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

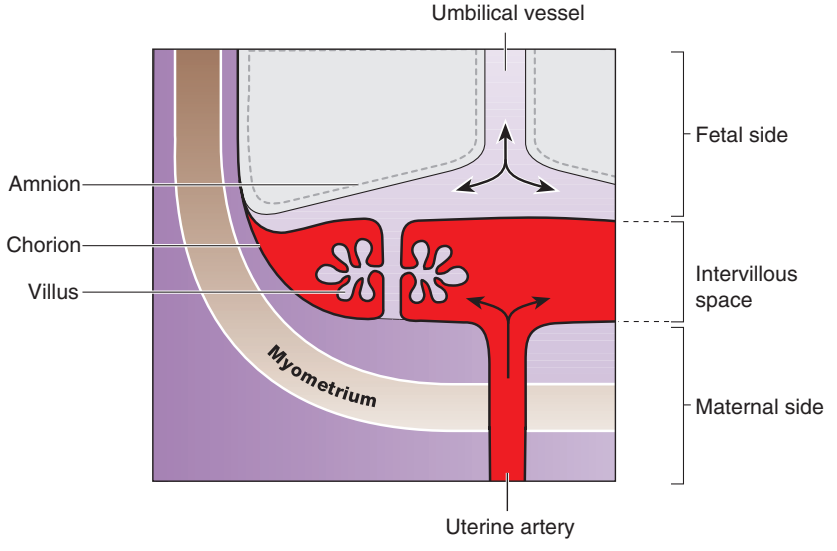

Figure 1.1 Diagram of placental structures showing blood perfusion.

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.

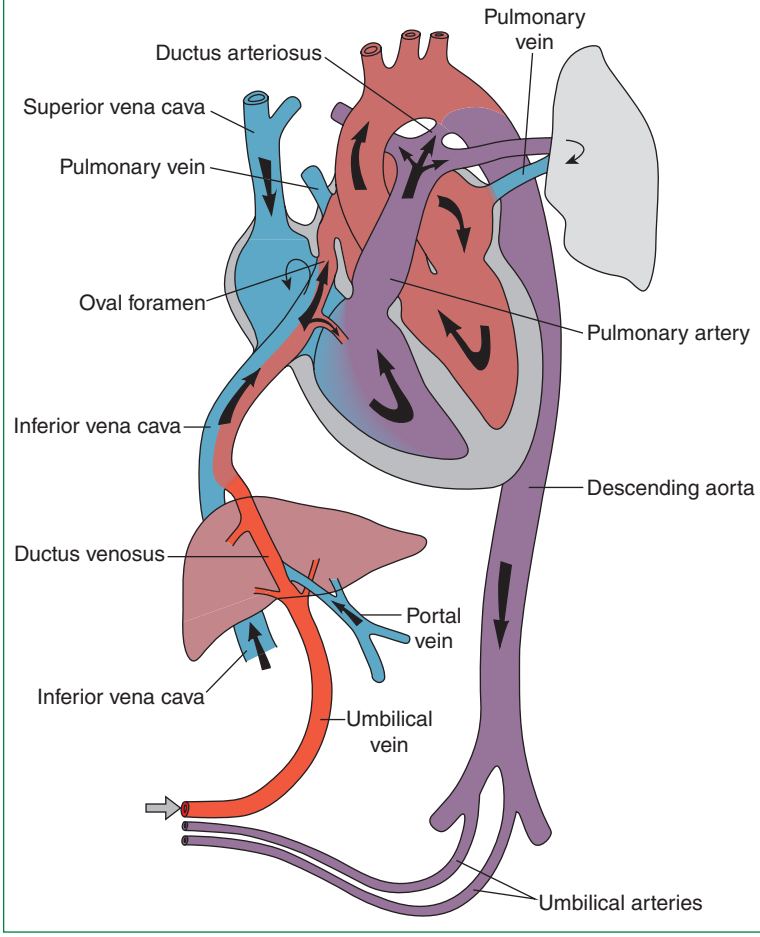

Figure 1.2 Diagram of the fetal circulation through the heart and lungs, showing the direction of flow through the foramen ovale and ductus arteriosus.

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.

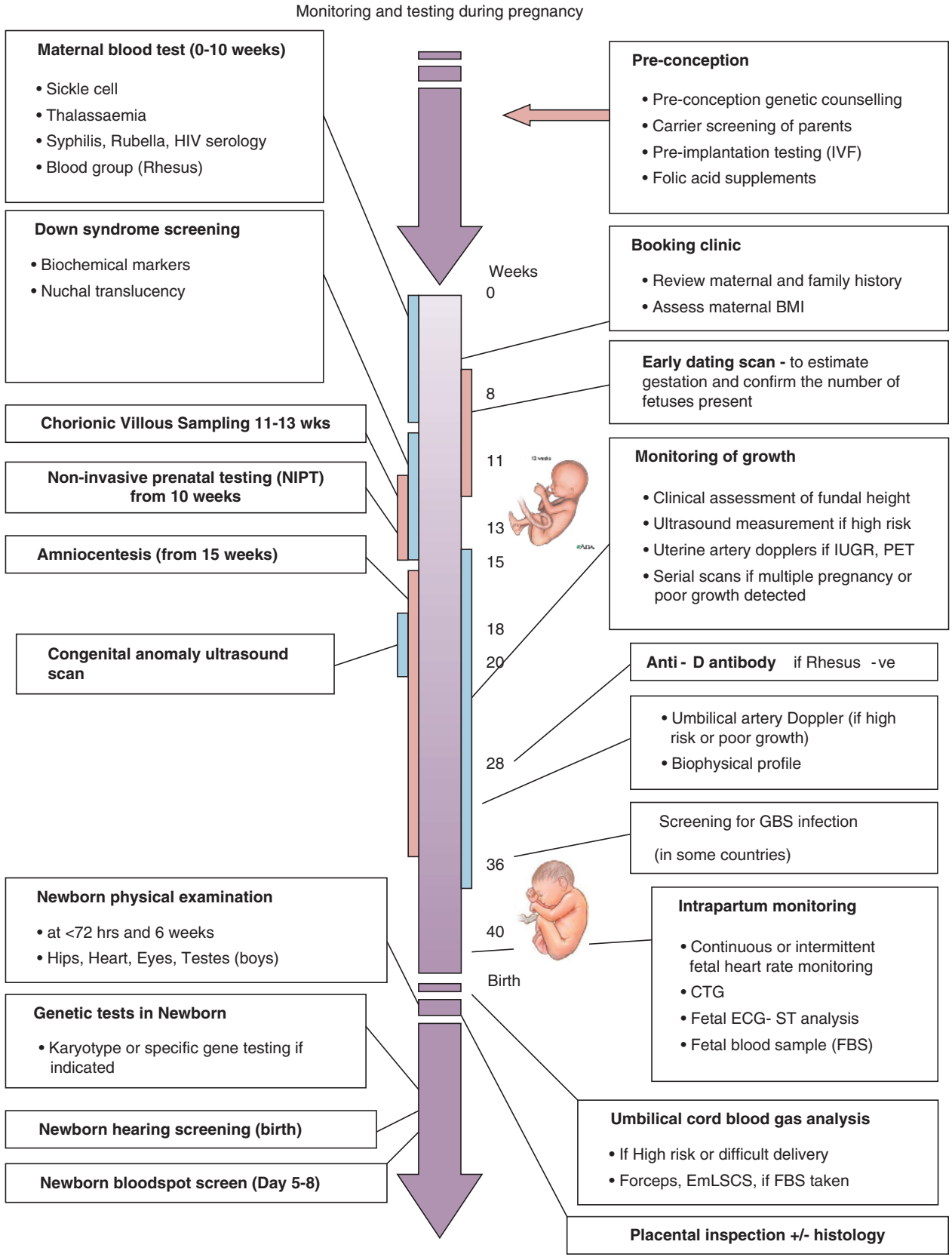

Figure 1.3 A timeline for fetal assessment and monitoring during pregnancy.

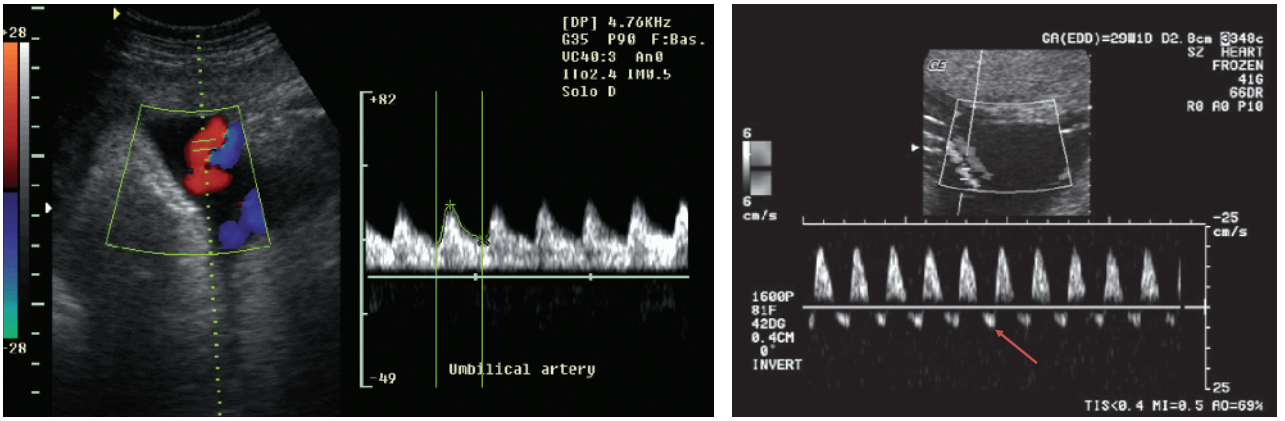

Figure 1.4 Doppler measurement of blood flow in the fetal umbilical artery. The left-hand panel shows normal forward flow throughout the cardiac cycle. The right-hand panel shows pathological reversed flow during diastole (see arrow).

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).

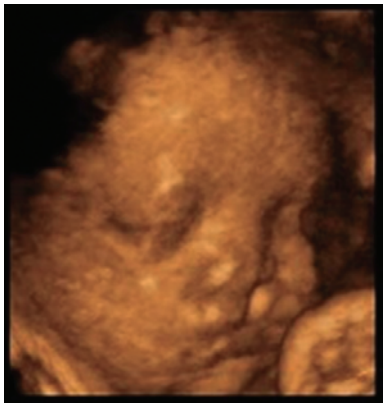

Figure 1.5 Cleft lip. Illustration courtesy of Dr Jason Ong.

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.

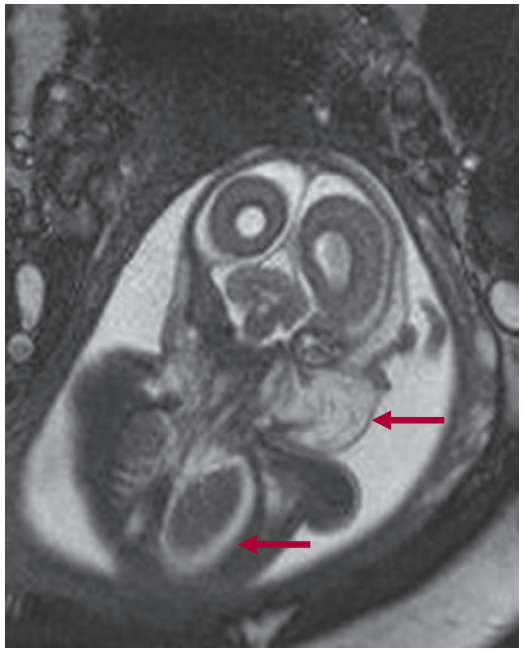

Figure 1.6 Fetal MRI scan (coronal view) showing large cystic hygroma on the left side of the neck (arrow) and an associated pleural effusion (arrow). Illustration courtesy of Dr Mike Weston.

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

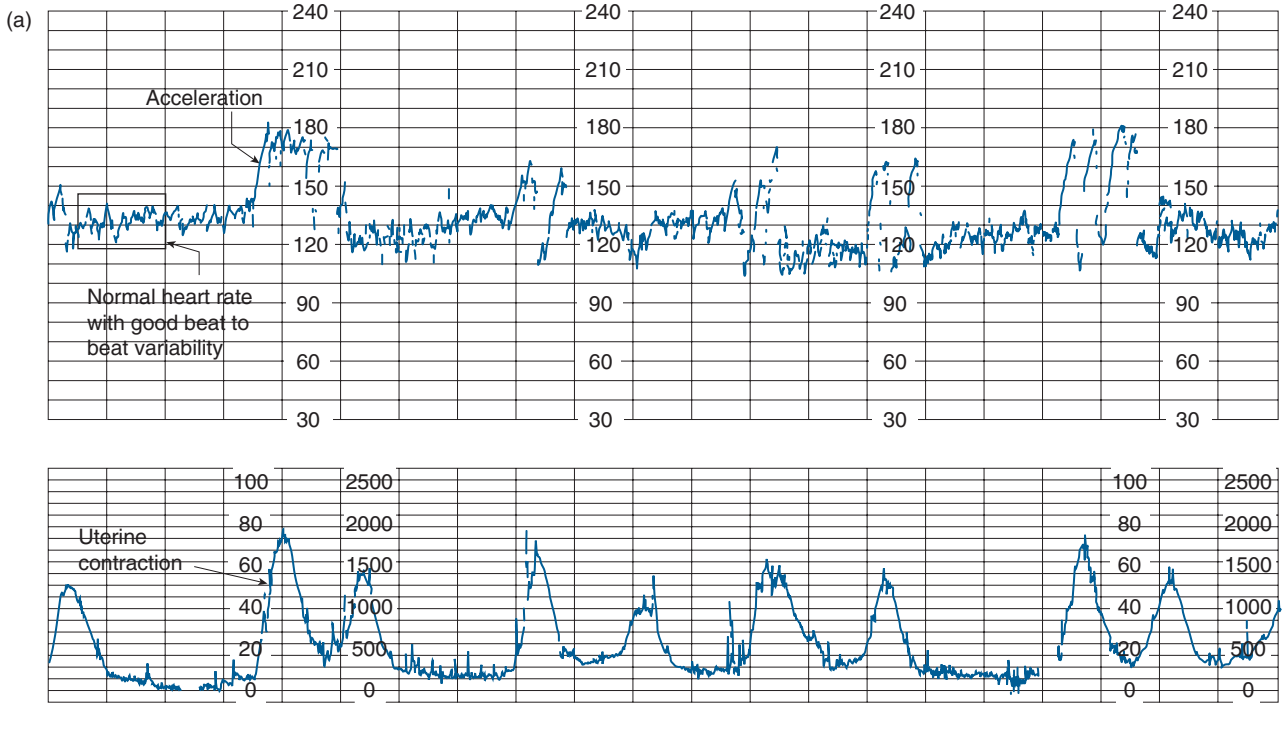

Figure 1.7a CTG showing fetal heart rate accelerations.

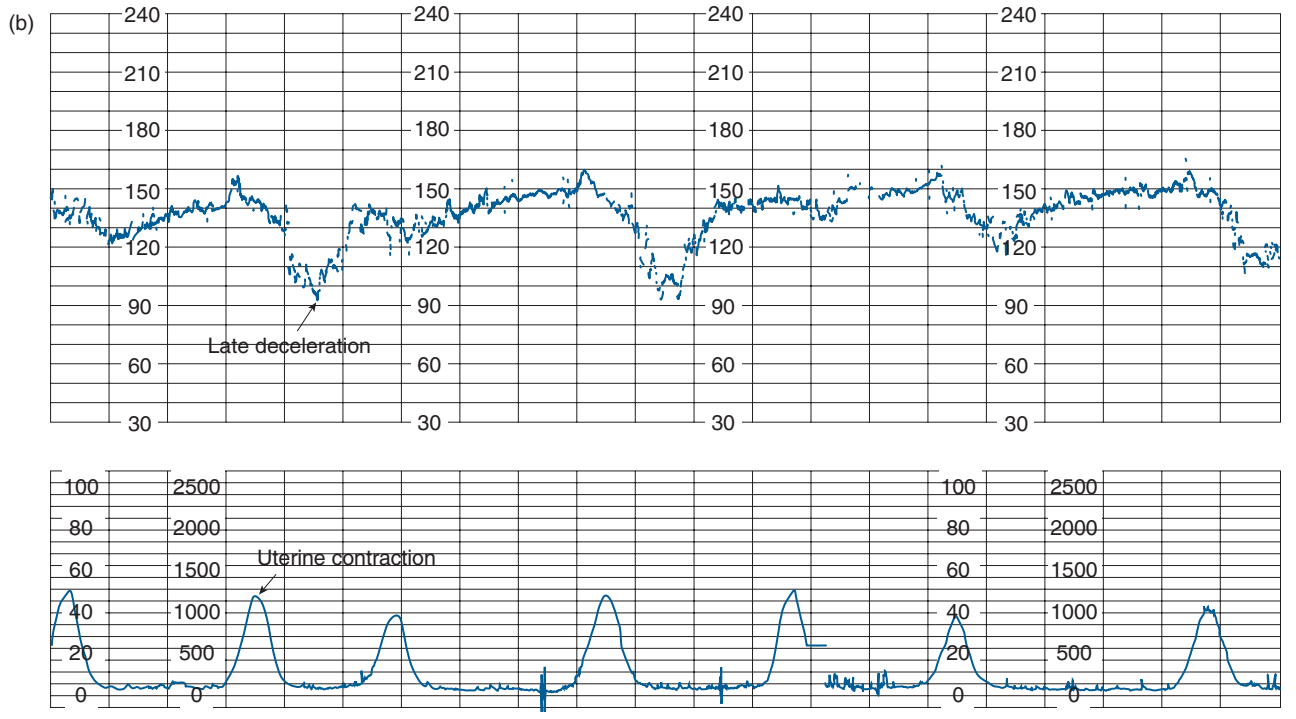

Figure 1.7b CTG showing late decelerations.

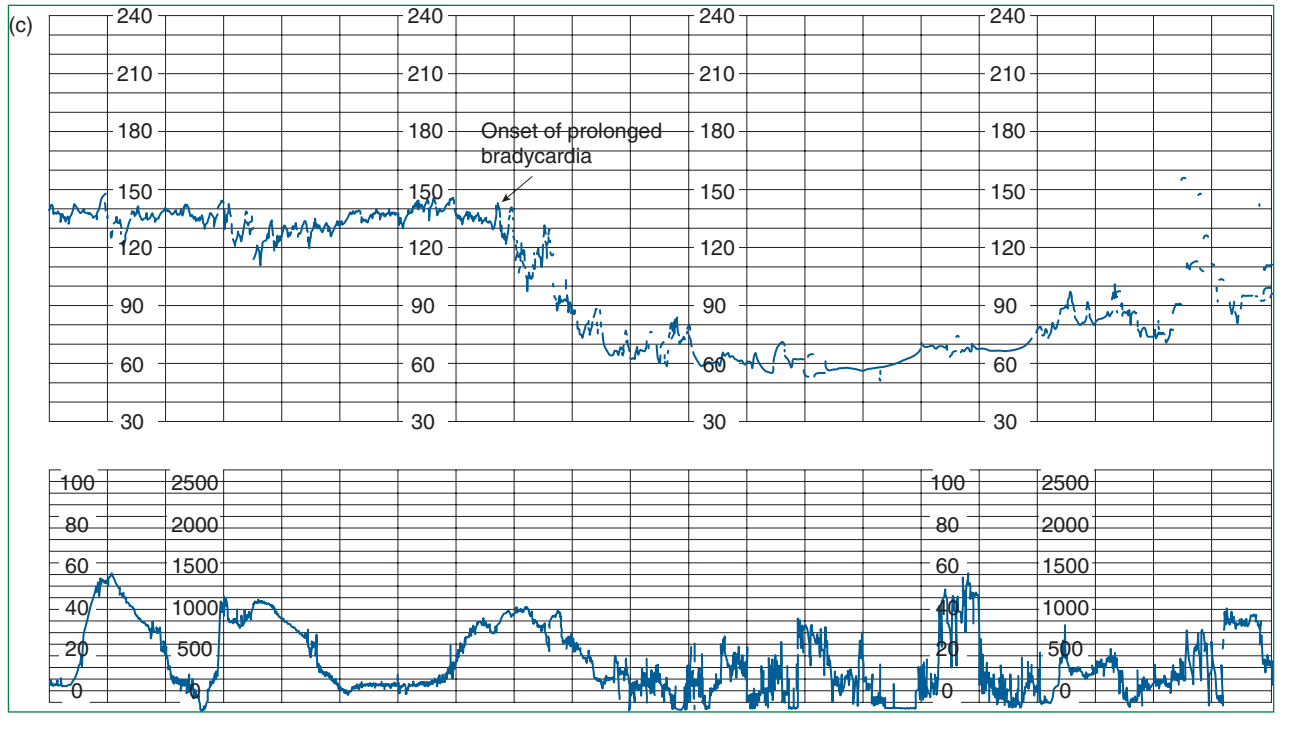

Figure 1.7c CTG showing normal heart rate followed by severe prolonged fetal bradycardia.

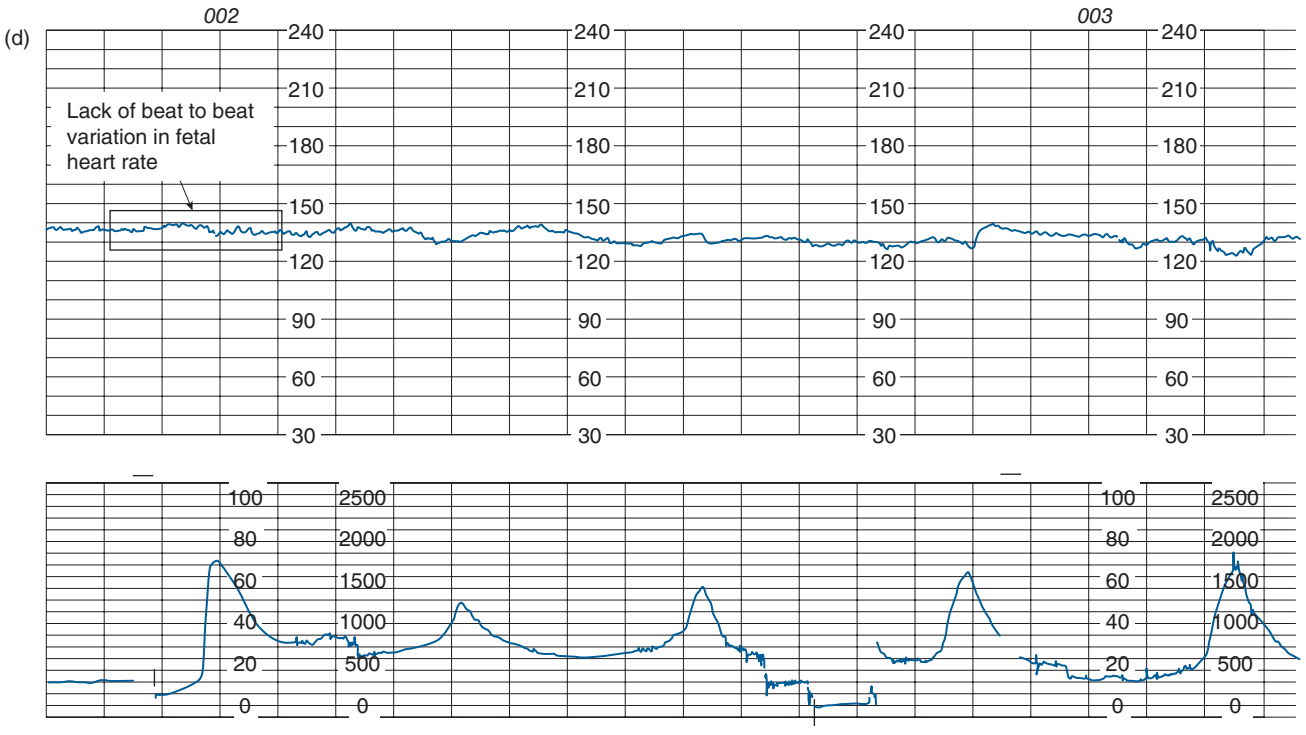

Figure 1.7d CTG showing loss of beat-to-beat variability.

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.

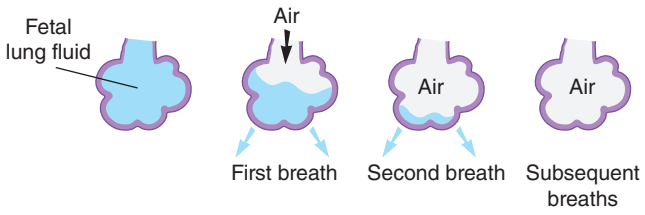

Figure 1.8 Clearance of lung fluid into the lymphatics with the first breaths.

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

The authors thank Dr Andrew Breeze for helping to review this chapter.

FURTHER READING

Hillman, N., Kallapur, S., Jobe, A. (2012) Physiology of transition from intrauterine to extrauterine life. *Clinics in Perinatology*, **2012;39** (4), 769–783.

NICE (2014) Guideline on intrapartum care for healthy women and babies. See https://www.nice.org.uk/guidance/cg190/chapter/1-recommendations.

Twiss, P., Hill, M., Daly, R., Chitty, L. (2014) Non-invasive prenatal testing for Down Syndrome. *Seminars in Fetal and Neonatal Medicine*, **2014, 19** (1), 9–14.

Now visit **www.essentialneonatalmed.com** to test yourself on this chapter.