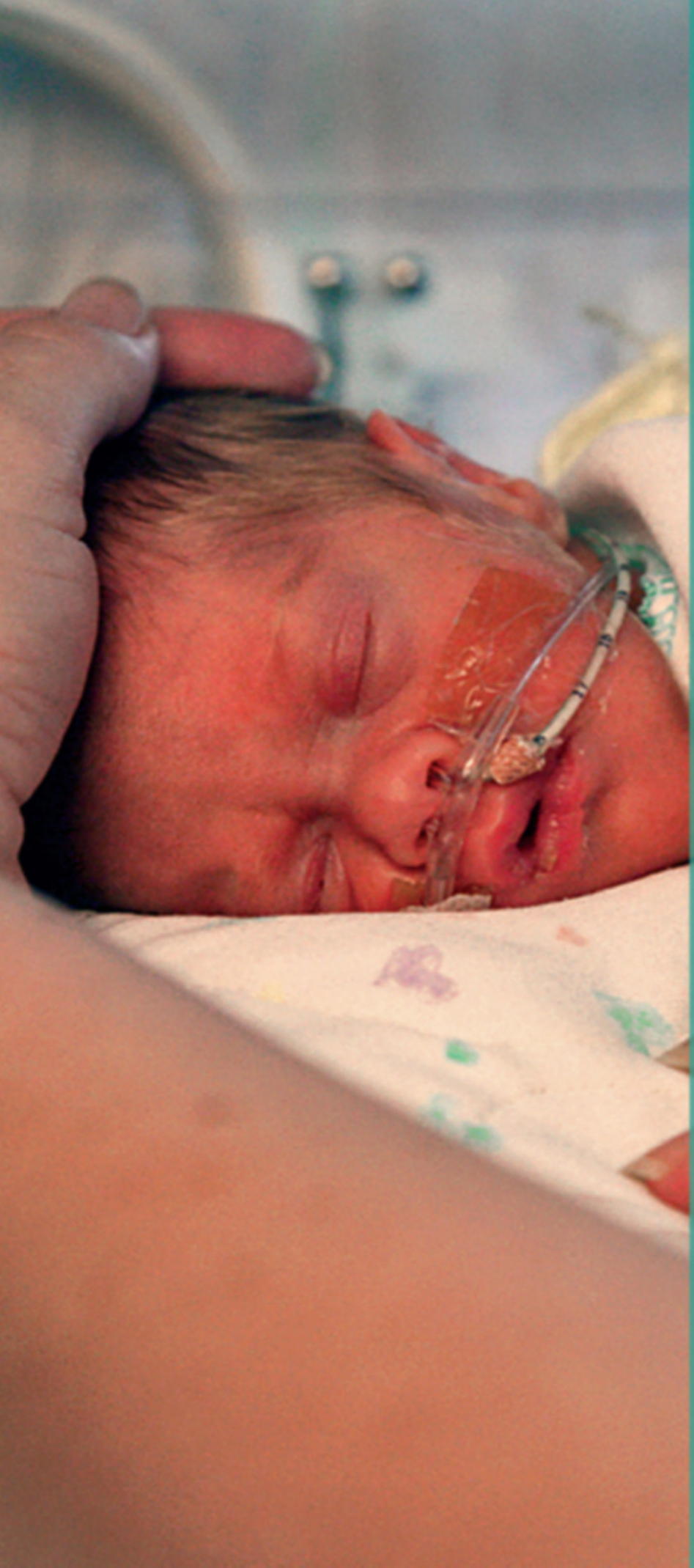

Neonatology at a Glance

Second Edition

Tom Lissauer
Avroy A. Fanaroff

WILEY-BLACKWELL

Neonatology at a Glance

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Contents

Preface

This book provides a concise, illustrated overview of neonatal medicine. We have aimed to cover the breadth of neonatology in under 100 double pages, with major topics confined to one or two double pages. This has been a challenging exercise as it would have been easier to write a longer book, but this format has forced us to identify the most important points and omit unnecessary details. The book has been designed to make learning easier and more enjoyable. Modern education emphasizes visual impact and this is reflected in this book. The layout, photographs and illustrations have been chosen to assist learning and make the book attractive and interesting. In addition, there are specific aids to learning, with boxes to highlight key points and questions and answers.

The book covers the preterm infant and the wide range of common or important neonatal clinical conditions and their management. It also puts neonatology into context, with sections on its history, epidemiology, perinatal medicine and a global overview, together with the care of the normal newborn and how to recognize the sick infant. The challenging topics of ethical issues, research, quality assurance, evidence-based medicine, when a baby dies, autopsy and neonatal outcome are also considered. Practical procedures are described, including neonatal resuscitation and neonatal transport; a description of cranial ultrasound and echocardiography have been included to inform the practicing clinician about them even if they do not perform these procedures themselves.

The book is written for pediatric interns and residents, medical students, neonatal nurse practitioners, neonatal nurses, therapists and midwives who care for newborn babies either on a neonatal unit or with their mothers in the normal newborn nursery (postnatal wards). Whilst the book describes the salient features of intensive care, such as stabilizing the sick infant and respiratory support, it is not a manual of neonatal intensive care, of which there are many.

The book has been a collaborative project between editors and contributors from both North America and the UK. Where practices differ between the two sides of the Atlantic this has been acknowledged and described. This collaboration has been highly educational and hugely enjoyable for the editors and contributors as well as improving the book by forcing us to concentrate on the principles of practice instead of the details.

This new edition has allowed us to update and revise the book. We would like to thank the many doctors, nurses and therapists whose positive comments about the book encouraged us to produce this 2nd edition. We would also like to thank our families for allowing us to spend so much time over many years on this project.

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1 Milestones in neonatology

The care of newborn infants has evolved over the last century from simple and empirical care to modern, evidence-based, high-tech medicine. Neonatal mortality has correspondingly declined dramatically from 40/1000 live births in 1900 to <4/1000 in the US and UK. Improved obstetric care and maternal health and nutrition have also contributed. It was only in the 1950s that medical care of healthy and sick newborn infants was transferred from obstetricians to pediatricians. The specialty of neonatology developed only in the 1960s, and the first certifying examination for physicians in the US was held in 1975.

Thermal regulation

- 1890s: Tarnier in France showed that a warm, controlled environment reduced mortality of infants <2 kg from 66% to 38% (Fig. 1.1).
- 1893: Budin, Tarnier's student, established the first unit for premature babies in Paris, emphasizing thermal regulation and breast-feeding.
- Early 1900s: premature babies in incubators were exhibited in fairs around Europe and the US (Fig. 1.2).
- 1950s: Silverman in the US conducted elegant randomized controlled trials to confirm the beneficial effects of thermal control (including humidity) on mortality.
- 2000s: Heat loss at delivery of extremely preterm babies minimized by plastic wrapping.

Nutrition

- 1880s: Tarnier and Budin recommend early feeding and intragastric 'gavage' feeding via a rubber tube inserted through the mouth.

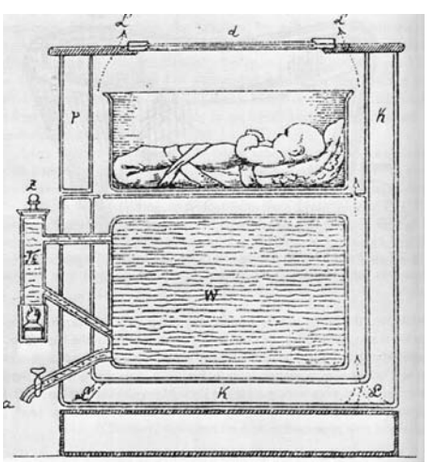

Fig. 1.1 The Tarnier incubator. The water was heated by the oil flame. The baby was kept warm by the heated air circulating around the incubator.

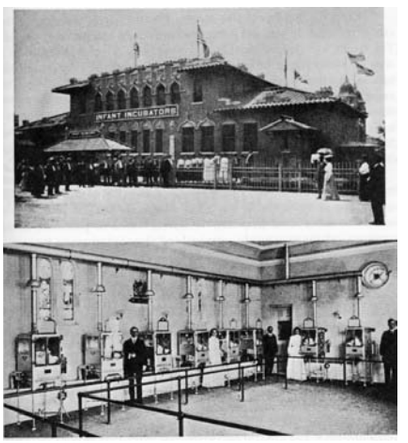

Fig. 1.2 Incubators with premature babies at the Pan-American Exposition, Buffalo, New York in 1901. (Source: Silverman WA. Incubator-baby side shows. *Pediatrics* 1979; **64**: 127. Courtesy of the American Academy of Pediatrics.)

- 1907: Rotch in US introduces infant formula. Breast-feeding declines as some believed formula was superior.
- 1940s: Gavage feeding via a nasogastric tube used in neonatal units.
- 1940s: Feeding of preterm infants delayed up to 4 days to avoid aspiration. Adverse effects (hypoglycemia, increased bilirubin and impaired development) recognized only in the 1960s, and early feeding reintroduced.
- 1960s: TPN (total parenteral nutrition) by central venous catheter introduced centrally, then via peripheral veins.
- 1960s: Infant formula associated with neonatal tetany from hypocalcemia and hemolysis from vitamin E deficiency.
- 1980s: Development of special formulas for very low birthweight infants.
- 1980s: Resurgence of use of breast milk. Human milk fortifiers developed for preterm infants.
- 2000s: Addition of long-chain polyunsaturated fatty acids (LCPUFA) to formula.

Rhesus hemolytic disease

Kernicterus, from bilirubin deposition in the brain from rhesus disease, was first described in 1938. Exchange transfusions became a common procedure in neonatal units and saved an estimated 8000 lives/year in the US alone.

- 1925: Hart describes first exchange transfusion – blood given via saphenous vein, removed from anterior fontanelle.
- 1940: Landsteiner discovers rhesus factor.
- 1945: Coombs develops Coombs test (direct antiglobulin test, DAT) to detect rhesus agglutinins.

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• 1947: Diamond describes exchange transfusion via umbilical vein with rubber catheter.
• 1963: Liley introduces intrauterine transfusion.
• 1964: Freda and Clarke develop prophylaxis with anti-D immunoglobulin.
• 1968: Rho(D) immune globulin prophylaxis introduced. Rhesus disease now almost completely prevented.

Antibiotics

Before antibiotics, mortality from neonatal sepsis was almost 100%, but it declined markedly when penicillin was introduced in 1944. The organisms causing sepsis have changed (Fig. 1.3).

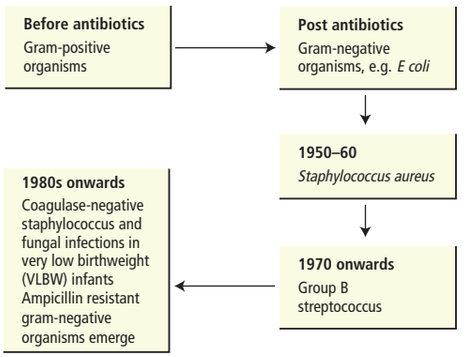

Fig. 1.3 Change with time of main organisms causing neonatal infection.

Respiratory distress syndrome (RDS)

Oxygen therapy, monitoring and respiratory support

Whereas about 25 000 infants died every year in the US from RDS in the early 1950s, by 2003 there were fewer than 500 such deaths. This has resulted from:
• understanding the pathogenesis of RDS, which enabled development of surfactant replacement therapy
• antenatal corticosteroids to induce surfactant and lung maturation
• developments in respiratory support:
  – oxygen therapy
  – continuous positive airway pressure (CPAP), introduced by Gregory
  – mechanical ventilators, first shown to improve survival by Swyer in Toronto and Reynolds in London (1965)
• ability to closely monitor vital signs and blood gases:
  – cardiorespiratory monitors for neonates
  – measurement of blood gases on small blood samples
  – umbilical/peripheral artery catheters
  – transcutaneous arterial O_2 and CO_2 monitors
  – non-invasive oxygen saturation monitors.

History of respiratory distress syndrome (surfactant deficiency)

• 1955: Pattle describes properties of surfactant.
• 1956: Clements isolates surfactant.
• 1959: Avery and Mead demonstrate lack of surfactant in preterm lungs.
• 1972: Liggins and Howie show that prenatal corticosteroids to the mother induce fetal lung maturity.
• 1980: Fujiwara – first surfactant replacement therapy.
• 1985: Multicenter clinical trials of natural and artificial surfactant replacement therapy.
• 1989: Surfactant therapy approved.

Key point

Since the 1950s RDS has been the major focus of research in neonatology. Understanding its pathophysiology and the biochemistry of surfactant has been the key to developing surfactant therapy and respiratory support, which have dramatically improved survival.

Development of neonatal intensive care

• 1922: First neonatal unit in US in Chicago by Hess; in UK by Crosse in Birmingham in 1945.
• 1960s and 1970s: Development of regional neonatal intensive care units with dedicated staff, introduction of CPAP and mechanical ventilation.
• 1970s: Ultrasound to identify intraventricular hemorrhage.
• 1970s: Ability to safely perform surgery in tiny infants.
• 1980s: Development of multicenter clinical trials, national and international.
• 1980s: ECMO (extracorporeal membrane oxygenation).
• 1990s: NO (nitric oxide) therapy for persistent pulmonary hypertension of the newborn.
• 2000s: Mild hypothermia shown to reduce morbidity of hypoxic–ischemic encephalopathy.

Challenges for the future

• Reduce prematurity, hypoxic–ischemic brain injury, neonatal infection, congenital abnormalities.
• Avoid complications of preterm infants: brain injury, necrotizing enterocolitis, bronchopulmonary dysplasia (chronic lung disease), retinopathy of prematurity.
• Practice evidence-based medicine.
• Improve quality assurance – reduce medication errors etc.
• Develop better non-invasive monitoring.
• Enhance nursery environment.
• Confront ethical dilemmas at the limit of viability.
• Improve/extend care at home of technology-dependent infants.
• Develop personalized medicine incorporating modern genetics.
• Global reduction of neonatal mortality, to achieve Millennium Development Goal target by 2015.

2 Epidemiology

Epidemiology is the study of factors affecting disease or death. In perinatal medicine the focus is on the prevalence and causes of illness and death and long-term disability in mothers, the fetus and newborn infants.

Definitions

Newborn infant

- **Preterm:** *<37 completed weeks of gestation.*
- **Term:** *37–41 completed weeks of gestation.*
- **Post-term:** *≥42 completed weeks of gestation.*
- **Low birthweight (LBW):** *<2500 g.*
- **Very low birthweight (VLBW):** *<1500 g.*
- **Extremely low birthweight (ELBW):** *<1000 g.*

Mortality

- **Maternal mortality ratio:** *the number of maternal deaths (during pregnancy and within 42 days postpartum) per 100 000 live births.*
- **Stillbirth:** *Variable definitions. In US, fetal death (no signs of life) ≥20 weeks' gestation. In the UK, fetus born with no signs of life after 24 weeks. For international comparison, WHO recommend defining stillbirth rate as fetal deaths >1000 g or >28 completed weeks per 1000 total births.*
- **Perinatal mortality rate (PMR):** *stillbirths plus early neonatal deaths (up to 6 completed days of life) per 1000 live and stillbirths (adjusted as above for international comparisons).*
- **Neonatal mortality rate (NMR):** *deaths in the first 4 weeks (27 completed days) of life per 1000 live births.*
- **Post-neonatal mortality rate:** *deaths from 28 days until 1 year per 1000 live births.*
- **Infant mortality rate:** *deaths in the first year of life per 1000 live births.*

These indicators are valuable as measures of the health of a region or country and allow comparisons between them and monitoring of changes over time.

Births

There are 4.3 million births per year in the US and 790 000 in the UK. The average age of a mother giving birth has risen to 25 years in the US and to 29 years in the UK (average age at first child 27 years). There has been a steady rise in the birth rate for women in their thirties and forties.

Maternal mortality

The huge reduction in maternal mortality is one of the most dramatic improvements in health outcomes in high income countries. In the US, maternal mortality declined from 582/100 000 live births in 1936 to 11.5/100 000 in 1990. This is due to reduced mortality from puerperal sepsis following the development of antibiotics, improved obstetric care, availability of blood and blood products, and better maternal health, including fewer pregnancies per woman. However, maternal mortality in the US has not continued to fall – it was 16.7/100 000 in 2008 (8 in the UK).

Perinatal mortality

The causes of perinatal mortality are shown in Fig. 2.1. The risk to the infant of perinatal death is about 100 times that for the mother. In the US, the perinatal mortality fell from 13/1000 live and stillbirths in 1980 to 6.6/1000 in 2005. The decline has occurred not only because of advances in neonatal care, but also from improved maternal health and nutrition and obstetric care.

Neonatal mortality

Neonatal mortality has declined steadily over the last 25 years (Fig. 2.2).

Gestational age and birthweight are the main risk factors for neonatal death. Rates of preterm birth vary widely between countries. The neonatal mortality rate is therefore largely determined by proportion of preterm deliveries, the birthweight distribution and gestation- or birthweight-specific mortality rates (Table 2.1). As mortality has been reduced, there is increased focus on survival at very low

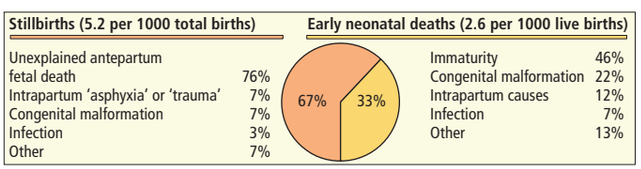

Fig. 2.1 Causes of perinatal mortality in UK (Confidential Enquiry into Maternal and Child Health, 2009).

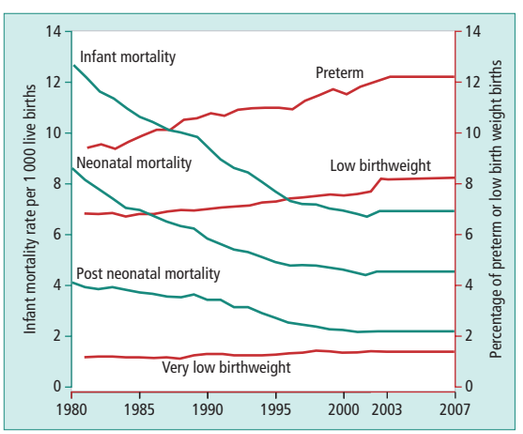

Fig. 2.2 Neonatal and infant mortality in the US have declined markedly since 1980. This is in spite of an increase in the proportion of infants born preterm or with low birth weight, mainly from the rise in maternal age and assisted reproduction. However, the proportion of very low birthweight (VLBW) infants has remained unchanged. (Source: Annual Summary of Vital Statistics – 2007; Heron M *et al. Pediatrics* 2009; **125**: 1–14.)

Table 2.1 Birthweight distribution and neonatal mortality (US, 2006).

Birthweight	Births (%)	Neonatal mortality rate (per 1000 live births)
>2500 g	91.7	0.8
2000–2499 g	5.2	5.6
1500–1999 g	1.6	17
<1500 g	1.5	209

gestational ages (22 to 25 weeks) and on non-fatal outcomes such as long-term disability (Fig. 2.3a, b, c). Now, half of babies born at 25 weeks' gestation are expected to survive and around half of these will have no or only mild impairment during childhood.

For information on global neonatal mortality see Chapter 72.

Epidemiologic data collection

Neonatal epidemiologic data are gathered through several systems including national vital registration (death certificates), rapid reporting audit systems and special neonatal databases such as the Vermont–Oxford Neonatal Network and NICHD (National Institute of Child Health and Human Development) Neonatal Research Network, which collect clinical data from a large number of neonatal units. Particularly informative are the population-based databases (Fig. 2.3a, b), and some combine obstetric and neonatal data with outcome data.

Infant mortality

The marked reduction in infant mortality since 1980 is shown in Fig. 2.2. With the decline in deaths from infectious diseases since the 1900s and more recently from sudden infant death syndrome, over two-thirds of infant deaths are in the neonatal period, and even after the first month of life many deaths are related to neonatal problems (Fig. 2.4). Sixty-six percent of all infant deaths occur in the 8.3% of infants born with low birthweight; 52% of infant deaths are among the 1.5% very low birthweight infants. Complications of preterm birth and congenital abnormalities are the largest contributors to both neonatal and infant deaths.

In 2007 the infant mortality rate was 6.8 per 1000 live births in the US and 5.0 in the UK. Compared with other countries, the US had only the 45th lowest infant mortality rate in 2007; the UK had the 36th lowest. A major reason for this relatively poor performance is the higher percentage of preterm infants born in the US (13%) compared to many other developed countries (5% in northern Europe). The preterm birth rate in the UK is rising and is now almost 10%. Both preterm birth prevalence and mortality risk in the US are influenced by ethnicity; the infant mortality of infants of black mothers is over twice that of infants of white or Hispanic mothers. The difference in the UK is similar.

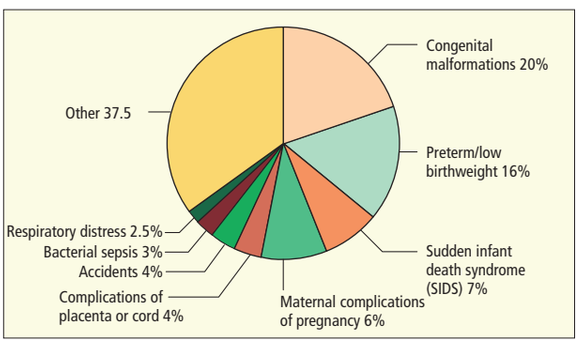

Fig. 2.4 Causes of infant mortality in the US, 2007 (source: www.cdc.gov/nchs/nvss/mortality_tables.htm).

The EPICure Studies

Two country-wide epidemiological studies of very preterm birth have been undertaken – the first in babies <26 weeks of gestation in the UK in 1995 and the second in babies born <27 weeks in England during 2006.

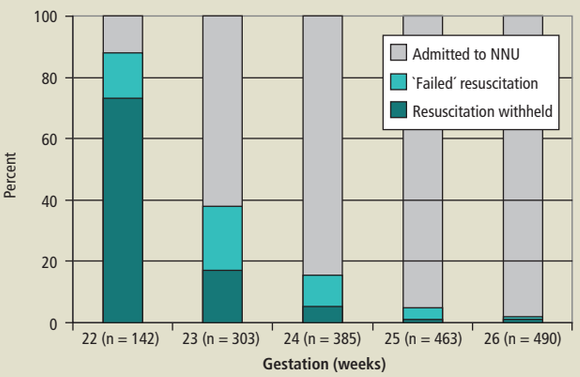

Fig. 2.3a Results of labor ward management for extremely preterm births, England 2006 (source EPICure 2; www.epicure.ac.uk).

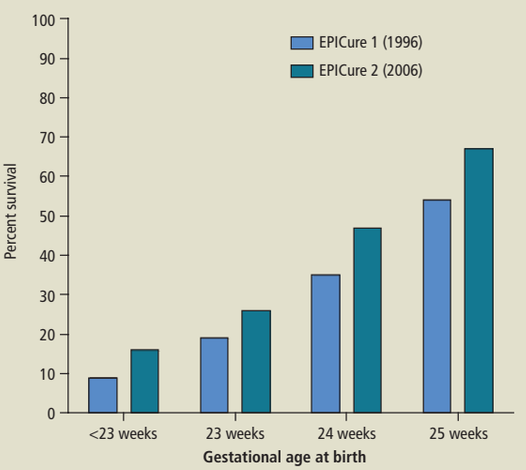

Fig. 2.3b Gestation-specific mortality rates for babies admitted for neonatal intensive care in England in 1995 and 2006 (sources Costeloe *Pediatrics* 2000; **106**: 659–671; www.epicure.ac.uk).

3 Perinatal medicine

The concept of perinatal care evolved from the development of maternal–fetal medicine (fetal medicine and high-risk obstetrics) linked to neonatal intensive care and associated pediatric specialties. This should allow a 'seamless' care plan for the baby extending from before birth to the newborn period for mothers or babies with complex problems. This requires expertise which is highly specialized, rapidly advancing and multidisciplinary. Such care is usually provided centrally as a tertiary service, though some services may be available locally (Fig. 3.1). The establishment of 'Pregnancy/Newborn Networks' allows experience and management protocols to be cascaded from the tertiary care center to other units to enhance collaborative working and minimize geographical variations in care.

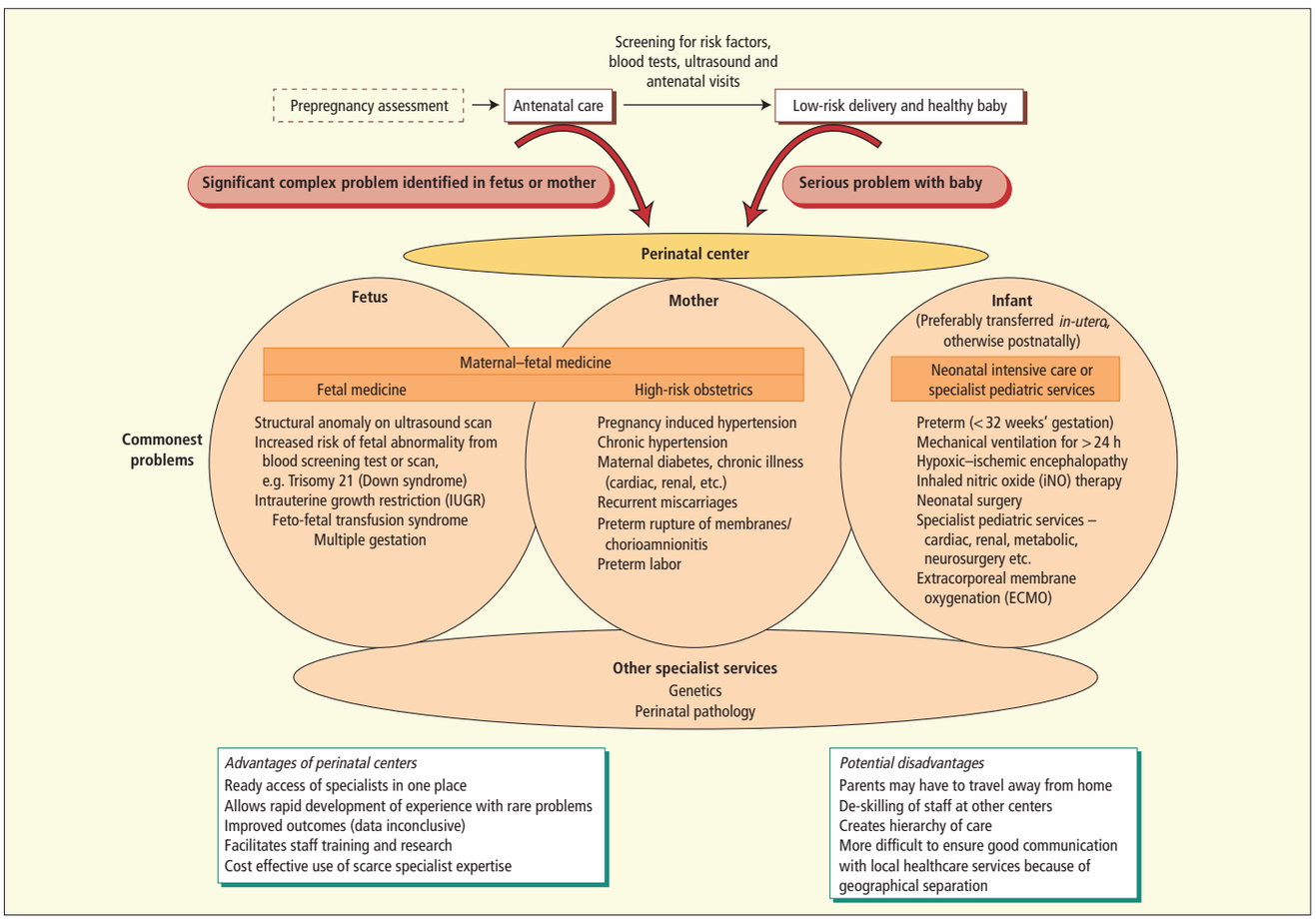

Fig. 3.1 Organization of tertiary perinatal care.

Neonatal involvement in perinatal care

An increasing number of neonatal conditions requiring neonatal intensive care or specialist pediatric services are recognized antenatally. This allows counseling (both obstetric and pediatric), multidisciplinary discussion and transfer, if necessary, before birth to a perinatal center (Fig. 3.2). Parents require information about their baby's condition and management options. Neonatologists, specialist pediatricians and pediatric surgeons are involved to provide information before the baby is born. In particular, interpretation of antenatal ultrasound scans may be difficult and may require input from fetal medicine specialists and specialist radiologists as prognosis may be difficult to define. Specialist assessment and counseling needs to be particularly prompt and within national legal boundaries if termination of pregnancy is considered.

Information about problems identified antenatally needs to be communicated to the neonatology and specialist pediatric teams so that appropriate assessment and follow-up are arranged postnatally.

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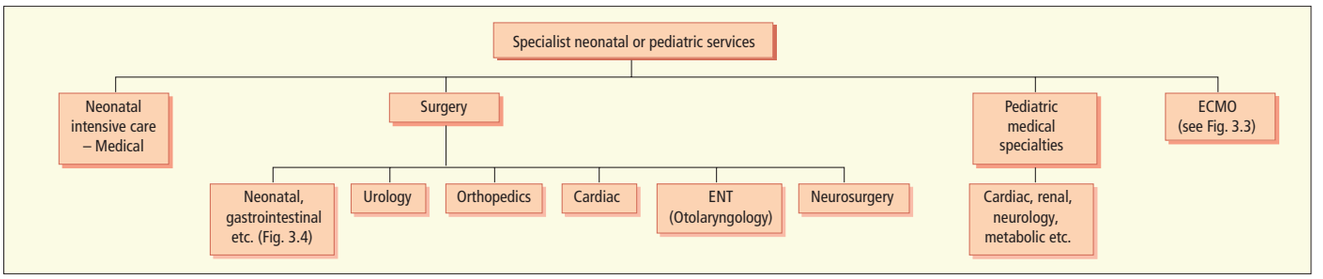

Fig. 3.2 Specialist neonatal care.

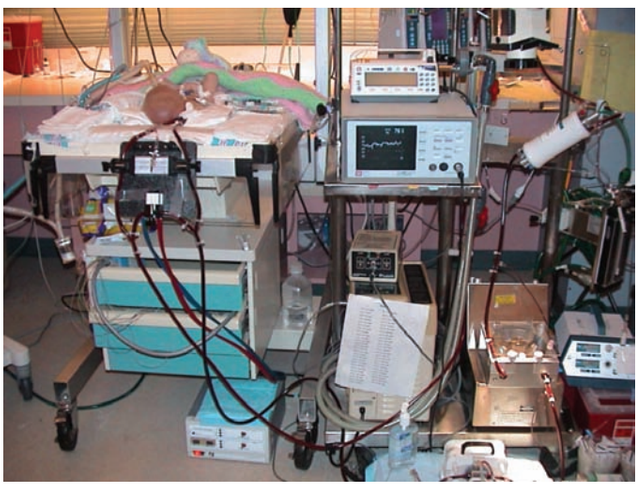

Fig. 3.3 An infant on extracorporeal membrane oxygenation (ECMO), which is provided at only a relatively small number of specialist centers.

Key point

It is not always possible to provide all these specialist services in a single center on one site. Collaboration between specialties is essential.

Levels of neonatal care

The different levels of care required by newborn infants are shown in Fig. 3.5.

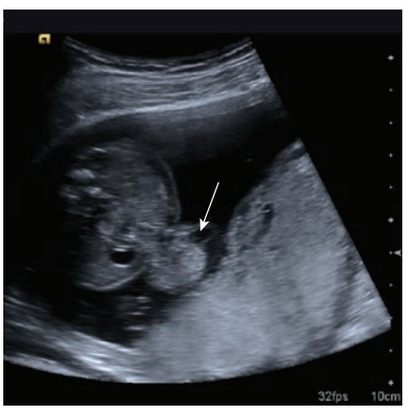

Fig. 3.4 Significant fetal abnormalities detected on prenatal ultrasound screening, such as the omphalocele (arrow) shown here, will need to be assessed in a perinatal center to allow review by fetal medicine specialist, parental counseling, consultation with pediatric surgeon by both doctors and parents and planning for delivery and treatment.

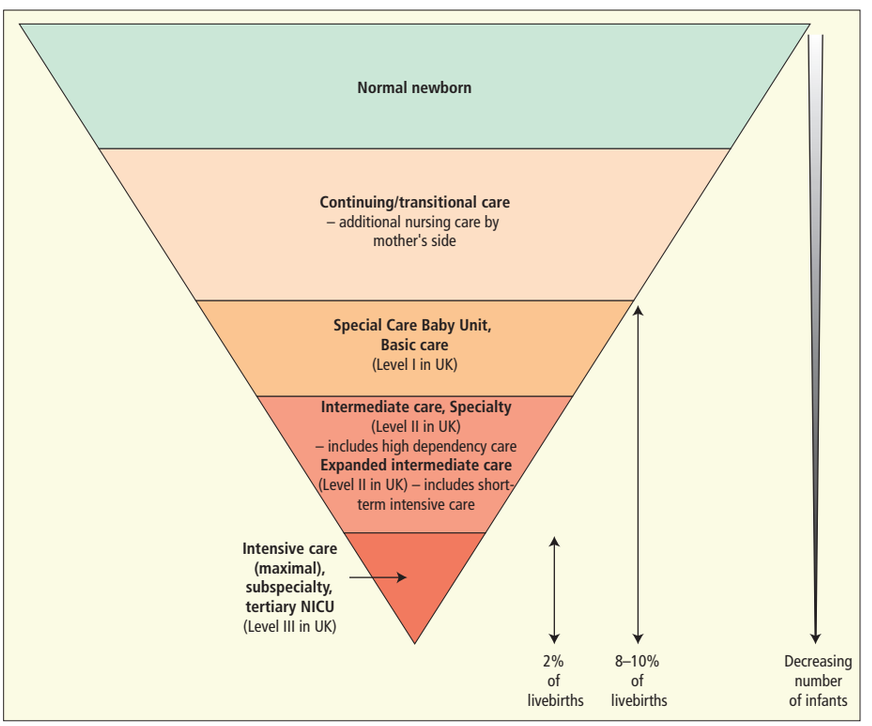

Fig. 3.5 Levels of neonatal care.

4 Prepregnancy care, prenatal screening, fetal medicine and surgery

Prepregnancy care

Provide advice for all mothers to optimize chances of healthy baby:
- Attend clinic for prenatal care.
- Avoid maternal smoking, alcohol, drug misuse, medication (unless essential).
- Toxoplasmosis exposure – avoid eating undercooked meat (and wear gloves when handling cat litter).
- *Listeria* infection – avoid unpasteurized dairy products and soft ripened cheeses, e.g. brie.
- Folic acid supplements preconceptually to 12 weeks – to reduce risk of neural tube defects and cardiac malformations in countries without folic acid fortification of foods, as in UK. Higher dose of folic acid if woman has had previous baby with neural tube defect.
- Check management of pre-existing maternal medical conditions.

Identify pregnancies at increased risk of fetal abnormality:
- previous child with congenital anomaly
- family history of an inherited disorder
- consanguineous relationship
- parents known carriers of an autosomal recessive disorder, e.g. thalassemia
- parents from ethnic group with specific risk, e.g. African American (sickle cell disease), Ashkenazi Jews (Tay–Sachs disease, a neurodegenerative disorder)
- parent with known chromosomal rearrangement.

Prenatal screening

Maternal blood

The routine screening tests vary geographically, but include:
- maternal blood group, antibodies for rhesus (D) and other red cell incompatibilities
- hepatitis B
- syphilis
- rubella
- HIV infection
- neural tube defects – by maternal serum alphafetoprotein (MSAFP), in some areas
- screening for chromosomal anomalies (see below)
- hemoglobin electrophoresis.

Chlamydia screening – US only

Ultrasound

Ultrasound screening recommended for all mothers before 20 weeks. Allows:
Gestational age calculation, optimal if 11–14 weeks' gestation.
Multiple pregnancy to be identified – number of viable fetuses and chorionicity determined.
Structural malformations detected – in up to 80% of major congenital malformations (first and second trimester).
Screening for trisomy 21 (Down syndrome). First trimester – nuchal translucency thickness combined with serum maternal hormones. Second trimester – four fetoplacental and maternal hormones in serum, adjusted for maternal age. Confirmed on amniocentesis or chorionic villous sampling. Detects 90% of babies with trisomy 21 for a 2.5% risk of fetal loss.
Fetal growth monitoring – by serial measurement of fetal head size (biparietal diameter and head circumference), abdominal circumference and femur length.
Amniotic fluid volume assessment to identify:
(i) oligohydramnios
  – from reduced fetal urine production, placental insufficiency and from prolonged rupture of the membranes
  – may cause pulmonary hypoplasia and limb and facial deformities from pressure on the fetus
(ii) polyhydramnios – associated with maternal diabetes, fetal bowel obstruction, CNS anomalies and multiple births.
Doppler ultrasound measurement of flow/velocity waveforms – maternal and fetal circulation (if indicated).

Examples of structural malformations identified on ultrasound (Figs 4.1–4.3)

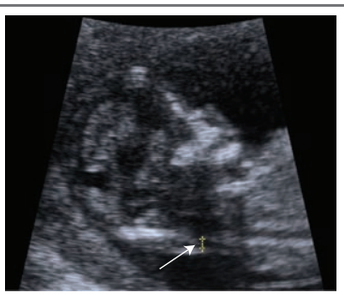

Fig. 4.1 Nuchal translucency (thickened fat pad at back of neck) associated with trisomy 21 (Down syndrome).

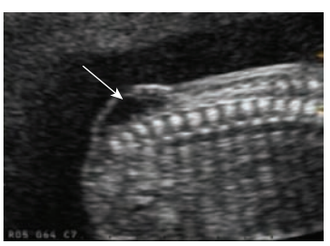

Fig. 4.2 Sacral myelocele. (Courtesy of Dr Venkhat Rahman.)

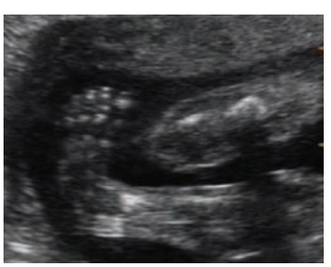

Fig. 4.3 Talipes equinovarus. (Courtesy of Dr Venkhat Rahman.)

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Fetal medicine

Fetal medicine (Fig. 4.4) may allow:

- identification of congenital anomalies
- option of termination of pregnancy to be offered for severe disorders
- therapy to be given for a limited but increasing number of conditions, e.g. fetal arrhythmias, intrauterine blood transfusion for rhesus disease
- optimal multidisciplinary discussion to impart information on prognosis and perinatal care
- optimal obstetric management of the fetus, e.g. timing of delivery
- neonatal management to be planned in advance, e.g. counseling and transfer to specialty center.

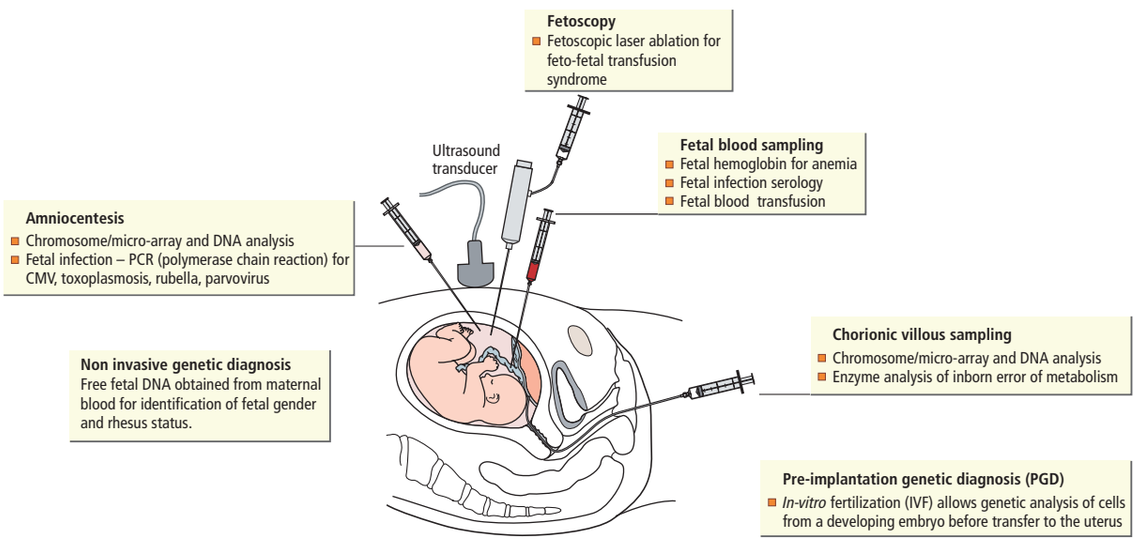

Fig. 4.4 Techniques in fetal medicine and their indications.

Fetal surgery

Creates media headlines as cutting-edge technology. However, the results are mostly poor as the malformations justifying fetal surgery are so severe and risk of premature labor is high. Now practiced only in a few centers and mainly restricted to randomized trials. Cases must be carefully selected and detailed follow-up results collected and published.

Open fetal surgery

Hysterotomy (uterus opened at 19–25 weeks' gestation) for open neural tube defects in the US. Randomized trial. May precipitate preterm delivery, outcome disappointing.

Fetoscopic/minimally invasive fetal surgery

In Europe, trial of fetal treatment of diaphragmatic hernia is being undertaken. As tracheal obstruction promotes lung growth, this is produced in the fetus by inflating a balloon in the trachea, inserted by tracheal intubation at fetoscopy.

Catheter shunts

Fetal pleural effusions, usually a chylothorax (lymphatic fluid) – inserted under ultrasound guidance (Fig. 4.5). One end of a looped catheter lies in the chest, the other end in the amniotic cavity. Neonatal course often satisfactory.

Congenital bladder neck obstruction – vesicoamniotic shunting. Controversial. Cohort studies indicate may be beneficial but a significant number of babies have chronic renal impairment and severe bladder dysfunction. Randomized controlled trial is being undertaken.

Dilatation of stenotic heart valves

Percutaneous catheter insertion under ultrasound guidance into the fetal heart. Experimental.

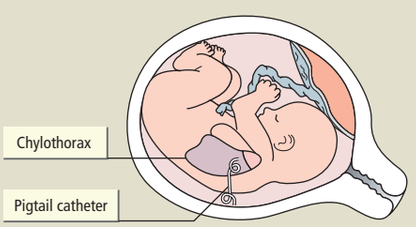

Fig. 4.5 Fetus with pigtail catheter to drain a pleural effusion.

5 Maternal medical conditions

Diabetes mellitus

Fetal mortality and morbidity are increased with maternal insulin-dependent diabetes (type 1), mainly from congenital malformations and intrauterine death. Good diabetic control, from preconception onwards, reduces malformations and mortality. This requires multidisciplinary management and close prenatal surveillance. The aim is for delivery at approximately 38 weeks, by induction if necessary.

Fetal problems

- Congenital malformations. Risk 6%, four times normal. Wide spectrum of malformations but specific increased risk of cardiac malformations and caudal regression syndrome (sacral agenesis).
- Macrosomia (Fig. 5.1). Maternal hyperglycemia results in fetal hyperinsulinemia, which promotes growth. Depending upon pre-pregnancy and gestational control of blood glucose; up to 25% of infants of diabetic mothers are macrosomic, with a birthweight >4 kg, compared with 8% of infants of non-diabetic mothers.
- Macrosomia predisposes to cephalopelvic disproportion and increased risk of delivery-related complications, both to the mother (cesarean section and forceps delivery) and the fetus; including birth injuries.
- Intrauterine growth restriction (IUGR). Threefold increase. Usually associated with maternal vascular disease.
- Polyhydramnios.
- Preterm labor. Occurs in 10%, either natural or induced.
- Intrauterine death – sudden, in third trimester. Less common with good diabetic control and induction at 38 weeks.

Neonatal problems

- Check for malformations and birth injuries.
- Hypoglycemia – common in first 48 hours due to hyperinsulinism. Monitor blood glucose before feeds until >45 mg% (>2.6 mmol/L). Hypoglycemia is prevented by early, frequent feeding, but may require gavage (nasogastric) feeds or intravenous glucose. Hypocalcemia and hypomagnesemia are often present.
- Polycythemia – plethoric appearance. Occasionally requires partial exchange transfusion.
- Hyperbilirubinemia.
- Respiratory distress syndrome – increased risk from delayed maturation of surfactant.
- Hypertrophic cardiomyopathy – uncommon. Asymptomatic or poor cardiac output (may be treated with β-blockers) for several weeks.
- Renal vein thrombosis – rare.

Fig. 5.1 Macrosomic infant with birthweight 4.8 kg at 38 weeks' gestation. There is excess fat and organomegaly (liver and heart).

Type 2 and gestational diabetes

Prevalence of type 2 diabetes is increasing and is associated with perinatal complications. Glucose intolerance from gestational diabetes complicates 1–2% of pregnancies and may require dietary or insulin treatment. May cause neonatal macrosomia, hypoglycemia and polycythemia. Also increases future risk of diabetes in later life.

Maternal red blood cell alloimmunization

Maternal antibody is formed to fetal red blood cell antigens, e.g. rhesus D, anti-Kell and anti-c. Before prophylaxis, rhesus disease was a major cause of fetal and neonatal morbidity and mortality.

Rhesus hemolytic disease

Etiology

See Fig. 5.2.

Presentation

- Antibodies found on routine antenatal antibody screen at first visit, 28 and 34 weeks.
- Previous pregnancy affected with hemolytic disease.
- Fetal hydrops on ultrasound.
- Detection of fetal anemia using ultrasound (middle cerebral artery blood flow increased for gestational age).
- Maternal polyhydramnios.
- Infant – jaundice, anemia, hydrops, hepatosplenomegaly.

Management

PRENATAL

- Increasing antibody levels on maternal blood screening – refer to specialist center if necessary.
- Fetal rhesus genotyping can be determined non-invasively through free fetal DNA detection in maternal plasma.
- Monitor with serial ultrasound for fetal anemia (usually by middle cerebral artery blood flow) and signs of hydrops.
- Amniocentesis – for amniotic fluid optical density (450 nm); rarely used as superseded by cerebral Doppler blood flow for anemia.
- Measure fetal hematocrit (from cordocentesis).

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Etiology

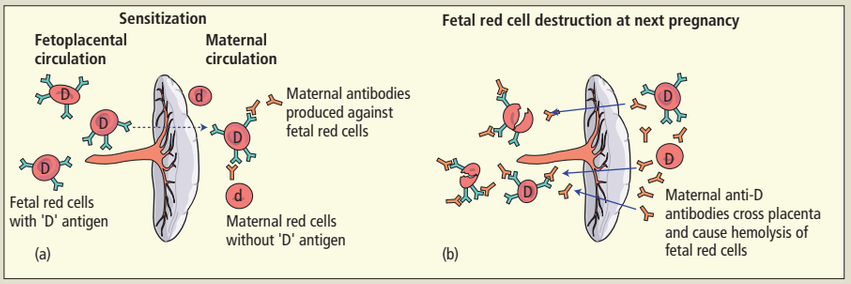

Fig. 5.2 (a) A small number of fetal red cells enter the maternal circulation and antibodies are formed. This usually occurs at delivery, but also at miscarriages, placental abruption, from blood transfusions and occasionally during normal pregnancies. (b) Maternal antibodies on re-exposure to fetal red cells at subsequent pregnancy cross the placenta and bind to fetal cells, causing hemolysis (see Table 5.1).

Table 5.1 Effect of hemolysis.

Fetus	*Infant*
Anemia – progressive	Anemia
Hepatosplenomegaly	Hyperbilirubinemia
Hydrops (edema, ascites)	
Death	

Key point

Over 50% of maternal red cell alloimmunization is now due to rarer red cell antigens (Kell and c).

- Intrauterine blood transfusion.
- Deliver preterm if necessary.

POSTNATAL

- Check cord blood for blood type, hemoglobin, bilirubin and direct antibody test (DAT).
- Monitor bilirubin closely as level may increase rapidly and cause high-frequency deafness or kernicterus.
- Start intensive phototherapy, adequate fluid balance and give IVIG (immunoglobulin) and perform an exchange transfusion if severe anemia or rapidly rising bilirubin concentration.
- May need 'top up' blood transfusion for anemia within first three months of age until endogenous hemopoiesis is normal.

Prevention

Anti-D gammaglobulin has almost eliminated rhesus disease. It is given to rhesus-negative mothers during pregnancy, after potentially sensitizing events, and after delivery.

Fifteen percent of white women are rhesus-negative; less than 2% of them become sensitized from inadequate or failed prophylaxis.

Perinatal alloimmune thrombocytopenia

Analogous to rhesus disease – maternal antibodies (HPLA1 in 80%) directed against fetal platelets cross the placenta. Affects 1 in 5000 births. May occur in first pregnancy. Intracranial hemorrhage secondary to fetal thrombocytopenia occurs in up to 25%, occasionally antenatally (at 20–24 weeks or during birth). If identified from a previously affected infant, prevention is by repeated maternal infusions of intravenous immunoglobulin (IVIG) and intrauterine platelet transfusions.

Thrombocytopenia after birth is treated with platelets that are negative for the platelet antigen. The role of IVIG postnatally is uncertain. The thrombocytopenia may persist for several weeks.

Other maternal medical conditions (Table 5.2)

Table 5.2 Other maternal medical conditions that may affect the infant.

Maternal condition	Significance for the infant
Maternal hyperthyroidism	If mother is controlled on treatment, fetus and infant are usually unaffected. Rarely causes: *Transient hyperthyroidism* – fetal tachycardia, and neonatal hyperthyroidism (1–3%) – tachycardia, heart failure, vomiting, diarrhea and failure to thrive (despite good intake), jitteriness, goiter and exophthalmos (protuberant eyes). Treated for 2–3 months *Transient hypothyroidism* – from maternal drug therapy
Maternal hypothyroidism	Worldwide; commonest cause is iodine deficiency. Important cause of congenital hypothyroidism, leading to short stature and severe learning difficulties. Rarely seen in the US or UK Mothers treated with thyroxine; neonatal problems are rare
Autoimmune thrombocytopenic purpura (AITP)	Maternal autoantibodies against platelet surface antigens cross the placenta and cause fetal thrombocytopenia. Most fetuses unaffected. Rarely requires treatment *in utero* with repeated intravenous platelet transfusions. If severe, may cause cerebral hemorrhage before birth or from birth trauma, but this is rare. Infants with severe thrombocytopenia or petechiae at birth should be given intravenous immunoglobulin. Platelet transfusions are reserved for platelet count <20 000 mm^3 (20×10^9/L) or active bleeding because of the anti-platelet antibodies. The platelet count declines over the first few days before increasing