonary insufficiency and coagulopathy and may contribute to metabolic disorders such as hypoglycaemia or acidosis.

Respiratory Abnormalities

- Respiratory distress syndrome (RDS) occurs in 60% of infants born at <30 weeks of age and is caused by immaturity of the lungs and surfactant deficiency. It presents with increased work of breathing, cyanosis and 'grunting'. The chest X-ray (CXR) shows widespread atelectasis with a granular appearance and widespread air bronchograms. Histologically, the lungs contain hyaline membranes, hence the previous terminology of hyaline membrane disease. RDS may be complicated by air leak (pneumothorax, pneumomediastinum, pulmonary interstitial emphysema) and is the precursor to bronchopulmonary dysplasia. Antenatal corticosteroids are given to mothers in preterm labour to induce surfactant production, which is associated with improved outcomes from RDS. Additionally, exogenous surfactant is administered prophylactically to infants <28 weeks gestation within hours of birth or as rescue in RDS. The strategy for ventilation in premature infants is to minimise ventilator induced lung injury. High-frequency oscillatory ventilation (HFOV) is used to reduce barotrauma and oxygen requirements. Inhaled nitric oxide (iNO) may be used as rescue therapy but may increase IVH and does not appear to improve long-term outcomes.
- Bronchopulmonary dysplasia (BPD), also known as chronic lung disease (CLD), is a late respiratory complication that occurs in 15–50% of VLBW infants. It is defined as oxygen dependency at 36 weeks PMA. Early CXR changes include a ground glass appearance, later progressing to patchy atelectasis, cystic changes, hyperexpansion and areas of emphysema. Long-term intubation and positive pressure ventilation are avoided if possible, as they are more likely to be associated with barotrauma, oxygen toxicity and the development of BPD. Postnatal steroids have been found to have adverse effects on development of the brain in premature infants and are no longer recommended to facilitate weaning from prolonged ventilation. BPD is associated with long-term morbidity that continues into later life. Infants may remain oxygen dependent for many months, although it is unusual to require oxygen after two years of age.
- Apnoea of prematurity occurs in approximately 25% of premature infants and 90% of ELBW infants. It is defined as a pause in breathing of more than 20 seconds or a pause associated with bradycardia and/or desaturation. Apnoeas may be:
  - Central: due to brainstem or peripheral chemoreceptor immaturity.
  - Obstructive: due to reduced airway tone, asynchrony of diaphragmatic or upper airway activity, excessive neck flexion or structural abnormalities.
  - Mixed: central and obstructive. This is the most common type.

  Premature infants respond to hypoxia by a brief increase in ventilation followed by apnoea

and have a blunted response to hypercapnia. Apnoea may have a number of triggers, including hypoxia, sepsis, intracranial haemorrhage, metabolic abnormalities, hypo/hyperthermia, upper airway obstruction, heart failure, anaemia, vasovagal reflexes and drugs (including prostaglandins and anaesthetic agents). Central control of ventilation matures with age, and normal responses to hypercapnia and hypoxia (increased ventilation) are seen by three weeks of age in term infants.

- Pulmonary haemorrhage occurs most commonly in ELBW infants and is associated with increased mortality.

Cardiovascular Abnormalities

- Patent ductus arteriosus (PDA). The ductus arteriosus is one of the fetal shunts and usually closes in response to increased oxygen tension and a fall in circulating prostaglandins by 48 hours in the majority of babies. Patent ductus arteriosus is common in preterm neonates, occurring in approximately 30% of VLBW infants due to low oxygen tension, continuing high prostaglandin levels, acidosis or expansion of the circulating volume. The PDA shunts blood from left to right, resulting in increased flow through the pulmonary circulation, decreased perfusion of the systemic circulation and a low diastolic pressure. PDA typically becomes symptomatic when pulmonary vascular resistance (PVR) falls at 5–10 days. Clinical manifestations include increased work of breathing and ventilatory requirements, bounding pulses, a continuous murmur with cardiomegaly and increased vascular markings seen on CXR. Diagnosis is confirmed by echocardiography. The physiologic consequences of the PDA depend upon the size of the shunt and the response of the heart and lungs to the shunt. Significant shunting may present with apnoea, respiratory distress or heart failure. Treatment for symptomatic PDA includes fluid restriction, diuretics and 'medical closure' with indomethacin, ibuprofen or paracetamol. Surgical closure is indicated if medical management fails or NSAIDs are contraindicated.

Central Nervous System Abnormalities

- Germinal matrix haemorrhage and intraventricular haemorrhage (GMH-IVH) usually occurs within the first few days of life due to germinal matrix fragility and disturbances of cerebral blood flow. The risk is inversely proportional to gestational age, as cerebral autoregulation has not yet developed and it is an important cause of brain injury in premature infants. Risk factors for IVH include hypotension, fluctuating blood pressure, hypoxia and hypocapnia. GMH-IVH is classified into four grades:
  - Grade I: germinal matrix haemorrhage
  - Grade II: IVH without ventricular enlargement
  - Grade III: IVH with ventricular enlargement
  - Periventricular haemorrhagic infarction (PVHI, previously Grade IV): IVH with extension into the periventricular white matter

  Patients with severe GMH-IVH (grades III and PVHI) have poorer neurodevelopmental outcomes. Management is supportive and focused on reducing further brain injury through preservation of cerebral perfusion and oxygenation; providing appropriate fluid, metabolic and nutritional support; and treating seizures.

  Post haemorrhagic ventricular dilatation (PHVD), the most common complication, occurs in approximately 25% of infants with GMH-IVH. Management involves early identification with regular cranial ultrasounds and intervention based on evidence of progressive dilatation. Neurosurgical intervention consists of temporising procedures such as serial lumbar punctures, ventricular access devices, ventricular reservoirs or subgaleal shunts. Subgaleal shunts reduce the need for daily CSF aspiration and prolong the time period before permanent shunt placement.
- Periventricular leukomalacia (PVL) describes histological changes in periventricular white matter seen in premature infants. It is associated with hypoxic-ischaemic injury, infection, impaired cerebral autoregulation,

cerebral 'steal' due to a large PDA and severe hypocapnia. Bilateral occipital cystic PVL is a very strong predictor of cerebral palsy, particularly spastic diplegia.

- Retinopathy of prematurity (ROP) is a developmental proliferative vascular disorder that occurs in the retina of preterm infants with incomplete retinal vascularisation. It is predominantly seen in LBW infants <32 weeks' gestation and is a common cause of potentially preventable childhood blindness worldwide. Risk factors for ROP are not completely understood; hyperoxia in the newborn period seems to increase the risk, with increased oxygen free radical activity believed to be an underlying mechanism. However, supplemental oxygen alone is not sufficient or required to cause ROP, and no 'safe' threshold for oxygen has been determined.

  ROP is classified into stages 1–5 according to four features: zone, stage, extent and presence or absence of 'plus' disease (vascular congestion and dilatation). Good neonatal care and ophthalmic screening and treatment can largely prevent ROP. However, 6% of premature babies have advanced disease (grades 3–5) and require intervention. Treatment consists of retinal ablative therapy (laser photocoagulation or cryotherapy) or intravitreal injection of an anti-vascular endothelial growth factor (VEGF) agent. In the later stages, other treatment options include scleral buckle or vitrectomy.

Gastrointestinal Abnormalities

- Necrotising enterocolitis (NEC) is a disease of prematurity and is associated with a high mortality. The risk of death increases with decreasing gestational age. It is associated with ischaemia or hypoxic injury to gut mucosa causing inflammation and transmural necrosis, affecting any part of the intestine but typically the terminal ileum, caecum or ascending colon. The severity of disease may be described using the modified Bell staging criteria (stages 1–3). NEC is associated with early feeding with formula milk and colonisation with pathogenic bacteria. It typically presents with abdominal distension, bloody stool and bilious aspirates during the second or third week of life when full feeds are commenced. Signs of sepsis may predominate and progress to apnoea with shock and disseminated intravascular coagulation. Abdominal X-ray shows thickened dilated bowel loops with intramural gas. Free gas indicates gut perforation and a poor outcome. There may be thrombocytopenia, coagulopathy, raised inflammatory markers and metabolic acidosis.

  Medical management includes fluid resuscitation with or without inotropes, correction of deranged clotting and platelets, parenteral nutrition (PN) and antibiotics. Fifty per cent of neonates with NEC require surgery due to perforation or failure of medical management. Surgical options include resection of necrotic bowel and formation of proximal stoma and distal mucous fistula, gut resection with primary anastomosis or proximal defunctioning jejunostomy and 'second look' at 24 hours if critically ill. Prognosis of NEC has improved with earlier recognition and treatment, with survival rates of approximately 70–80% in affected infants. Long-term complications include short bowel syndrome, intestinal strictures, poor growth and impaired neurodevelopmental outcome. However, approximately half of survivors have no significant sequelae.

Metabolic Abnormalities

- Hypoglycaemia. Hepatic glycogen stores develop in the last few weeks of gestation, and therefore premature infants are prone to hypoglycaemia (blood glucose <2.6 mmol l^{-1}) if exogenous glucose is not delivered. Maintenance fluids with 10% dextrose are usually required with added sodium after 24 hours. Hyperglycaemia can also have adverse consequences, including osmotic diuresis, IVH and ROP.

Haematological and Coagulation Abnormalities

- Anaemia of prematurity (AOP). The haematocrit falls soon after birth in newborn infants, predominantly due to impaired production of erythropoietin. The decline occurs earlier and is more pronounced in preterm infants and is referred to as AOP. Premature infants have a lower haemoglobin concentration (130–150 g l^{-1}) compared to

term infants (180–200 g l^{-1}). They are at particular risk of impaired oxygen delivery due to the increased likelihood of concomitant respiratory disease, higher concentrations of haemoglobin F (70–80%) and the need to avoid hyperoxia, which increases the risk of BPD and ROP.

- Coagulation abnormalities. The activity of vitamin K–dependent clotting factors in preterm infants is approximately 30% that of adult levels, and plasma concentrations are significantly lower at birth. Neonatal coagulation reference ranges for healthy preterm and term neonates should be used. Prophylactic transfusion of fresh frozen plasma (FFP) to correct abnormalities is not usually required unless bleeding is encountered. All neonates are given a dose of vitamin K after birth to prevent vitamin K–deficient bleeding (previously known as haemorrhagic disease of the newborn).

Infection

- Sepsis is a major cause of morbidity and mortality in premature infants and is associated with increased likelihood of poor neurodevelopmental outcome and growth impairment. It may present with non-specific signs, including hypothermia, hyperthermia, tachycardia, bradycardia, apnoea, increased oxygen requirements, metabolic acidosis or feeding problems. A decrease in platelet count of >30% is frequently seen, for which the differential diagnosis is IVH or NEC. Early onset infection is usually acquired from the mother, such as Group B streptococci and *Escherichia coli*. Nosocomial infections, such as *Staphylococcus aureus*, Klebsiella or Pseudomonas, often present after the first week of life. Late onset infection may be due to *Candida albicans* or Gram-negative organisms, particularly in association with indwelling catheters.

Outcomes

Advances in neonatal intensive care have extended the survival of preterm infants such that around 50% of babies born at 24 weeks and around 90% of those born at 27 weeks survive; however, the levels of morbidity are high. Outcomes are better in female infants, singleton pregnancies and when antenatal steroids have been given. ELBW neonates are more susceptible to complications. First year survival for babies with a birth weight of <500 g is approximately 15%, 500–749 g is 50% and >750 g is 85%.

Conduct of Anaesthesia in the Premature Infant

Preoperative Assessment and Preparation

Anaesthesia and surgery in the premature neonate are high risk. Evidence-based guidelines on how best to anaesthetise this patient group are lacking. Close collaboration with the neonatologists and careful attention to detail is required. Consent should be discussed with the parents in accordance with GMC guidance and questions answered fully.

Operative location: For the ELBW and LBW infants, it is advantageous for surgery to take place on NICU. This reduces the need for transfer and handling, minimising heat loss; enables ventilation to continue on the neonatal ventilator; and provides ready availability of the neonatal team. If these vulnerable infants must be taken to theatre, the utmost care should be taken not to displace intravenous lines or the tracheal tube (TT) during transport and positioning.

Temperature control: Provide under-warming with either a 3M Bair Hugger® or TransWarmer®, warm the theatre environment to 25°C, minimise heat loss (use a heat moisture exchanger and cover the head), warm IV fluids and use clear surgical drapes (lightweight, to improve visualisation of baby and TT during surgery). Take care when removing drapes to preserve fragile skin.

Monitoring: Check that monitoring is reliable as access to the baby will be limited once surgery is under way. Two oxygen saturation probes should be placed: one preductal on the right hand and the other postductal. End-tidal CO_2 monitoring is mandatory; however, this may significantly under-read. Transcutaneous CO_2 monitoring provides a very useful trend, particularly where changes in lung compliance are anticipated. Ensure that an appropriately sized blood pressure (BP) cuff is used. Measure core temperature either nasally or rectally. Near-infrared spectroscopy (NIRS) may provide another useful 'trend monitor'; however, it is not properly validated in

neonates <2.5 kg, and specific thresholds for intervention are not known.

Vascular access: Invasive monitoring is extremely useful in the septic baby requiring inotropes or when cardiovascular instability is anticipated. The ability to take blood samples intraoperatively is the gold standard but is not always possible. Due consideration must be given when inserting arterial lines in premature infants due to the risk of thrombosis and distal ischaemia. Anaesthetists should aim to preserve peripheral veins, as neonatal long lines are likely to be required for PN. Extension lines with three-way taps should be placed on all cannulae and should be bubble-free.

Intraoperative Management

Airway: Premature neonates will often be intubated and ventilated already. An oral uncuffed TT of 2.5–3 mm internal diameter is usual. If intubation is required, checklists are helpful to ensure that all staff are fully prepared. Once the TT is secure, check the position meticulously as minor changes in head position may result in endobronchial intubation or accidental extubation. Recheck the position every time the baby is moved. Use equipment with as little dead space as possible.

Ventilation: Ventilation may be provided via a neonatal ventilator or HFOV on NICU, or an anaesthetic machine in theatre. Ventilatory strategies should aim to avoid hyperventilation, SpO_2 > 95%, high peak inspiratory pressures and barotrauma. Permissive hypercapnia is acceptable. The baby may need to be hand ventilated via an Ayres T piece if compliance is variable. An air/oxygen mix should be used and hyperoxia avoided.

The optimal SpO_2 for preterm infants who receive supplemental oxygen therapy has not been fully established. However, based on the available evidence, the most prudent target range is between 90–95%. This range minimises both the low and high extreme oxygenation levels that have been associated with adverse outcomes and mortality.

Circulation: It is important to avoid haemodynamic instability and conditions that impair cerebral autoregulation, such as hypotension and fluctuations in BP. Hypotension due to hypovolaemia (e.g. acute blood loss) should be treated with volume expansion, taking care to avoid excessive volume loading. Fluid shifts up to 60–80 ml kg^{-1} may be significant in laparotomy for NEC but will vary according to the type of surgery. Isotonic fluids should be used (0.9% saline, Hartmann's or Ringer's lactate) given as boluses of 10 ml kg^{-1} and titrated to BP, heart rate, capillary refill time and base excess. However, in many cases, volume expansion alone is insufficient to maintain adequate BP levels, and inotropic therapy is required.

Blood should be transfused to maintain a Hct of 35–45% in newborn infants, replacing calcium as necessary. Babies with NEC may require blood, platelets, FFP and cryoprecipitate during surgery. The World Society of Surgery suggests a target Hb of 110 g l^{-1} for neonates with an oxygen requirement or those that are ventilated.

Blood glucose should be monitored regularly and glucose-containing maintenance fluids continued during surgery. This fluid should not be used for bolus administration. Usual rates for preterms are 100 ml $kg^{-1}day^{-1}$ or 4–5 ml $kg^{-1}hr^{-1}$.

Anaesthesia and analgesia: Volatile anaesthesia can be provided if surgery is being undertaken in theatre. If operating in NICU, continuation of morphine infusions with additional fentanyl boluses is usual. Intraoperative remifentanil may be a useful alternative. Some anaesthetists will also give boluses of ketamine, with the rationale that surgical stress and unmanaged pain is likely to have more deleterious effects than any concerns about neurotoxicity. Multimodal analgesia is favoured. Paracetamol should be dosed according to gestational age with special care taken to avoid accidental overdose. Regional anaesthesia is particularly useful if extubation is planned at the end of surgery. A morphine nurse-controlled analgesia (NCA) can be set up with NICU settings (smaller boluses, no background if <5 kg).

Neurotoxicity: The effect of anaesthetic drugs such as midazolam, isoflurane and ketamine on the developing brain have been investigated in the last decade. These agents were found to cause widespread apoptosis with persistent memory and learning impairment in animal models. The existence of an association between general anaesthesia at a young age and subsequent neurodevelopmental deficits has not been fully elucidated; however, the GAS study has shown no association at five years follow-up. The relevance to clinical practice in other settings remains unclear, but only essential surgery should be performed in early life.

Postoperative Management

A thorough handover to NICU is mandatory, with all members of the multidisciplinary team present. Extremely premature neonates will usually remain intubated and ventilated until a time when they can safely be weaned from invasive ventilation.

Conduct of Anaesthesia in the Ex-Premature Infant

Preoperative Assessment

Clinical features of ex-premature infants include:

- Ongoing oxygen requirements, CLD with reduced lung compliance, asthma, tracheomalacia, susceptibility to respiratory infection
- Acquired subglottic stenosis (SGS) as a consequence of prolonged intubation in infancy
- Residual shunts or pulmonary hypertension
- Gastro-oesophageal reflux disease
- Neurodevelopmental delay and/or seizures
- Impaired renal concentrating ability
- Chronic anaemia
- Failure to thrive

Intraoperative Management

- Anticipate difficulty with vascular access.
- A smaller TT size may be required if SGS is present.
- Ventilation may be difficult with cases of CLD, particularly in laparoscopic surgery.
- The infant may have increased sensitivity to opioids.
- Use regional blocks where possible. Spinal anaesthesia for inguinal hernia repair may be suitable in experienced hands and can reduce postoperative apnoeas, provided supplemental sedation is avoided.

Postoperative Management

- Ex-premature infants are susceptible to postoperative apnoeas up to 60 weeks PMA and may require nasal continuous positive airway pressure (CPAP) or ventilation after surgery. Local protocols regarding postoperative destination, apnoea monitoring and overnight stay should be in place.

Key Points

- The impact of premature birth is lifelong, affects multiple organ systems and is associated with reduced life expectancy.
- Modern neonatal intensive care has improved survival of extremely premature and low birth weight babies, although problems associated with CLD, poor growth and developmental delay are common.
- Premature babies commonly present for surgery in association with PDA, NEC or ROP.
- Surgery is high risk, and close collaboration with the neonatal team is required to ensure the baby is in optimal condition for surgery.
- Ex-premature infants may have a wide range of disabilities and be susceptible to postoperative apnoeas. Poor venous access should be expected.

Further Reading

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