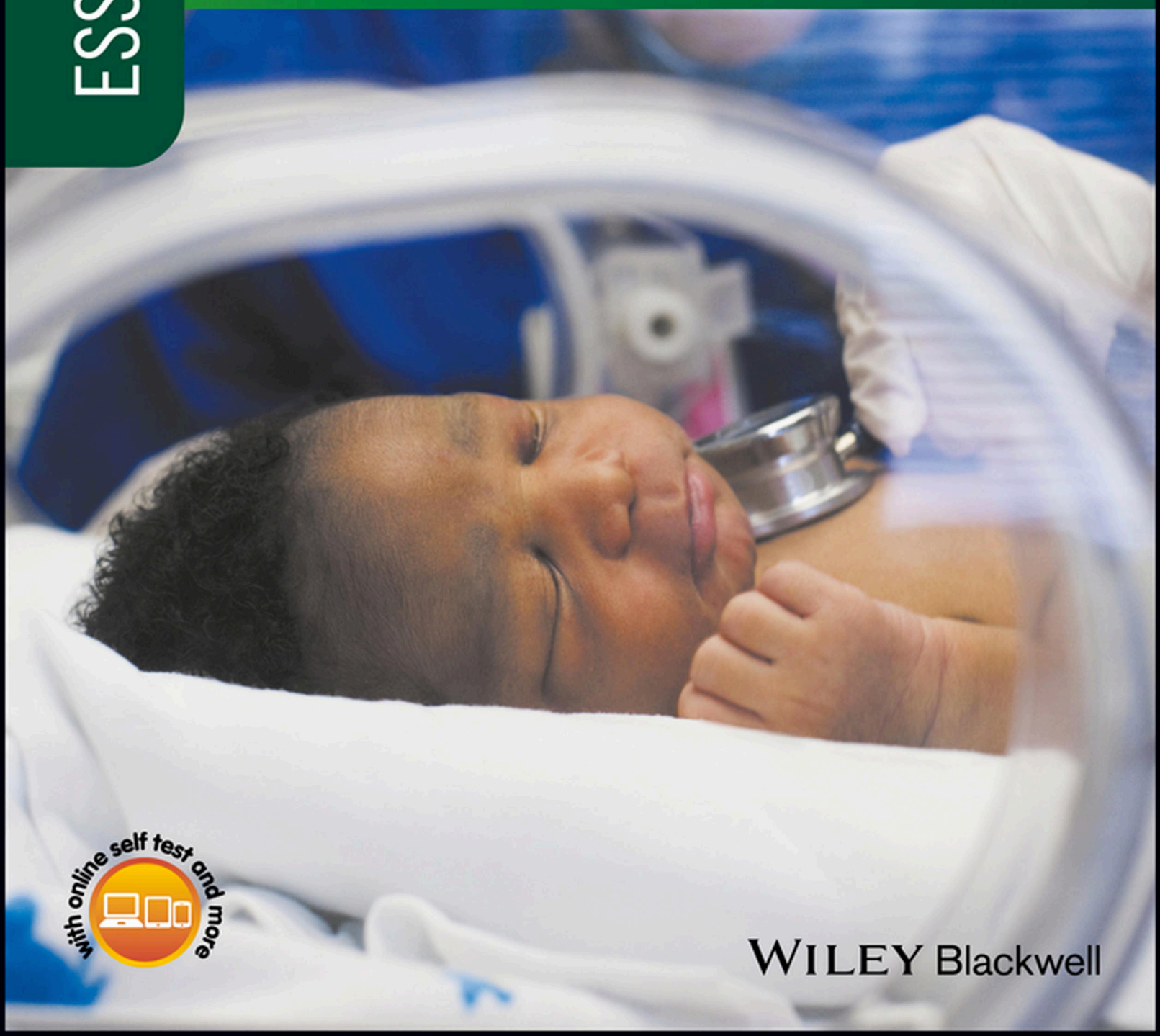
ESSENTIALS

ESSENTIAL NEONATAL MEDICINE

SUNIL SINHA | LAWRENCE MIALL | LUKE JARDINE

SIXTH EDITION



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Essential Neonatal Medicine

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Sixth Edition

Sunil Sinha
Professor of Paediatrics
University of Durham
Consultant Neonatologist
James Cook University Hospital
Middlesbrough, UK

Lawrence Miall
Consultant Neonatologist, Leeds Children's Hospital
Honorary Senior Lecturer, University of Leeds
Leeds Teaching Hospitals NHS Trust
Leeds, UK

Luke Jardine
Senior Staff Specialist Neonatology, Mater Mothers' Hospital
Honorary Researcher, Mater Research
Associate Professor, The University of Queensland
Australia

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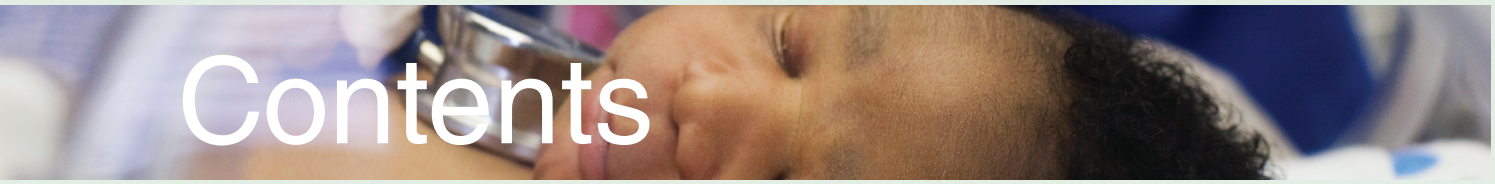

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Preface to the Sixth Edition

Neonatology is coming of age as a speciality – when the First Edition of this book was published 30 years ago, neonatal medicine was evolving rapidly and the emphasis was rightly on improving survival, especially at the margins of extreme prematurity. Now, survival is greater than 90% down to 28 weeks, and survival at 24 weeks – previously regarded as the threshold of viability – exceeds 60%.

With this improvement in survival, emphasis has begun to turn to the quality of care, quality of family support, and to the longer-term outcomes of graduates of the neonatal intensive care unit. Parents and siblings are now routinely welcomed into the nursery, whereas 30 years ago they may have been restricted in their visiting, and family-centred and family integrated care is becoming the normal. There is an increasing emphasis on risk reduction and minimizing harm – whether through hospital-acquired infections, injury from lines and procedures, or preventing ventilator-associated lung injury with the use of minimally invasive ventilation. There is also a greater recognition of the subtle but significant developmental and health challenges faced by only moderately pre-term babies, who are considerably greater in number than the extreme preterm babies.

To reflect this evolution this book has also evolved, with new chapters on palliative and end-of-life care, a greater emphasis on developmental and family care, and comprehensively updated chapters to include the latest developments in diagnostic imaging and genetic testing available. We believe that *Essential Neonatal Medicine* offers a comprehensive introduction to modern neonatology for trainee doctors, neonatal nurses, nurse practitioners and allied health professionals. We thank the many colleagues who have made it possible.

Dr Sunil Sinha
Dr Lawrence Miall
Dr Luke Jardine

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We would especially like to thank our families for their support with this project and their understanding during the many evenings we spent writing this book.

And finally, we are indebted to the babies and their families that it has been our privilege to treat, who have taught us so much over the years.

Preface to the First Edition

There has been an explosion of knowledge over the last decade in fetal physiology, antenatal management and neonatal intensive care. This has brought with it confusion concerning novel methods of treatment and procedures as well as the application of new techniques for investigating and monitoring high-risk neonates. The original idea for this book was conceived in Brisbane, and a *Primer of Neonatal Medicine* was produced with Australian conditions in mind. We have now entirely rewritten the book, and it is the result of cooperation between Australian and British neonatologists with, we hope, an international perspective.

We are aware of the need for a short book on neonatal medicine which gives more background discussion and is less dogmatic than other works currently available. We have written this book to give more basic information concerning physiology, development and a perspective to treatment which will be of value equally to neonatal nurses, paediatricians in training, medical students and midwives. Whilst collaborating on a project such as this we are constantly aware of the variety of ways for managing the same condition. This is inevitable in any rapidly growing acute speciality, and we make no apologies for describing alternative methods of treatment where appropriate. Too rigid an approach will be to the detriment of our patients!

A detailed account of all neonatal disorders is not possible but common problems and their management are outlined giving an overall perspective of neonatology. Attention has been given to rare medical and surgical conditions where early diagnosis and treatment may be lifesaving. It is easy to be carried away with the excitement of neonatal intensive care and forget the parents sitting at the cotside. Our approach is to care for the parents as well as their baby, and we have included two chapters on parent–infant attachment as well as death and dying. The final chapter deals with practical procedures and gives an outline of the commonly performed techniques used in the care of the high-risk newborn. We have also provided an up-to-date neonatal Pharmacopoeia as well as useful tables and charts for normal age-related ranges.

Malcolm I. Levene
David I. Tudehope
M. John Thearle

Abbreviations

ABR	auditory brainstem response
ADHD	attention deficit hyperactivity disorder
ALTE	acute life-threatening events
ART	assisted reproductive technology
ASD	atrial septal defect
BE	base excess
BPD	bronchopulmonary dysplasia
CAH	congenital adrenal hyperplasia
CCAM	congenital cystic adenomatous malformation
CDH	congenital diaphragmatic hernia
CFM	cerebral function monitoring
CHARGE	coloboma, heart defects, choanal atresia, retardation, genital and/or urinary abnormalities, ear abnormalities
CHD	congenital heart disease
CLD	chronic lung disease
CPAP	continuous positive airway pressure
CVP	central venous pressure
DDH	developmental dysplasia of the hip
DIC	disseminated intravascular coagulation
EBM	expressed breast milk
ELBW	extremely low birthweight
FASD	fetal alcohol spectrum disorder
FES	fractional excretion of sodium
FHR	fetal heart rate
FRC	functional residual capacity
GFR	glomerular filtration rate
GIFT	gamete intrafallopian transfer
GORD	gastro-oesophageal reflux disease
HCV	hepatitis C virus
HIE	hypoxic–ischaemic encephalopathy
HMF	human milk fortifiers
ICH	intracerebral haemorrhage
IDM	infants of diabetic mothers
IPPV	intermittent positive pressure ventilation
ITP	idiopathic thrombocytopenic purpura
IUGR	intrauterine growth restriction
IVF	*in vitro* fertilization
IVH	intraventricular haemorrhage
LBW	low birthweight
LMP	last menstrual period
LVH	left ventricular hypertrophy
MAS	meconium aspiration syndrome
NAS	neonatal abstinence syndrome
NCPAP	nasal continuous positive airway pressure
NICU	neonatal intensive care unit
NIPPV	non-invasive positive pressure ventilation
NTD	neural tube defects
PCV	pneumococcal conjugate vaccine
PDA	patent ductus arteriosus
PEEP	positive end-expiratory pressure
PET	pre-eclampsia

PICC	peripherally inserted central catheter
PIE	pulmonary interstitial emphysema
PIP	peak inspiratory pressure
PMR	perinatal mortality rate
PPHN	persistent pulmonary hypertension of the newborn
PROM	premature rupture of membranes
RDS	respiratory distress syndrome
ROP	retinopathy of prematurity
RVH	right ventricular hypertrophy
SGA	small for gestational age
SIDS	sudden infant death syndrome
SLE	systemic lupus erythematosus
TAR	thrombocytopenia with absent radii
TGA	transposition of the great arteries
ToF	tetralogy of Fallot
TORCH	toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex virus
TPN	total parenteral nutrition
TSH	thyroid-stimulating hormone
TTN	tachypnoea of the newborn
TTTS	twin-to-twin transfusion syndrome
UAC	umbilical arterial catheter
UVC	umbilical venous catheter
VACTERL	vertebral anomalies, anal atresia, cardiovascular anomalies, tracheoesophageal fistula, oesophageal atresia, renal and/or radial anomalies, limb defects
VAPS	volume-assured pressure support
VCV	volume-controlled ventilation
VILI	ventilator-induced lung injury
VLBW	very low birthweight
VSD	ventricular septal defect
VUR	vesico-ureteric reflux
WHO	World Health Organization

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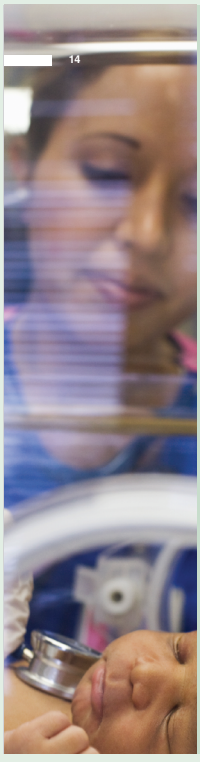

CHAPTER 2

Perinatal epidemiology and audit

Key topics

- Definitions of terms commonly used in perinatal medicine
- The role of perinatal and neonatal audit
- Classification of perinatal deaths
- Factors affecting perinatal death rates
- Prevention of perinatal mortality and low birthweight
- Changing trends

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- Changing trends

Key topics give a summary of the topics covered in the chapter.

postductal (either foot) of more than 3% is also suggestive of duct-dependent CHD.

CLINICAL TIP

The preductal oxygen saturation should never be lower than the postductal saturation. If it is, consider complex CHD such as transposition of the great arteries or double outlet right ventricle.

Abdomen

Distension suggests **intestinal obstruction** or an intra-abdominal mass. A scaphoid abdomen suggests diaphragmatic hernia. A lax abdominal wall with much redundant skin is seen in the 'prune-belly' syndrome. **Divarication** of the rectus muscles may produce a midline bulge in the abdominal wall. No treatment is required and the condition disappears with age.

Liver

This is normally palpable up to 1 cm below the costal margin. Hepatomegaly may be due to lung hyperinflation, cardiac failure, sepsis, hepatitis, intrauterine infection or haemolysis.

Spleen

The tip can be palpated in about a quarter of normal infants. Splenomegaly suggests infection (prenatal or postnatal) or haemolysis.

Kidney

May be palpable normally, particularly if the baby is relaxed. Moderate kidney enlargement may be due to hydronephrosis, dysplastic or cystic kidneys or rarely a Wilms' tumour. An adrenal mass (e.g. haemorrhage or neuroblastoma) is difficult to distinguish from a renal mass.

Umbilicus

Vessels

Normally, two thick-walled arteries and a thin-walled vein are seen, surrounded by clear Wharton's jelly. In 1–2% of infants there is a single umbilical artery, sometimes with other congenital malformations. If a single umbilical artery is found and the fetus has had a normal prenatal anomaly scan, no further investigations are required. If not, a renal ultrasound should be undertaken.

Stump

- The cord usually separates by 10 days, leaving a yellow or greenish eschar. A red flare around the base of the cord may reflect early sepsis and should be taken seriously. Discharge and cellulitis are also signs of infection. Discharge of urine or meconium from the stump suggests a patent urachus or patent omphalomesenteric duct, respectively. Exomphalos and gastroschisis are discussed in Chapter 17.
- **Umbilical granuloma** (a small red fleshy swelling at the stump) is due to excessive granulation and *if symptomatic* can be treated by the application of a silver nitrate stick on one or two occasions. Always protect the surrounding skin with barrier cream. Regular wiping with alcohol wipes can also act as an effective sclerosant. Most resolve spontaneously.
- **Umbilical hernia** is particularly common in African babies or those born prematurely, and usually develops in the first month or so of life. These hernias require no treatment, and usually regress by 18 months. They do not strangulate. Distinguish from exomphalos minor.

Genitalia

Establish that the baby has passed urine. This should occur within 24 hours of birth. If in doubt, a 'urine bag' can be attached over the genitalia.

Clinical tips highlight key information to be aware of.

Subcutaneous fat necrosis

This term is applied to well-demarcated indurated areas in the skin occurring where pressure has been applied (e.g. forceps blades on the face). It is noted in some babies with birth asphyxia, especially after therapeutic hypothermia. Fat necrosis can lead to hypercalcaemia, often lasting many weeks and so the plasma calcium concentration should always be checked in a baby with subcutaneous fat necrosis.

Sternomastoid tumour

Often associated with torticollis, this benign fibroblastic swelling is described in Chapter 6.

Organ injuries

Liver and spleen

Subcapsular haematoma of the liver can occur after a breech extraction or following external cardiac massage. It may also result from 'atraumatic' vertex deliveries. Rupture of the liver or spleen is more likely to occur where there is hepatosplenomegaly (rhesus haemolytic disease, diabetic mother). In babies who have been home, visceral trauma is highly associated with non-accidental injury (physical abuse).

Adrenals

Adrenal haemorrhages may occur with breech extraction, although they are usually a postmortem finding and are unsuspected in live infants. They are more commonly associated with overwhelming bacterial infection and disseminated intravascular coagulopathy.

Kidneys

Ruptured kidneys may occur very rarely during delivery in breech preterm infants.

Testicles

Testicular bruising and haemorrhage are commonly seen in breech presentations. No treatment other than simple analgesia is necessary.

Injuries sustained in the neonatal intensive care unit (NICU)

An increasing number and range of traumatic lesions are due to iatrogenic insults sustained in the modern NICU. These lesions occur predominantly in preterm infants, and relate to the invasive procedures and technology used to treat increasingly small and fragile infants (Table 7.4; Figs 7.7 and 7.8). Most of these are preventable, and good risk management processes should be put in place to ensure that their occurrence is minimized or prevented. Honest explanation to the parents and urgent appropriate treatment can mitigate the adverse effects. Superficial extravasation injuries can be treated by urgent flushing with large volumes of subcutaneous saline.

Table 7.4 Postnatal iatrogenic injury occurring in newborns, often on the NICU.

Skin lesions	Extravasation injury due to leakage of intravenous solutions Injury from saturation monitor pressure (Fig. 7.7) Calcified heel nodules from repeated heel-pricks Chemical burns from skin antiseptics (Fig. 7.8) Scarring from chest drains or central line insertion
Rib or limb fractures	Associated with severe osteopenia of prematurity (see Chapter 21)
Direct trauma from catheters, tubes and needles	Digit damage, nerve palsies, amputation, retained foreign bodies
Vascular injury	Thrombotic or ischaemic injury following insertion of peripheral arterial lines Inappropriate infusion via an arterial line (e.g. inotropes)
Respiratory injuries	Nares or septum can be damaged by pressure on nasogastric tubes or poorly fitting CPAP nasal prongs Subglottic stenosis from excessively large endotracheal tube
Postural deformities	Scaphocephaly External rotation of hips and feet These can be minimized by good positioning and developmental care (see Chapter 24)
Nosocomial infection	Poor infection prevention and control measures Poor hand-washing or asepsis technique Overcrowding in the NICU

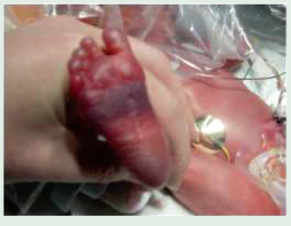

Figure 7.7 Bruising to the foot from SaO_2 probe.

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This book has a companion website at:

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with:

- Figures from the book in PowerPoint format
- Interactive self-assessment questions and answers
- Further reading list

CHAPTER 1

The fetus, placenta and changes at birth

Key topics

Essential Neonatal Medicine, Sixth Edition. Edited by Sunil Sinha, Lawrence Miall and Luke Jardine.

Companion website: www.essentialneonatalmed.com

Introduction

The discipline of 'perinatal medicine' spans the specialities of fetal medicine and neonatology. The obstetrician must have a thorough knowledge of pregnancy and its effects on the mother and fetus, as well as fetal development and physiology. The neonatologist specialises in the medical care of the infant immediately after birth, but must also have a thorough understanding of fetal development and physiology. This chapter reviews fetal assessment and physiology to provide the paediatrician and neonatal nurse with a better understanding of normal perinatal adaptation, and the adverse consequences arising from maladaptation.

Placental function

The **placenta** is a fetal organ that has three major functions: transport, immunity and metabolism.

The uterus is supplied with blood from the uterine arteries, which dilate throughout pregnancy, increasing blood supply 10-fold by term. Maternal blood bathes the intervillous space and is separated from fetal blood by the chorionic plate. Transport of nutrients and toxins occurs at this level. Oxygenated fetal blood in the capillaries of the chorionic plate leaves the placenta via the umbilical vein to the fetus (Fig. 1.1).

Transport

The placenta transports nutrients from the mother to the fetus, and waste products in the other direction. This occurs in a number of ways, including simple diffusion (for small molecules) and active transport, which is used for larger molecules. The placenta is crucially also responsible for gaseous exchange of oxygen and carbon dioxide. Oxygen diffuses from the mother (PO_2 = 10–14 kPa, 75–105 mmHg) to the fetus (PO_2 = 2–4 kPa, 15–30 mmHg), where it binds to fetal haemoglobin. This has a higher affinity for oxygen than maternal haemoglobin for a given PO_2. The dissociation of oxygen from maternal haemoglobin is also facilitated by a change in maternal blood pH.

Immunity

The placenta **trophoblast** prevents the maternal immune system from reacting against 'foreign' fetal antigens. Rejection does not occur because the trophoblastic cells appear to be non-antigenic, although it is known that fetal cells can cross into the maternal circulation where they can trigger an immune reaction (e.g. rhesus haemolytic disease). Maternal IgG antibody – the smallest of the immunoglobulins – can cross the placenta, where it provides the newborn with innate immunity to infectious diseases. These IgG antibodies can also cause perinatal disease such as transient hyperthyroidism (see Chapter 21).

CLINICAL TIP

Because IgG antibody crosses the placenta, the presence of IgG antibody in the newborn's blood does not necessarily mean it has been congenitally infected. This is of particular relevance when testing newborns for HIV infection, where a positive IgG may just reflect maternal exposure. Instead, direct tests (e.g. viral RNA by PCR) are required (see Chapter 10).

Metabolism

The placenta is metabolically active and produces hormones, including human chorionic gonadotropin (hCG) and human chorionic thyrotropin (hCT). It also detoxifies drugs and metabolites. Oestriol cannot be produced by the placenta

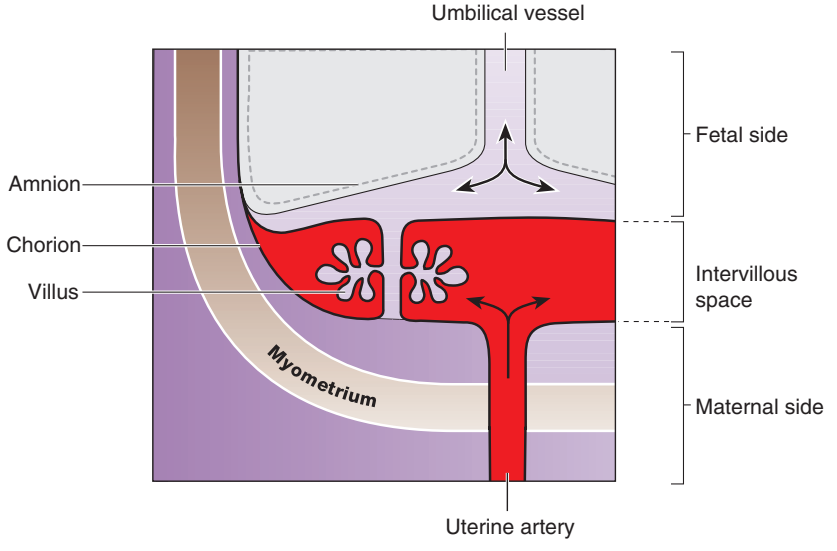

Figure 1.1 Diagram of placental structures showing blood perfusion.

alone. This is done by the fetal liver and adrenal glands. The metabolites are then sulphated by the placenta to form oestrogens, one of which is oestriol.

Because of its metabolic activity, the placenta has very high energy demands and consumes over 50% of the total oxygen and glucose transported across it.

Fetal homeostasis

The placenta is an essential organ for maintaining fetal homeostasis, but the fetus is capable of performing a variety of physiological functions:

- The liver produces albumin, coagulation factors and red blood cells.
- The kidney excretes large volumes of dilute urine from 10–11 weeks' gestation, which contributes to amniotic fluid.
- Fetal endocrine organs produce thyroid hormones, corticosteroids, mineralocorticoids, parathormone and insulin from 12 weeks' gestation.
- Some immunoglobulins are produced by the fetus from the end of the first trimester.

Fetal circulation

The fetal circulation is quite different from the newborn or adult circulation. The umbilical arteries are branches of the internal iliac arteries. These carry deoxygenated blood from the fetus to the placenta, where it is oxygenated as it comes into close apposition with maternal blood in the intervillous spaces. Oxygenated fetal blood is carried in the single umbilical vein, which bypasses the liver via the ductus venosus to reach the inferior vena cava (IVC). It then passes into the IVC and enters the right atrium as a 'jet', which is shunted to the left atrium across the foramen ovale (Fig. 1.2). From here it passes into the left ventricle and is pumped to the coronary arteries and cerebral vessels. In this way the fetal brain receives the most oxygenated blood. Some relatively deoxygenated blood is pumped by the right ventricle into the pulmonary artery, but the majority bypasses the lungs via the ductus arteriosus (DA) to flow into the aorta, where it is carried back to the placenta. Only 7% of the combined ventricular output of blood passes into the lungs. The right ventricle is the dominant ventricle, ejecting 66% of the combined ventricular output.

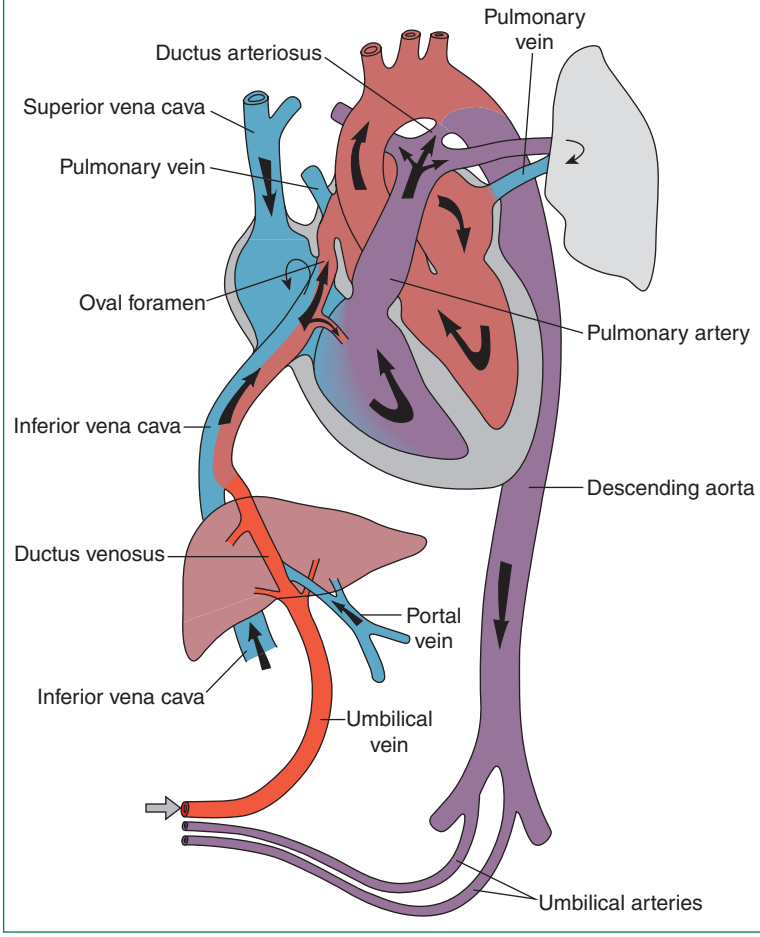

Figure 1.2 Diagram of the fetal circulation through the heart and lungs, showing the direction of flow through the foramen ovale and ductus arteriosus.

In summary, there are three shunts:

1. The **ductus venosus** bypasses blood away from the liver to the IVC.
2. The **foramen ovale** shunts blood from the right atrium to the left atrium.
3. The **ductus arteriosus** shunts blood from the pulmonary artery to the aorta.

The last two shunts only occur because of the very high fetal pulmonary vascular resistance and the high pulmonary artery pressure that is characteristic of fetal circulation.

Umbilical vessels

There are two umbilical arteries and one umbilical vein, surrounded by protective 'Wharton's jelly'. In 1% of babies there is only one umbilical artery, and this may be associated with growth retardation and congenital malformations, especially of the renal tract. Chromosomal anomalies are also slightly more common.

CLINICAL TIP

It used to be common practice to arrange a renal ultrasound if there was only one umbilical artery – this is no longer required as antenatal imaging of the kidneys is sufficiently high quality.

Assessment of fetal well-being

Assessment of fetal well-being is an integral part of antenatal care. It includes diagnosis of fetal abnormality, assessment of the fetoplacental unit and fetal maturity, and the monitoring of growth and well-being in the third trimester and during labour (Fig. 1.3).

Assessment of maturity

Ultrasound

Early measurement of fetal size is the most reliable way to estimate gestation, and is considered to be even more reliable than calculation from the date of the last menstrual period (LMP). Ultrasound measurements that correlate well with gestational age include crown–rump length (CRL; until 14 weeks), biparietal diameter (BPD) or head circumference (HC) and femur length. The HC measurement at 14–18 weeks appears to be the best method for assessing the duration of pregnancy. In in-vitro fertilization (IVF) pregnancy the date of fertilization is used to calculate the gestation.

Assessment of fetal growth and well-being

Clinical assessment

Monitoring fundal height is a time-honoured method of assessing fetal growth. Unfortunately, up to 50% of small-for-gestational age fetuses are not detected clinically.

Ultrasound

Serial estimates of BPD, HC, abdominal circumference and femur length are widely used to monitor growth, often on customized fetal growth charts. In fetuses suffering intrauterine growth restriction (IUGR), head growth is usually the last to slow down. Estimating fetal weight by ultrasound has become very accurate and provides critical information for perinatal decision-making about the timing of delivery.

Ultrasound imaging and Doppler blood flow

The location of the placenta can be confidently established using ultrasound. This is important to rule out placenta previa (a cause of antepartum haemorrhage) and to avoid cutting through the placenta at caesarean section. Doppler flow velocity waveforms of the umbilical artery are now used to assess fetal well-being. In near-term IUGR fetuses, abnormal Doppler waveforms are a reliable prognostic feature. As fetal blood flow becomes compromised there is reduced, then absent or reversed flow during diastole. Reversed diastolic flow may be an ominous sign and is associated with a high risk of imminent fetal demise (see Fig. 1.4). If end-diastolic flow (EDF) is absent, detailed Doppler studies of the middle cerebral artery (MCA) and ductus venosus are indicated. The umbilical artery Doppler flow pattern is used to determine the frequency of ongoing surveillance. In more preterm babies (32–37 weeks), EDF may be maintained even in severe compromise. Evidence of cerebral redistribution should trigger intensive regular monitoring. Timing of delivery will be based on Doppler patterns, gestation and estimated fetal weight. Doppler measurement of peak systolic blood flow velocity in the MCA is useful in the assessment of fetal anaemia and isoimmunization. As anaemia becomes severe, the velocity increases (see Chapter 20).

Amniotic fluid volume

Amniotic fluid (liquor) is easily seen on ultrasound, and the 'single deepest pool' or maximum pool size in four quadrants is measured (amniotic fluid index). This is often combined with non-stress testing (NST), counting movement and breathing. Both excess (polyhydramnios) and reduced (oligohydramnios) amniotic fluid volumes can be associated with adverse fetal outcome (see Table 1.1). Some centres assess fetal well-being using the 'biophysical profile scan', which includes fetal movements and tone and liquor volume.

Fetal breathing movements

The breathing movements of the fetus show marked variability. The fetus breathes from about 11 weeks' gestation, but this is irregular until 20 weeks. Fetal breathing promotes a tracheal flux of fetal lung fluid into the amniotic fluid. An absence of amniotic fluid (oligohydramnios) can lead to pulmonary hypoplasia. Abnormal gasping respiration, extreme irregularity of breathing in a term fetus and complete cessation of breathing are visible by ultrasound.

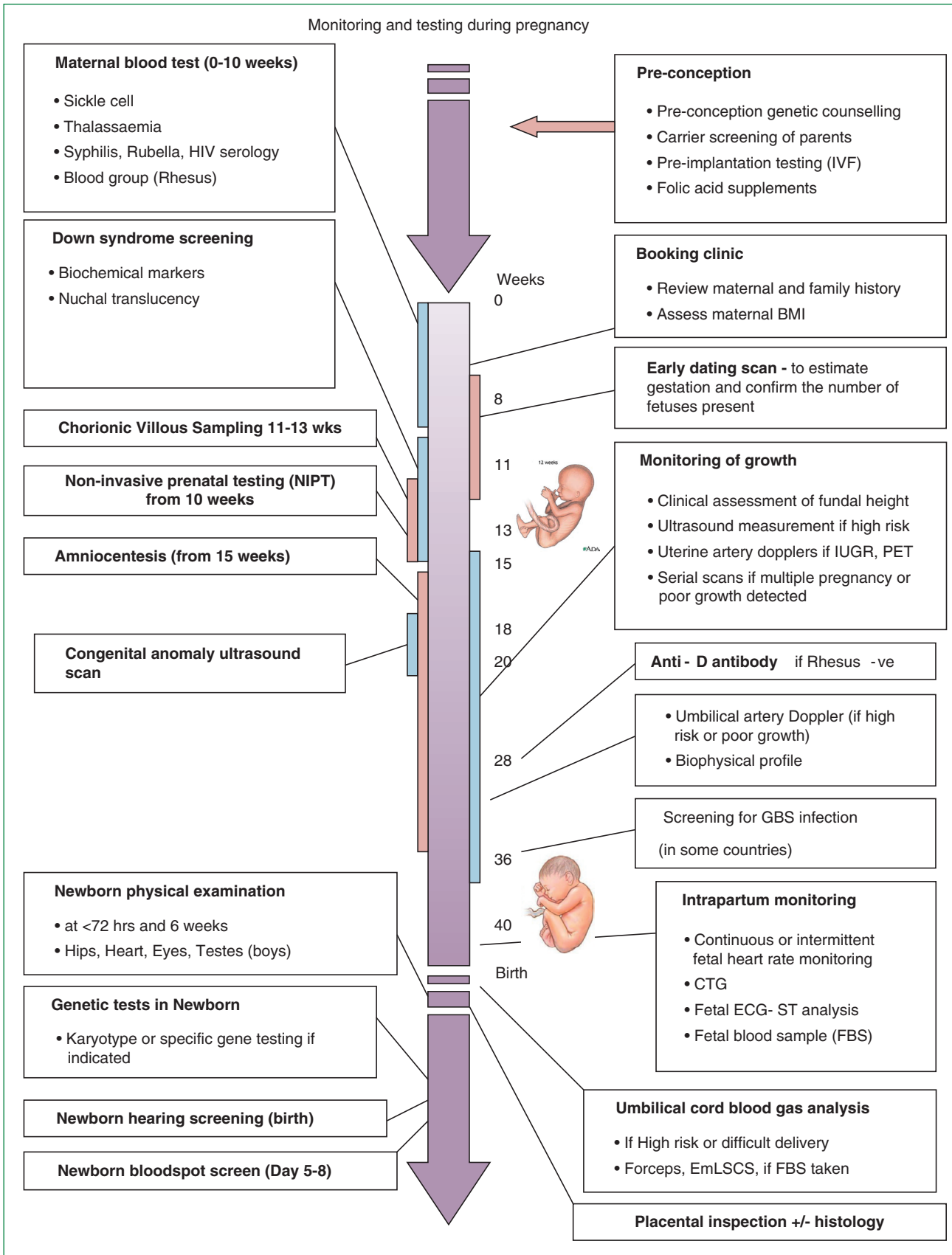

Figure 1.3 A timeline for fetal assessment and monitoring during pregnancy.

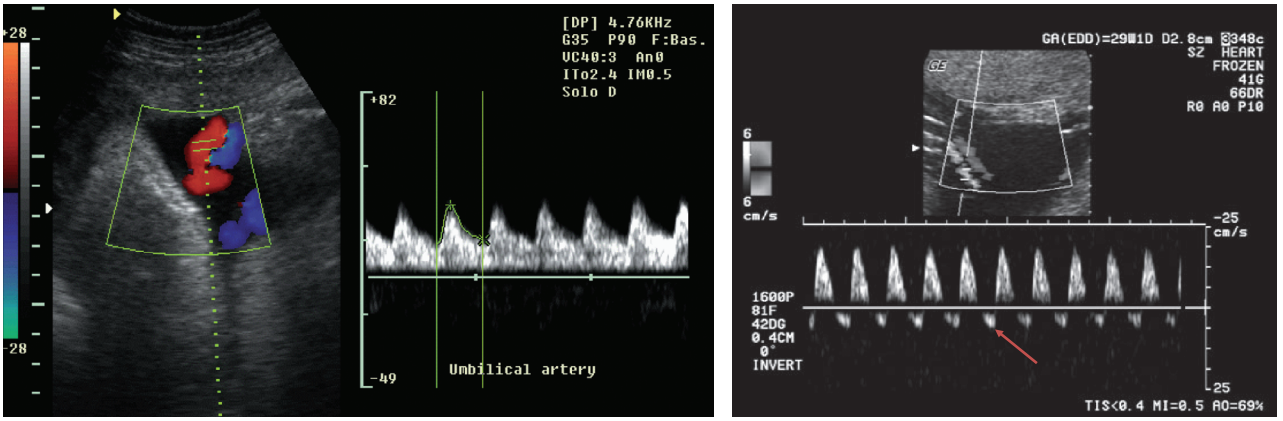

Figure 1.4 Doppler measurement of blood flow in the fetal umbilical artery. The left-hand panel shows normal forward flow throughout the cardiac cycle. The right-hand panel shows pathological reversed flow during diastole (see arrow).

Fetal heart rate monitoring, non-stress test and biophysical profile

The response of the fetal heart to naturally occurring Braxton Hicks contractions or fetal movements provides information on fetal health during the third trimester. A normal fetal heart trace has a baseline heart rate of 110–160 beats per minute, with good beat-to-beat variability and at least two accelerations and no decelerations in a 20-minute period. If abnormal, a further assessment with ultrasound is recommended to gather further information about fetal well-being. Depending on gestation, an abnormal fetal heart rate will sometimes necessitate early delivery of the baby.

In late pregnancy the biophysical profile combines the NST and ultrasound assessment of fetal movements. A score (2) is given for each of: heart rate accelerations, fetal breathing movements, fetal limb movements, movement of the trunk and adequate amniotic fluid depth. A normal well fetus will score 10/10, and a score of less than 8 is abnormal.

Table 1.1 Causes of abnormal amniotic fluid volumes and fetal consequences.

Causes of Polyhydramnios	**Causes of Oligohydramnios**
Maternal diabetes	Preterm rupture of membranes (PPROM)
Twin-to-twin transfusion syndrome (recipient)	Twin-to-twin transfusion (donor)
Obstruction to swallowing or absorption of liquor • Oesophageal atresia • Duodenal atresia • Abnormal swallowing Abnormal swallowing • Congenital myotonic dystrophy • Trisomy 18	Severe fetal growth restriction (IUGR) Renal anomalies • Renal agenesis (Potter's syndrome) or severe renal dysplasia. • ARPCKD • Posterior urethral valves (in males) Chromosomal anomalies
Fetal consequences of polyhydramnios	**Fetal consequences of oligohydramnios**
Increased risk of preterm labour and PPROM	Increased risk of pulmonary hypoplasia
Abnormal presentation (e.g. transverse or breech)	If severe, risk of fetal deformation

ARPCKD, Autosomal recessive polycystic kidney disease

Screening during pregnancy

Maternal blood screening

Screening programmes vary from country to country. In the UK, all pregnant women are routinely screened for syphilis, hepatitis B, immunity to rubella and haemoglobinopathies (sickle cell disease, thalassaemia), and HIV screening is strongly encouraged.

Fetal imaging

Ultrasound examination of the fetus for congenital abnormalities is now offered as a routine procedure. Major malformations of the central nervous system, bowel, heart, genitourinary system and limbs should be detected. Some disorders, such as twin-to-twin transfusion, pleural effusion and posterior urethral valves are amenable to fetal 'surgery'. In-utero surgery for congenital diaphragmatic hernia remains experimental. Advanced '4D' (3D seen in real time) ultrasonography allows visualization of the external features of the fetus, such as the presence of cleft lip (see Fig. 1.5).

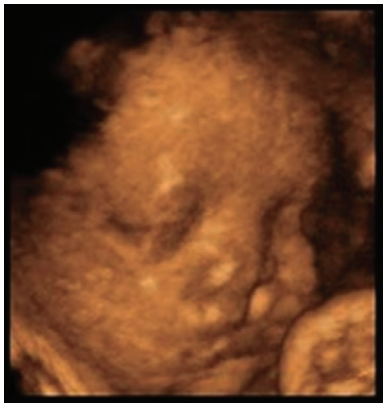

Figure 1.5 Cleft lip. Illustration courtesy of Dr Jason Ong.

Fetal magnetic resonance imaging (MRI) is now feasible and appears safe in pregnancy. The large field of view, excellent soft-tissue contrast and multiple planes of construction make MRI an appealing imaging modality to overcome the problems with ultrasound in cases such as maternal obesity and oligohydramnios, but MRI cannot be used for routine screening. It is useful in the assessment of complex anomalies such as urogenital and spinal anomalies, some fetal cardiac disorders, complex head and neck malformations (Fig. 1.6) and congenital diaphragmatic hernia. Its main use is to provide further information about fetal brain development when abnormalities are suspected on ultrasound.

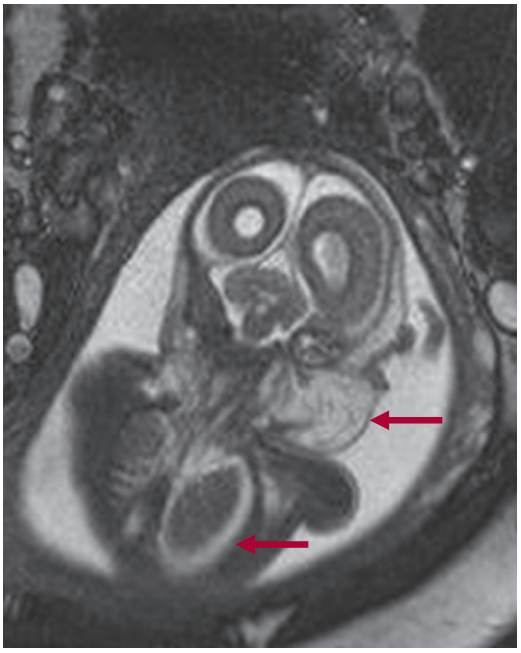

Figure 1.6 Fetal MRI scan (coronal view) showing large cystic hygroma on the left side of the neck (arrow) and an associated pleural effusion (arrow). Illustration courtesy of Dr Mike Weston.

Down's syndrome screening

Trisomy 21 affects 1 in 600 fetuses and 1 in 1000 live births. The incidence rises with maternal age (from 1 in 880 at 30 years to 1 in 100 at 40 years), but as more younger women are pregnant screening in the UK is offered to all pregnant women, regardless of age. The screening tests vary and are summarized in Table 1.2. If the risks after screening are high, then a diagnostic test (amniocentesis or chorionic villus sampling; CVS) is offered.

Table 1.2 Screening tests for Down's syndrome in UK.

Screening test	Timing (weeks of gestation)	Comments
Nuchal fold thickness	11–13	Measures translucency at nape of neck, which is increased in trisomy 18 and some cardiac defects. Gives age-related risk.
NIPT (Non-invasive prenatal testing)	10–22	Measures cell-free fetal DNA in the maternal circulation and can test for Trisomy 21 and other aneuploidies. Sensitivity is >99% and false positive rate 0.2%. Does not screen for neural tube defects. Only requires a maternal blood sample.
Triple test AFP hCG Oestriol	10–14	Gives age-related risk. AFP very high with neural tube defects.
Combined test Nuchal fold hCG h-PAPP	11–13	Biochemical screening with nuchal fold measurement to give age-related risk.
Quadruple test hCG AFP Oestriol Inhibin A	15–20	Suitable for late booking when nuchal fold measurement no longer reliable. Gives age-related risk.

AFP, alpha-fetoprotein; hCG, human chorionic gonadotropin; PAPP, pregnancy-associated plasma protein A.

CLINICAL TIP

It is important to remember that screening tests give a *risk* for Down's syndrome (higher or lower than the age-related risk), but they do not give a definitive diagnosis. Some parents find it very difficult to understand that even if the risk is only 1 in 100, they may still be the couple that go on to have an affected child. Parents need to be counselled carefully before undertaking screening.

Amniocentesis

Amniocentesis is valuable for the diagnosis of a variety of fetal abnormalities. Trisomy 13, 18 and 21 can be detected by PCR within 48 h, and the cells cultured for chromosome analysis (14 days) or to study enzyme activity. Ultrasound-guided amniocentesis is undertaken by passing a needle through the anterior abdominal wall into the uterine cavity. The risk of miscarriage is less than 1%. Larger volumes of amniotic fluid may be removed (amnioreduction) as a treatment for polyhydramnios, although this treatment may need to be repeated frequently.

Chorionic villus sampling

CVS involves the transcervical or transabdominal passage of a needle into the chorionic surface of the placenta after 11 weeks' gestation to withdraw a small sample of tissue. Because of the 1% risk of miscarriage, the test is reserved for the detection of genetic or chromosomal abnormalities in at-risk pregnancies, rather than as a mere screening test. Preliminary chromosomal results can be obtained within 24–48 hours by fluorescence in-*situ* hybridization (FISH) or quantitative PCR. Direct analysis requires cell culture (14 days), but comparative genomic hybridization (CGH) array testing is now used in most laboratories to analyze the chromosomes in detail.

Fetal blood sampling (cordocentesis)

Fetal blood sampling is an ultrasound-guided technique for sampling blood from the umbilical cord to assist in the diagnosis of chromosome abnormality, intrauterine infection, coagulation disturbance, haemolytic disease or severe anaemia. It can also be used for treatment, with in-utero transfusion of packed red blood cells during the same procedure. There is a 1% risk of fetal death, although this can be higher in babies who are already hydropic.

Fetal monitoring during labour

Intrapartum monitoring

In low-risk pregnancies, intermittent auscultation of the fetal heart rate (FHR) is all that is required. Continuous electronic monitoring of the FHR can be performed non-invasively with a cardiotocograph (CTG) strapped to the abdominal wall, or invasively with a fetal scalp electrode.

The CTG trace allows observation of four features:

- Baseline heart rate
- Beat-to-beat variability
- Decelerations:
  - **Early**: slowing of the FHR early in the contraction with return to baseline by the end of the contraction.
  - **Late**: repetitive, periodic slowing of FHR with onset at middle to end of the contraction.
  - **Variable**: *v*ariable, intermittent slowing of FHR with rapid onset and recovery.
  - **Prolonged**: abrupt fall in FHR to below baseline lasting at least 60–90 s; pathological if last >3 min.
- **Accelerations**: transient increases in FHR >15 bpm lasting 15 s or more. These are normal and are reassuring. The significance of absent accelerations as a single feature is not known.

The interpretation of the CTG must then be classified as normal, non-reassuring or abnormal (Box 1.1; see also Table 1.3 and Fig. 1.7a–d).

Although fetal heart rate monitoring has been in widespread use for over 30 years, it has not been shown to reduce morbidity in term infants. It has, however, increased the rate of instrumental and caesarean section delivery. There is no evidence that routine FHR monitoring in the low-risk fetus improves outcome. Intermittent auscultation seems to be acceptable in these cases.

Fetal scalp pH

This is used in conjunction with CTG monitoring. In the presence of an abnormal FHR, fetal scalp pH measurement may be helpful. Clinical decisions are made on the severity of the pH and lactic acidaemia (Table 1.4).

Fetal electrocardiogram (ECG)

The direct measurement of fetal ECG via a fetal scalp electrode can allow a more reliable FHR trace to be obtained than transabdominal Doppler assessment. When used in conjunction with a CTG it allows S-T waveform analysis (STAN). This

Box 1.1 Interpretations of the cardiotocograph.

- *Normal*: all three features fall into a reassuring category. Continue monitoring.
- *Non-reassuring*: One non-reassuring feature and two normal features. Start conservative measures such as left lateral position, intravenous fluids, consider tocolysis.
- *Abnormal*: One abnormal feature or two non-reassuring features, or significant bradycardia. Obtain a fetal blood sample and consider expediting delivery.

Table 1.3 Features of an intra-partum CTG (NICE 2014).

	What to look for on the CTG		
	Baseline heart rate (bpm)	**Variability around baseline**	**Decelerations**
Normal or 'reassuring'	100–160	5 bpm or more	None or early
'Non- reassuring'	161–180	<5 bpm for 30–90 min	Variable decelerations: • Dropping from baseline by ≤60 bpm and taking <60 s to recover. • Present for over 90 min. • Occurring with more than half of all contractions. OR Variable decelerations: • Dropping from baseline by >60 bpm or taking >60 s to recover. • Present for up to 30 min. • Occurring with more than half of all contractions. OR Late decelerations (at or after the peak of the contraction): • Present for up to 30 min. • Occurring with more than half of contractions.
Abnormal	Above 180 or below 100 bpm	<5 bpm for over 90 min	Non-reassuring variable decelerations (see above) which are: • Still observed 30 min after starting conservative measures. • Occurring with more than half of contractions. OR Late decelerations: • Present for over 30 min. • Does not improve with conservative measures. • Occurs with over 50% of contractions. OR Bradycardia, or a single prolonged deceleration lasting 3 min or more

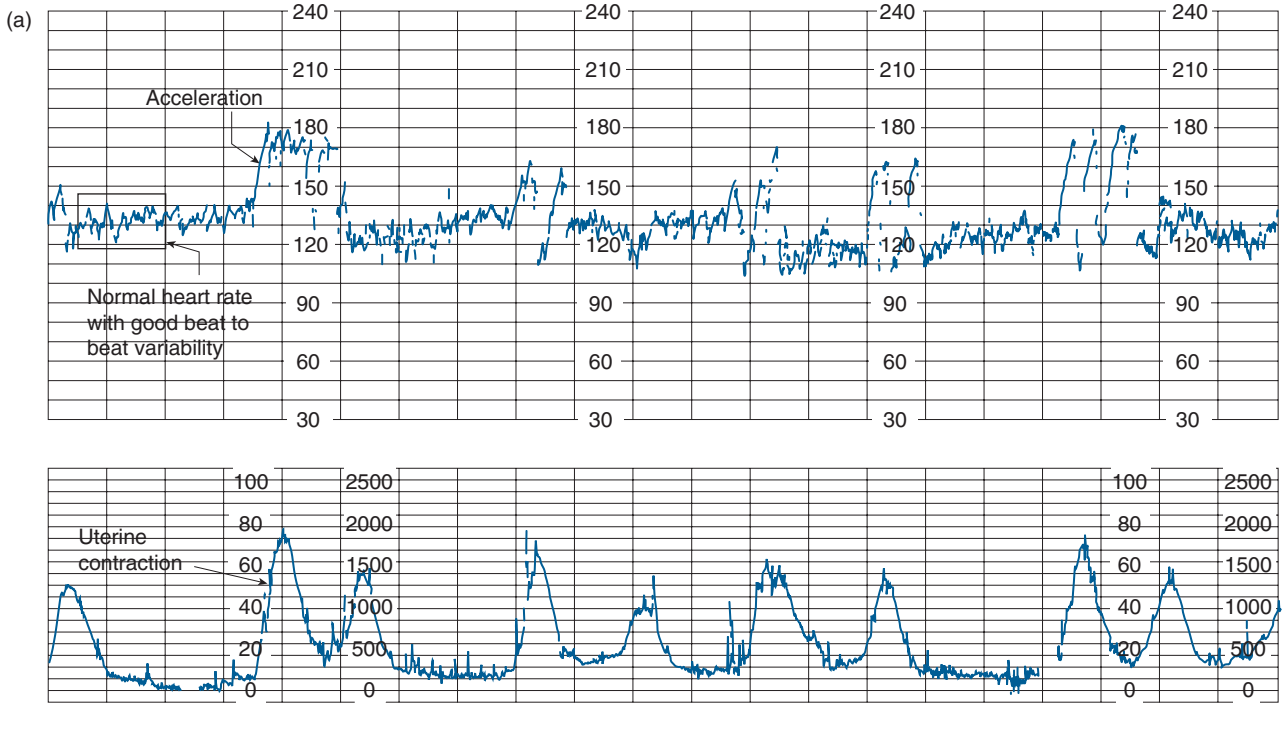

Figure 1.7a CTG showing fetal heart rate accelerations.

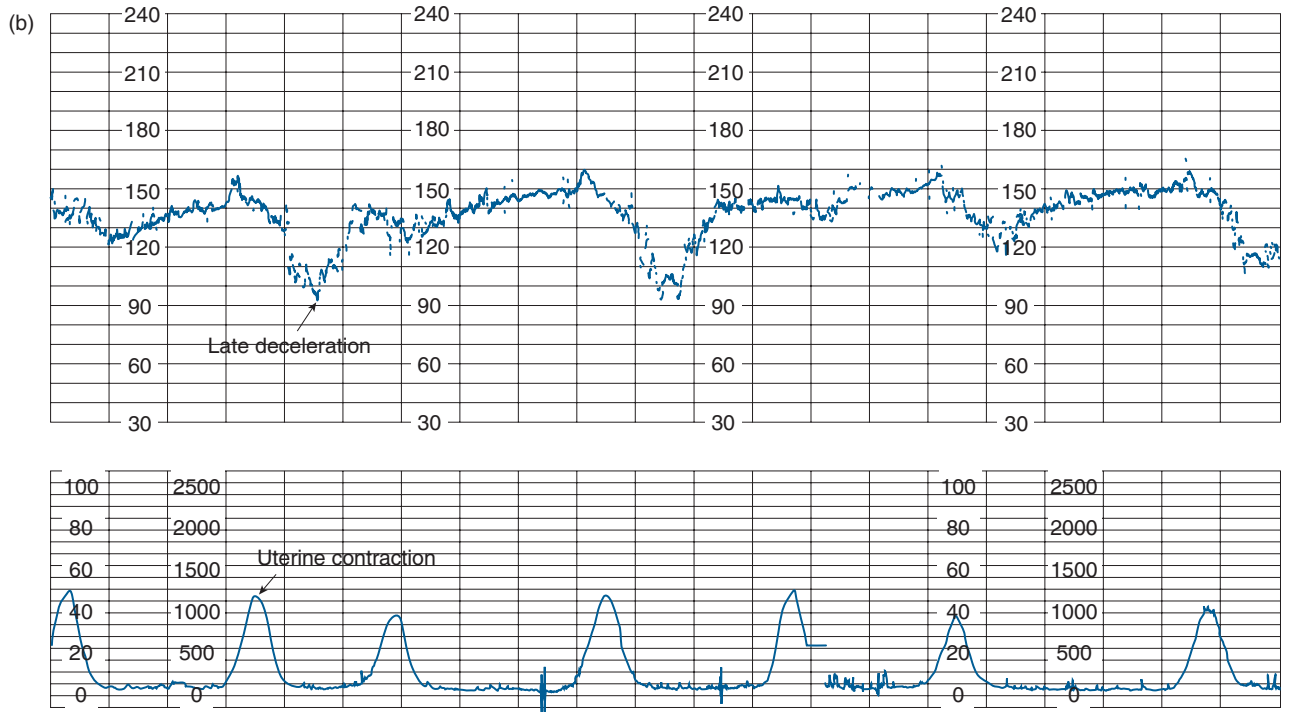

Figure 1.7b CTG showing late decelerations.

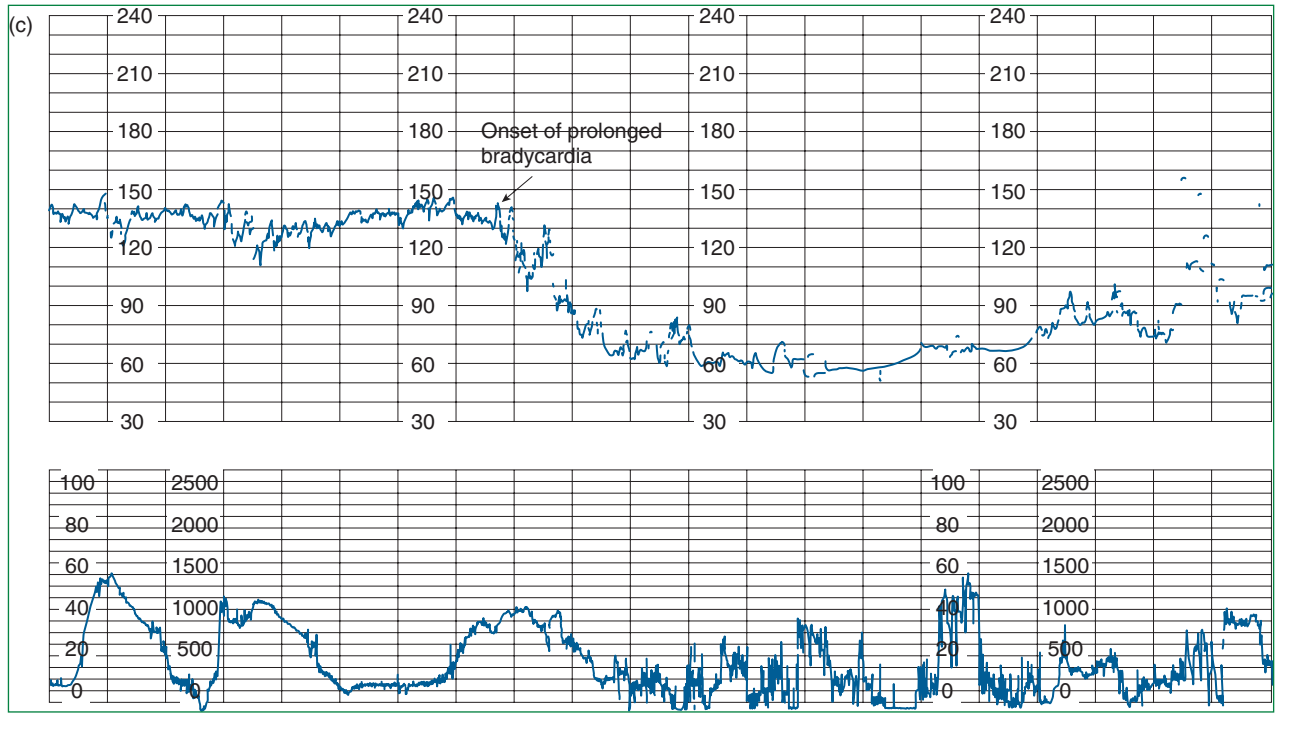

Figure 1.7c CTG showing normal heart rate followed by severe prolonged fetal bradycardia.

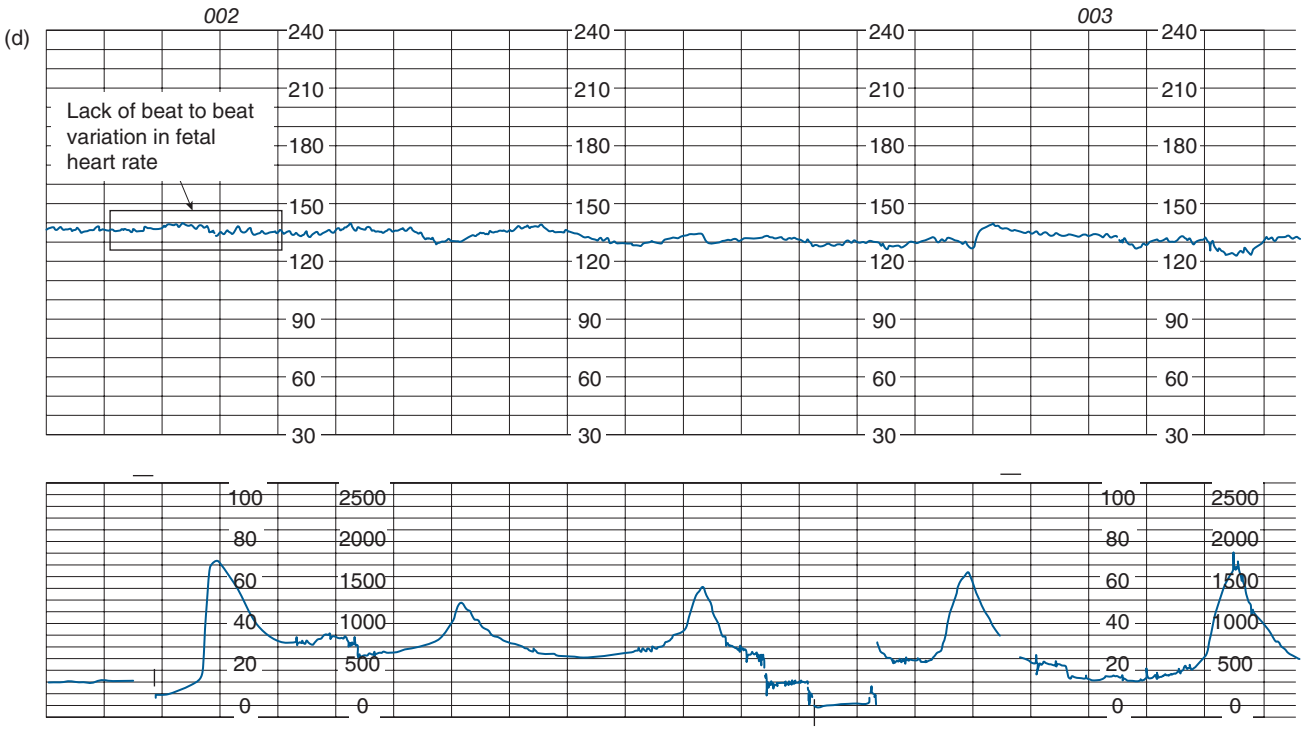

Figure 1.7d CTG showing loss of beat-to-beat variability.

Table 1.4 Clinical decisions based on blood acidosis.

Lactate (mmol l^{-1})	pH	Action
≤4.1	≥7.25	No action, continue to monitor fetus electronically
4.2–4.8	7.21–7.24	Repeat pH within 30 min
≥4.9	≤7.20	Deliver urgently

may reduce operative delivery for suspected fetal compromise, but it has not been widely adopted due to conflicting evidence of its value.

CLINICAL TIP

Software is now available to allow real-time central monitoring and recording of CTGs. This can aid clinical decision-making and improves clinical governance.

Fetal compromise

'Fetal distress' is a commonly used but emotive clinical term which usually refers to a stressed fetus showing signs of compromise, presumed due to a lack of oxygen. 'Fetal compromise' may be used to describe the 'at-risk' fetus, for example evidence of severe IUGR or abnormal Doppler flow. Factors causing fetal compromise are listed in Table 1.5.

Fetal compromise may lead to:

- A reduction in fetal movements.
- Passage of thick meconium into the amniotic fluid (this can be normal at term).

Table 1.5 Causes of fetal compromise.

Maternal	Hypotension Hypertension, including pre-eclampsia Diabetes mellitus Cardiovascular disease Anaemia Malnutrition Dehydration
Uterine	Hypercontractability, usually due to excessive use of oxytocin (Syntocinon) or prostaglandins
Placental	Abnormal placentation Abruption Vascular degeneration
Umbilical	Cord prolapsed True knot in cord Cord entanglement (e.g. monochorionic twins)

- FHR abnormality on CTG or fetal scalp electrode, as described above.
- Metabolic acidosis (pH <7.20) on fetal scalp sample or arterial umbilical cord blood gas sample.

Physiological changes at birth

At birth, the baby changes from being in a fluid environment, with oxygen provided via the umbilical vein, to an air environment, with oxygenation dependent on breathing. This remarkable adaptation requires considerable changes to the respiratory and cardiovascular systems within the first minutes after delivery. Other adaptations required include maintenance of glucose homeostasis (see Chapter 21) and thermoregulation (see Chapter 24).

While the fetus is *in utero* the lungs are filled with lung fluid, which is produced at up to 5 ml kg^{-1} per hour in response to the secretion of chloride ions in the pulmonary epithelium. During labour, rising adrenaline levels 'switch off' lung fluid secretion and reabsorption begins. At birth the baby generates enormous negative pressures (–60 cmH_2O), which fill the lungs with air. With the first two or three breaths much of the fetal lung fluid is expelled, while the remainder is absorbed into pulmonary lymphatics and capillaries over the first 6–12 hours (See Fig 1.8). Sometimes these clearance mechanisms fail and the lungs remain 'wet'; this is known as transient tachypnoea of the newborn (see Chapter 13). The stimulus for the first breath is a combination of cold, physical touch, rising carbon dioxide levels and cessation of placental adenosine. It is also in part a reflex reaction to emptying of the lungs of fluid (Hering–Breuer deflation reflex).

With the first few breaths the arterial oxygen tension (P_aO_2) increases from 2–3.5 kPa (15–25 mmHg) to 9–13 kPa (68–98 mmHg). This rise in oxygen tension results in constriction of the ductus arteriosus: this is functionally closed by 10–15 hours, but not anatomically closed until 4–7 days.

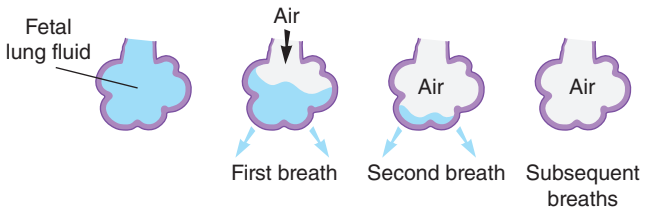

Figure 1.8 Clearance of lung fluid into the lymphatics with the first breaths.

There is also a marked fall in pulmonary vascular resistance, so that the pulmonary blood flow increases, the right ventricular pressure falls, and blood stops shunting from the right to left atrium across the foramen ovale.

The foramen ovale takes some time to close, and in 10% of babies it remains patent through life. With cord occlusion there is a marked decrease in blood flow in the IVC, and the ductus venosus closes.

Many factors may interfere with these physiological changes at birth. If there is severe birth asphyxia or respiratory distress, then blood may continue to be shunted through fetal channels, leading to persistent pulmonary hypertension of the newborn (PPHN) (see Chapter 16).

CLINICAL TIP

If a fetus is born to a mother who has not been through labour, then the molecular lung fluid reabsorption mechanisms are not fully activated and the baby may remain breathless for several hours after birth (tachypnoea of the newborn; TTN). This is more common after elective caesarean section.

SUMMARY

There have been huge advances in the understanding of fetal development, and conditions such as severe anaemia and pleural effusion are now amenable to treatment *in utero*. Screening for congenital abnormality has become more reliable. Ultrasound monitoring of fetal well-being – including Doppler measurements – allows intervention at earlier gestations, but the risk of continued fetal compromise must be balanced against those of preterm delivery. Good communication between the perinatal team is essential.

Acknowledgements

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FURTHER READING

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CHAPTER 2

Perinatal epidemiology and audit

Key topics

Essential Neonatal Medicine, Sixth Edition. Edited by Sunil Sinha, Lawrence Miall and Luke Jardine.

Companion website: www.essentialneonatalmed.com

Introduction

Conception, embryonic and fetal development, parturition and subsequent neonatal growth and development form a continuum. Obstetricians and neonatologists have, however, arbitrarily divided this into rigid categories, which are used to audit standards of care during the perinatal and subsequent periods. Unfortunately, international agreement regarding some of the terminology is lacking, and definitions within this developmental continuum given here are those used in the UK and Australia. It is recommended that the international reader familiarises themselves with local terminology and data.

Definitions of terms commonly used in perinatal medicine

- **Gestational age**: this is calculated from the first day of the last normal menstrual period to the date of birth, and is expressed in completed weeks.
- **Term delivery** occurs when the infant is born at or after 37 and before 42 weeks' gestation.
- **Preterm delivery** occurs if the infant is born less than 37 weeks' gestation. In the UK and Australia, 6–9% of infants are born preterm.
- **Extremely Preterm delivery** occurs if the infant is born at less than 28 weeks' gestation.
- **Very Preterm delivery** occurs if an infant is born at or after 28 weeks' gestation, and less than 32 weeks' gestation.
- **Moderately Preterm delivery** occurs if an infant is born at or after 32 weeks' gestation and less than 34 weeks' gestation.
- **Late Preterm delivery** refers to an infant born at or after 34 weeks' gestation and less than 37 weeks' gestation.
- **Post-term delivery** occurs if the infant is born at or after 42 completed weeks of gestation. Approximately 1% of infants are born post-term.
- A **live birth** is one in which there are signs of life (breathing, heartbeat or spontaneous movement) after complete expulsion from the mother, irrespective of the gestational age or birthweight.
- A **stillbirth**, or fetal death, in the UK is defined as an infant delivered at or after 24 weeks of pregnancy who shows no signs of life and has no heartbeat. In Australia, stillbirth is defined as an infant born at or after 20 weeks' gestation and/or weighing 400 g with no signs of life. As the definition varies from country to country, comparison of figures may be misleading.
- The stillbirth rate is expressed as the number of infants born dead at or after 24 weeks per 1000 live births and stillbirths.
- **Low birthweight** (LBW) refers to any infant who weighs less than 2500 g at birth (World Health Organization, 2016). In the UK and Australia, approximately 6% of live births are LBW. These infants are either born too early (preterm), or have grown inadequately in the uterus and are classed as 'small for gestational age'. Some LBW infants may be both preterm and small for gestational age.
- **Very low birthweight** (VLBW) infants are those who weigh less than 1500 g at birth. Approximately 1–1.5% of liveborn infants are VLBW.
- **Extremely low birthweight** (ELBW) infants are those who weigh less than 1000 g at birth. This category accounts for approximately 0.7% of all births.
- **Small for gestational age** (SGA). This term is generally synonymous with the fetus who has suffered intrauterine growth restriction (IUGR). Diagnosis depends on accurate assessment of gestational age (See Chapter 1) and plotting of weight on an appropriate growth chart. There is no international consensus on the definition of SGA, which varies from less than the 10th, 5th or 3rd percentiles or more than two standard deviations below the mean birthweight. Accordingly, incidence figures will vary. In the UK, SGA is defined as a baby weighing below the 10th centile for gestational age. Asymmetrical SGA refers to a baby whose weight is below the 10th centile, but whose head is above the 10th centile. This usually indicates late-onset IUGR (See Chapter 12).
- **Neonatal death** is death occurring within 28 days of birth in an infant whose birthweight was at least 500 g or, if the weight was not known, an infant born after at least 22 weeks' gestation.
- **Neonatal death rate** in the UK and Australia refers to the number of deaths within 28 days of birth of any child who had evidence of life after birth. Birthweight and/or gestational age criteria apply as for PMR.
- **Perinatal mortality rate** (PMR):

$$\text{PMR} = \frac{\text{Number of still births and neonatal deaths}}{\text{Number of stillbirths and live births}} \times 1000$$

- **Extended Perinatal Mortality Rate** (EPMR) refers to the total number of stillbirths and neonatal deaths per 1000 registered births.
- **Postneonatal death rate** (or late infant deaths) refers to the number of deaths of liveborn infants dying after 28 days but before one year of age per 1000 live births.
- **Infant death** is death occurring within one year of birth in a liveborn infant whose birthweight was at least 500 g, or at least 22 weeks' gestation if the birthweight was not known. This category includes neonatal deaths as defined above.

The role of perinatal and neonatal audit

By collecting epidemiological data and monitoring clinical indicators, it is hoped to improve care and clinical practice. Audit may identify variations in morbidity or mortality which warrants further investigation. The process can also facilitate collaboration and research.

Outcomes for preterm infants are discussed in Chapter 11. In many countries, large networks collect outcome data and the reader is recommended to familiarise themselves with their local network. Examples of these networks include the National Institute of Child Health and Human Development (NICHD), the Australia and New Zealand Neonatal Network (ANZNN), the National Neonatal Audit Programme (NNAP) in the UK, the Vermont Oxford Network in the USA, and the Canadian Neonatal Intensive Care Unit Network. The International Network for Evaluating Outcomes in Neonates (iNeo) is a collaboration between national neonatal networks including Australia and New Zealand, Canada, Israel, Japan, Spain, Sweden, Switzerland and the UK.

Classification of perinatal deaths

It is often difficult for clinicians to agree on the cause of death in a diverse group of patients. In Australia, the Perinatal Society of Australia and New Zealand (PSANZ) have developed a hierarchical classification, the PSANZ Perinatal Death Classification (PSANZ-PDC), to aid in the identification of the single most important factor which led to the chain of events that resulted in the perinatal death, and the PSANZ-Neonatal Death Classification (PSANZ-NDC) to identify the single most important factor in the neonatal period which caused the death (Chan *et al.*, 2004).

All perinatal deaths should be reviewed by a Perinatal Mortality Committee (or a Death Review Committee), including deaths of infants born within the service who may have died elsewhere. Membership of the committee should be multidisciplinary. The committee serves a number of functions which may include:

- Consistent classification of all deaths according to local requirements.
- Evaluation of factors surrounding and contributing to death.
- Development of recommendations for improving processes of care.
- Feedback to clinicians and parents based on above recommendations.
- Implementation of action required based on above recommendations.
- Data collection and documentation of perinatal deaths.

Perinatal loss can have significant social and psychological impacts on the family and staff. Following a perinatal death, parents should be allowed to spend private time with their baby, they should be offered the opportunity to create mementos (e.g. footprints, lock of hair). Pastoral care services should be available if requested. Mothers may require advice with regards to lactation, and ongoing support services may be necessary.

The role of autopsy

The most reliable cause of death is obtained by an experienced perinatal pathologist conducting an autopsy examination, but even following such examination the precise cause of death may remain undetermined, particularly when the infant dies before birth. Even if the cause of death is known, autopsy can still have a valuable role in confirming this and may sometimes identify previously unrecognized abnormalities. Unfortunately, autopsy rates appear to be declining. If still possible, the placenta should also be examined by a perinatal pathologist, and in some cases this alone may elicit the aetiology of a perinatal death.

CLINICAL TIP

The role of the coroner. Most jurisdictions have a Coroners' Act (or equivalent) which requires all reportable deaths, including those where cause of death cannot be explained with certainty or those dying in an unusual circumstance, to be reported to the coroner or other responsible official. Usually, a stillborn child is not reportable.

Factors affecting perinatal death rates

Perinatal deaths have a wide range of causes. They can result from maternal conditions, problems in the placenta, conditions affecting the fetus or newborn, or a combination of the above. Sometimes the cause of perinatal death is not identifiable. The 2014 MBRRACE-UK report showed the extended PMR was approximately 5.9 per 1000 live births, approximately 70% of which are stillbirths and 30% are neonatal deaths (Manktelow *et al.*, 2016). The main causes of neonatal death were congenital abnormalities (27.9%), neurological (11.9%) and extreme prematurity (11.7%).

Maturity is of course an important factor in the PMR (see Fig. 2.1). The extreme preterm infant is discussed in Chapter 11. Multiple births have a much higher PMR, and this is discussed in Chapter 3. The sex of the fetus or infant is also important, with males known to have a slightly higher rate than females. Mortality rates also vary between regions and countries, and have been decreasing over time (see http://www.who.int/gho/child_health/mortality/neonatal_infant/en/)

CLINICAL TIP

Maternal factors which increase the risk of perinatal mortality include lower social class, coexisting medical condition, poor nutrition, underutilization of antenatal services, age <20 years, age >40 years, indigenous status, and use of assisted reproductive technology (ART).