

# Special considerations in the premature and ex-premature infant

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## Abstract

Mean survival rates for babies born at 24 weeks and 27 weeks are currently 50% and 90% respectively, although levels of morbidity for the most premature infants may be high. This article describes the clinical conditions unique to the premature and ex-premature infant, and some common surgical procedures and special considerations for the conduct of anaesthesia in this vulnerable population.

**Keywords** Apnoea; pain; premature infant; respiratory distress syndrome

## Definitions

- Full-term neonate: 37–42 weeks' gestation and aged less than 1 month.
- Premature neonate: less than 37 weeks' gestation.
- Extreme preterm neonate: less than 28 weeks' gestation.
- Post-conceptual age: gestational age plus post-natal age.
- Low birth weight (LBW): less than 2500 g.
- Very low birth weight (VLBW): less than 1500 g.
- Extremely low birth weight (ELBW): less than 1000 g.

## Clinical consequences of prematurity

The neonatal period is one of major physiological changes, with transition from intrauterine to extrauterine life. The premature infant has to undergo these same changes, but in the context of incomplete organ development.

### Respiratory distress syndrome and chronic lung disease

Respiratory distress syndrome (RDS) results from immaturity of the lungs, particularly the production of surfactant in the premature infant. RDS is typified by tachypnoea, dyspnoea, cyanosis and 'grunting', non-compliant lungs, widespread atelectasis on chest radiograph and the presence of hyaline membranes in terminal airways (previous terminology: hyaline membrane disease).

RDS is invariable in infants born at less than 28 weeks' gestation.

Antenatal corticosteroid administered to mothers in preterm labour induces surfactant production and reduces the incidence of RDS.

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## Learning objectives

After reading this article, you should be able to:

- define the terms prematurity, extreme prematurity and post-conceptual age
- list the well-known complications of premature infants
- explain the basic principles of anaesthetizing a premature infant

RDS may be complicated by air leak (pneumothorax, pneumomediastinum, pulmonary interstitial emphysema) and lead to bronchopulmonary dysplasia (BPD) and chronic lung disease (CLD).

BPD is defined as oxygen dependency for more than 28 days after birth and an abnormal chest radiograph. The chest radiograph changes in early BPD may be indistinguishable from the ground glass appearance of RDS, but later radiographs show patchy atelectasis and cystic changes with hyperexpansion and areas of emphysema.

The course of RDS has been greatly ameliorated by modern neonatal intensive care practice. Exogenous surfactant is administered prophylactically within hours of birth. Nasal continuous positive airway pressure (nCPAP) is the method of choice for ventilatory support, and results in an increase in functional residual capacity (FRC), reduction in atelectasis and improved work of breathing. Intermittent positive pressure ventilation (IPPV) increases the risk of BPD and is used only if necessary (e.g. for the administration of surfactant, for VLBW infants at <28 weeks, and if oxygenation with nCPAP is inadequate with a fraction of inspired oxygen (FiO<sub>2</sub>) >50–60%). Babies are extubated to nCPAP as soon as possible.

Different ventilation modes are used to reduce volu/barotrauma. These include various forms of patient-triggered ventilation (such as pressure support and proportional assist ventilation) and minimization of excessive tidal volumes (volume targeted ventilation and high frequency oscillation).<sup>1</sup> The use of strategies to allow permissive hypercapnia may also reduce the risk of ventilator-induced injury.

Steroids have an adverse effect on development of the brain and are no longer used to facilitate weaning from long-term ventilation.

CLD occurs in 15–50% of VLBW infants. The severity of CLD is estimated from the duration of nCPAP and oxygen dependency, rather than the duration of ventilation.

Ex-premature babies are susceptible to respiratory infection in childhood, particularly in the first year of life. Reversible obstructive airway disease is common and they may have acquired subglottic stenosis as a consequence of prolonged intubation.

### Apnoea of prematurity

Apnoea is a pause in breathing of more than 20 seconds or one of less than 20 seconds associated with bradycardia and/or cyanosis.

Apnoea of prematurity is commonly seen in neonatal units, and may be classified as central (brainstem, peripheral chemoreceptor immaturity), obstructive (reduced tone, asynchrony of

diaphragm/upper airway activity, excessive neck flexion, structural abnormalities) or of mixed cause.

In adult life, hypoxia and hypercapnia increase ventilation. Premature and newborn term babies respond to hypoxia by a brief increase in ventilation followed by apnoea and have a blunted response to hypercapnia. In the term infant, normal responses to hypercapnia and hypoxia are seen by 3 weeks of age, but this is delayed in premature infants.

Apnoea in premature infants is exacerbated by hypoxia, sepsis, intracranial haemorrhage, metabolic abnormalities, hypo/hyperthermia, upper airway obstruction, heart failure, anaemia, vasovagal reflexes and drugs, including prostaglandins and anaesthetic agents.

Apnoeas are treated by stimulation, bag-mask ventilation, addressing underlying abnormalities, the use of respiratory stimulants such as caffeine or aminophylline, nCPAP or ventilation.

Term neonates are at low risk of postoperative apnoea after routine minor surgery at 44 weeks post-conception. However, in premature neonates the probability of postoperative apnoeas decreases to less than 1% only at 60 weeks post-conception.

### Patent ductus arteriosus

The arterial duct is one of the fetal shunts and is closed in 3–4 days in 90% of term and 'well' premature babies. The duct closes in response to a rise in oxygen tension after birth and a fall in circulating prostaglandins. Patent ductus arteriosus (PDA) is seen in 50% of VLBW infants due to low oxygen tension, continuing high prostaglandin levels, or abnormal stimuli such as acidosis and expansion of the circulating volume.

Aorto-pulmonary shunting through the PDA causes high pulmonary blood flow, worsening RDS, cardiac failure and low diastolic pressure. PDA is a risk factor for intraventricular haemorrhage, necrotizing enterocolitis and CLD. PDA typically becomes symptomatic at 5–10 days as pulmonary vascular resistance falls; it presents with worsening respiratory function, bounding pulses, a continuous murmur and chest radiograph that shows cardiomegaly and increased lung shadowing. Diagnosis is confirmed by echocardiography.

Conventional treatment for symptomatic PDA is fluid restriction, diuretics (furosemide) or medical closure with indomethacin or ibuprofen. Non-steroidal anti-inflammatory drugs (NSAIDs) may worsen renal function, and have been associated with gastrointestinal haemorrhage and perforation. These agents are contraindicated in the presence of thrombocytopenia. Surgical closure of symptomatic PDA is indicated for failed medical treatment or when NSAIDs are contraindicated.

### Necrotizing enterocolitis

Necrotizing enterocolitis (NEC) occurs mainly in preterm infants, with an incidence of about 7% and a mortality of 15–30%. It has a multifactorial aetiology, but common features include prematurity and poor mucosal integrity, hypoxia, early feeding with formula milk and colonization with pathogenic bacteria.

NEC causes inflammation and transmural necrosis and can affect any part of the intestine, typically the terminal ileum, caecum and ascending colon. The classical presentation is of abdominal distension, bloody stool and bile-stained aspirates, but signs of sepsis may predominate, with vague non-specific

signs progressing to apnoea with shock and disseminated intravascular coagulation (DIC). Intestinal perforation may cause a localized mass and the abdominal wall may be reddened in the presence of peritonitis. NEC is associated with pneumatosis (gas within the bowel wall), and a characteristic appearance on a radiograph of dilated thickened loops of bowel with intramural gas. Free gas may be visible on horizontal shoot-through in the presence of a perforation. Investigations may also reveal low platelet count, raised C-reactive protein and metabolic acidosis. Babies with severe disease may have exposed T antigen on red blood cells, which leads to haemolysis in the presence of transfused blood products containing anti-T antibodies. Blood products with low-titre anti-T antibodies will be required for T-antigen-positive infants (packed cells reconstituted in SAG-M are safe).

Treatment of NEC consists of general supportive measures, antibiotics, and resting the gut with 7–10 days of total parenteral nutrition. Half the infants with NEC require surgery for intestinal perforation or following failure of medical treatment. Surgical options include: laparotomy for resection of necrotic bowel and formation of a proximal stoma and distal mucous fistula; gut resection and primary anastomoses; placement of a peritoneal drain in those unsuitable for laparotomy; or for infants with inoperable disease, proximal defunctioning jejunostomy and 'second look' laparotomy at 24 hours if the baby survives.

### Intraventricular haemorrhage

Survival of extreme preterm infants has improved considerably in recent years. However, 21% of babies born at less than 25 weeks' gestation have severe disability, and 41% have significant cognitive impairment. A major determinant of cerebral impairment is germinal matrix intraventricular haemorrhage (IVH), particularly complicated by ventricular enlargement, parenchymal infarction or cystic periventricular white-matter injury. Major IVH usually occurs within the first few days of life and is detected by cranial ultrasound.

Factors that have been shown to increase the incidence of IVH or later neurodevelopmental delay include RDS, hypotension or fluctuating blood pressure, the use of hypertonic infusions and aggressive volume expansion.

The normal lower limit of mean arterial blood pressure (MAP) is roughly equivalent to the gestational age on the first day of life, with a MAP of at least 30 mmHg for all infants by day 3 of life.

Management of hypotension requires judicious use of volume expansion (crystalloid or colloid) and the early use of inotropic agents such as adrenaline, dopamine or dobutamine. Aggressive volume expansion should be avoided, especially in the first few days of life.

Periventricular leukomalacia describes histological changes in periventricular white matter seen in premature infants. The pathogenesis of periventricular leukomalacia is associated with hypoxic-ischaemic or toxic injury, infection, impaired cerebral autoregulation, cerebral 'steal' due to a large PDA and severe hypocarbia. Bilateral occipital cystic periventricular leukomalacia is a very strong predictor of cerebral palsy.

### Retinopathy of prematurity and oxygen toxicity

Retinopathy of prematurity (ROP) is seen in LBW infants less than 32 weeks' gestation. Hyperoxia in the first weeks of life

causes vasoconstriction of retinal vessels, which leads to retinal ischaemia and a subsequent vasoproliferative phase. Good neonatal care, ophthalmic screening and treatment can prevent ROP.

There is concern that even brief exposure to high oxygen levels is associated with increased morbidity and mortality in VLBW infants; fluctuations in oxygen levels should be avoided and oxygen saturation maintained between 88–95%, not exceeding 95%. Newborn resuscitation should be carried out with room air rather than 100% oxygen.<sup>2</sup>

### Temperature control

Thermoregulation in the neonate is limited and easily overwhelmed by environmental conditions. There is a great potential for heat loss (high body surface area to body weight ratio, increased thermal conductance, increased evaporative heat loss through the skin) and limited heat production through brown fat metabolism. The preterm baby is particularly vulnerable as the immature skin is thin and allows major heat (and evaporative fluid) losses. The principle of anaesthesia in these infants is for minimal handling in a warm environment.

### Developmental aspects of pain perception

Pain pathways develop during the second and third trimester. By 26 weeks' gestation premature neonates respond to tissue damage by withdrawal reflexes and activation of the stress response. Pathways between the thalamus and somatosensory cortex function by 29 weeks' gestation. The precise gestational age when a neonate is able to perceive pain is unknown.

### Anaesthetic agents in the premature infant

Recent work has investigated the effects of exposure of the developing brain to anaesthetic drugs such as midazolam, nitrous oxide, isoflurane and ketamine. In animal experiments prolonged exposure to these agents were found to cause widespread apoptosis with persistent memory/learning impairments. The mechanism appears to be due to blockade of glutamate and  $\gamma$ -aminobutyric acid receptors. The relevance to clinical practice is unclear, but only essential surgery should be performed in early life.

### Conduct of anaesthesia in the premature infant

**General considerations:** anaesthesia and surgery in the premature neonate is high risk, require careful collaboration with the neonatal intensive care unit (NICU), and close attention to detail for successful outcomes.

- Consent should be discussed with the parents and questions answered fully.
- A full history should be taken, with particular note of cardiorespiratory status, acid–base balance, full blood count (including platelet count), coagulation, urea, and electrolytes, fluid balance, drugs and infusions.
- The baby should be carefully examined. Identify the site and state of intravenous lines. If intubated, assess bilateral air entry, size and length of the tracheal tube, recent chest radiograph and ventilator settings.
- Surgery can take place in the NICU (PDA ligation is frequently performed in the NICU). The advantages are a thermoneutral environment, use of neonatal ventilator and minimal handling of

the infant. Disadvantages include limited access and light for surgeons. Laparotomy for NEC may be difficult because of hypovolaemia, significant third-space losses, bleeding and coagulopathy. Extreme care should be taken if transporting the neonate to theatre, in particular not to displace intravenous lines or the tracheal tube.

- Anaesthesia monitoring should be as standard for any operating room. Ventilator dead-space should be minimized but end tidal carbon dioxide may still significantly under-read. A T-piece should be available for hand ventilation with an air/oxygen mixer. Oxygen saturation should not exceed 95%.
- Invasive arterial monitoring is useful in the septic patient receiving inotropes, or when cardiovascular stability is anticipated. An umbilical arterial catheter may be present from birth; its distal end should be sited above the diaphragm between the sixth and tenth vertebrae. Peripheral arterial cannulation (radial, posterior tibial, dorsalis pedis) is aided by a 'cold' light. The femoral or axillary artery may be used. The brachial artery should be avoided because it is an end artery with poor collateral flow.
- Central venous access may be useful if large-volume transfusions are anticipated or inotropes are required. An umbilical venous catheter may be present from birth and is useful for the first week of life. The tip of the umbilical venous catheter should be in the inferior vena cava at the level of (but not in) the right atrium. Ultrasound guidance may be useful to aid in femoral venous cannulation.
- Blood for transfusion and a means for warming infused fluids should be available.
- The temperature of the operating room should be raised to 25 °C and there should be a means of warming the baby (overhead heater and/or hot air).
- The surgical drapes should be lightweight, ideally transparent plastic, so that the baby (and the tracheal tube) can be clearly seen. Drapes should not be stuck to the fragile skin. The surgeons must not rest their hands on the infant.
- Anaesthesia should be induced only when all are fully prepared. The baby is intubated orally, either with an uncuffed tracheal tube (2.0–3.0 mm internal diameter (ID)). The tracheal tube should be carefully strapped in place (not tied to a bonnet), and the position rechecked every time the infant is moved.
- Avoid hyperventilation, oxygen saturation greater than 95%, high-peak inspiratory pressures and barotrauma. Permissive hypercarbia is acceptable.
- Isotonic fluids should be used during surgery (0.9% saline, Hartmann's or Ringer's lactate), given as boluses of 10–20 ml/kg and titrated to blood pressure, heart rate, capillary refill time and base excess if available. Avoid swings in blood pressure and excessive volume loading. Blood should be transfused to maintain a haematocrit of 36% in the newborn infant (high levels of fetal haemoglobin) and 30% in the chronically transfused infant.
- Blood glucose should be monitored and glucose-containing maintenance fluids continued during surgery (e.g. 10% dextrose ( $\pm$  added sodium) 4 ml/kg/hour).
- Multimodal analgesia should be used for pain relief (e.g. regional anaesthesia, local anaesthetic infiltration, paracetamol and opioids, most commonly fentanyl). Epidural catheters can be inserted via the caudal route. Sucrose analgesia may be useful in the NICU for painful interventions such as cannulation.

- The child may have CLD, reduced lung compliance, reversible obstructive airway disease, gastro-oesophageal reflux, impaired renal concentrating ability, chronic anaemia, failure to thrive, neurodevelopmental delay and/or seizures, subglottic stenosis and difficult venous access.
- The child will be susceptible to postoperative apnoeas up to 60 weeks post-conception and may require postoperative nCPAP or ventilation; oral caffeine may be considered, particularly if previously used.

### Special situations

#### Anaesthesia for NEC

- Careful preoperative resuscitation and correction of acid–base balance and coagulopathy. Platelet transfusion and fresh-frozen plasma may be required.
- Fluid shifts during surgery may be significant, requiring up to 60–80 ml/kg of volume resuscitation.

#### Anaesthesia for PDA ligation

- Careful positioning for left thoracotomy and placement of clip on arterial duct.
- Place pulse oximeter or arterial line on lower half of the body to detect accidental ligation of descending aorta; persistent desaturation after reinflation of the lung indicates accidental ligation of pulmonary artery. Correct placement of clip is indicated by rise in blood pressure, particularly diastolic blood pressure.
- Intercostal nerve block by surgeon is useful (under direct vision).

#### Anaesthesia for hernia repair

- Caudal anaesthesia or ilioinguinal nerve block and paracetamol for postoperative analgesia can be used.

- Regional anaesthesia (spinal or caudal anaesthesia) may be suitable in experienced hands and may reduce postoperative apnoeas, provided supplemental sedation is avoided.

#### Anaesthesia for ventriculoperitoneal shunt

- Prolonged exposure in a cold theatre may result in hypothermia.
- May require morphine for postoperative analgesia (in combination with paracetamol and ibuprofen); the child is at risk for postoperative apnoeas. ◆

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