Development and General Characteristics of Preterm and Term Newborn

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Abstract

The embryonic phase is a critical stage of development. Fetal growth is mostly influenced by maternal, uteroplacental factors, as well as genetic and environmental factors. During pregnancy, noninvasive screening tests are used to evaluate a baby's health. Severe acute or chronic intrauterine hypoxic stress in utero are responsible for compromised circulation, organ dysfunction, and threaten survival or intact survival. The objective of modern obstetrics is the accurate detection of suboptimal fetal growth. Currently, sonography plays a critical role in providing a reliable estimate of fetal biometry, thus confirming the clinical suspicion of growth restriction and substantially influencing pregnancy management. Preterm birth, defined as birth at less than 37 weeks of gestation, is the main determinant of adverse infant outcome in terms of both survival and quality of life: the more preterm these infants are, the more serious are the complications. Because of advances in the care of these very vulnerable infants, survival at the earliest gestation is continuosly improving.

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1.1 Salient Points

- Fetal hemoglobin has a higher affinity for oxygen than adult hemoglobin, which facilitates diffusion of oxygen from the maternal circulation to the fetus.
- A continuous placental supply of glucose provides the substrate for energy metabolism to the fetus, and this converts after birth to intermittent feeding.
- Individual characteristics based on the race, obstetric history, and the constitution of the parents, especially of the mother, should be taken into account to improve diagnostic accuracy and the construction of customized fetal growth charts and for the antenatal detection of the true small fetus, whose risk of adverse perinatal outcomes is substantially increased.
- Hypoxemia produces various circulatory adaptations in the fetus that enhance fetal survival, including the development of tachycardia, hypertension, redistribution of blood flow toward the brain, myocardium and adrenals, and depression of fetal breathing and skeletal muscle activity.
- The goal in the management of the preterm fetus is to deliver the most mature fetus possible, at least at 32–34 weeks, in the best possible condition by improving fetal and maternal monitoring.
- The history of family, pregnancy, and delivery together with the first examination at birth has a pivotal role on assessing neonatal well-being.
- A baby's well-being is determined by periconceptional events.
- Signs of immaturity should be recognized and a favorable environment should be created.

1.2 Part 1 The Development from Fetus to Newborn

1.2.1 Developmental Phases of the Fetus

The embryonic phase is a critical stage of development, when systems undergo important basic development.

The third week after conception marks the beginning of the embryonic period. It ends at the end of the tenth week, when the embryo comprises three layers from which all organs will develop.

The second fetal phase begins after the tenth week and continues until the end of pregnancy. During this phase, organs (liver, kidneys) begin to function.

From the 16th to 20th weeks, the fetus undergoes a rapid growth spurt. Fat develops under a thin skin. Cardiac output increases. Meconium accumulates in the bowel. The fetus hiccups and spends time awake and asleep.

Fetal development slows down between the 21st and 24th weeks. By the 24th week, the fetus weighs approximately 1.3 pounds (600 g).

Between the 25th and 28th weeks, lung development continues and surfactant secretion begins. By the 28th week, 90% of fetuses will survive *ex utero* with appropriate support.

From the 29th to the 40th weeks, the amount of body fat rapidly increases. Thalamic brain connections, which mediate sensory input, form. Bones are fully developed. Most of the major systems and organs are complete. The immune system develops.

By weeks 35–40, the fetus is sufficiently developed for life outside the uterus without any more support than that which would be required by any newborn baby delivered at term. At 37 weeks, the fetus will continue to add approximately one ounce (28 g) per day to its body weight and it will be 48–53 cm (19–21 inches) in length at birth.

1.2.2 Fetal Constitutional Characteristics

1.2.2.1 The Central Nervous System (CNS)

The CNS is formed by four subdivisions of the neural tube that develop into distinct regions of the central nervous system.

The neural tube is initially open both cranially and caudally. These openings close during the fourth week. Failure of closure of these neuropores can result in neural tube defects such as anencephaly or spina bifida.

The dorsal part of the neural tube comprises the alar plate, which is primarily associated with sensation. The ventral part of the neural tube comprises the basal plate, which is primarily associated with motor control.

The spinal cord is a long, thin, tubular bundle of nervous tissue and supports cells that extend from the brain. The brain and spinal cord together make up the central nervous system. The spinal cord functions primarily for the transmission of neural signals between the brain and the rest of the body but also contains neural circuits that independently control numerous reflexes and central pattern generators.

1.2.2.2 The Fetal Circulation

The essential difference between the circulatory system of a fetus and that of the baby after birth is that the lungs are not in use: the fetus obtains oxygen and nutrients from the mother through the placenta and the umbilical cord. Blood from the placenta is carried to the fetus by the umbilical vein. A large proportion enters the fetal ductus venosus and passes to the inferior vena cava, while the remainder enters the liver from vessels on its inferior border. The branch of the umbilical vein that supplies the right lobe of the liver joins the portal vein and blood then passes to the right atrium. In the fetus, there is an opening between the right and left atria (the foramen ovale), and most of the blood flows from the right into the left atrium, thus bypassing pulmonary circulation. The majority of blood flow is then into the left ventricle from where it is pumped through the aorta to supply the various organs. Blood then flows from the aorta through the internal iliac arteries to the umbilical arteries and reenters the placenta, where carbon dioxide and other waste products from the fetus are taken up and enter the maternal circulation. A small proportion (about 4%) of the blood from the right atrium does not enter the left atrium but enters the right ventricle and is pumped into the pulmonary artery. In the fetus, a connection between the pulmonary artery and the aorta, called the ductus arteriosus, directs most of the blood away from the lungs (which are not being used for respiration at this point, as the fetus is suspended in amniotic fluid).

An important concept of the fetal circulation is that fetal hemoglobin has a higher affinity for oxygen than adult hemoglobin, which facilitates diffusion of oxygen from the maternal circulation to the fetus. The circulatory system of the mother is not directly connected to that of the fetus, so gas exchange takes place at the placenta. Oxygen diffuses from the placenta to the chorionic villus, an alveolus-like structure, from which it is then carried to the umbilical vein. Fetal hemoglobin enhances the fetal ability to draw oxygen from the placenta because the oxygen dissociation curve is shifted to the left, which has the effect of oxygen being taken up at a lower concentration than by adult hemoglobin. This enables fetal hemoglobin to take up oxygen from adult hemoglobin in the placenta, which has a lower partial pressure of oxygen than at the lungs after birth.

A developing fetus is highly susceptible to anomalies of growth and metabolism, increasing the risk of birth defects.

1.2.2.3 Fetal Metabolism

A continuous placental supply of glucose provides the substrate for energy metabolism to the fetus, and this converts after birth to intermittent feeding. While the fetus is dependent on maternal glucose as the main source of energy, it can also use lactate, free-fatty acids, and ketone bodies under some conditions (e.g., starvation or hypoxia). Fetal glucose utilization is augmented by insulin produced by the developing fetal pancreas in increasing amounts as gestation proceeds; this enhances glucose utilization in insulin-sensitive tissues (skeletal muscle, liver, heart, adipose tissue), which increase in mass and thus glucose requirement during late gestation. Glucose-stimulated insulin secretion increases with gestation. Glycogen stores are maximal at term, but even the term fetus only has sufficient glycogen available to meet energy needs for 8–10 h, and this store can be depleted even more quickly if demand is high. At 27 weeks' gestation, only 1% of a fetus's body weight is fat; this increases to 16% at 40 weeks. Inadequate glucose substrate can lead to hypoglycemia and fetal growth restriction. In cases of intrauterine growth restriction, fetal weight-specific tissue-glucose uptake rates

and glucose transporters are maintained or increased, while synthesis of amino acids into protein and corresponding insulin-like growth factor (IGF) signal transduction proteins are decreased. These observations demonstrate the mixed phenotype of the intrauterine growth restriction (IUGR) fetus that has an enhanced capacity for glucose utilization, but a diminished capacity for protein synthesis and growth. Excess substrate can also lead to problems, as with infants of diabetic mothers (IDM). Thus, the normal fetus has a considerable capacity to adapt to changes in glucose supply (Way 2006).

1.2.2.4 Regulation of Fetal Growth

Fetal growth depends on many different aspects, mostly influenced by maternal and uteroplacental factors.

Role of the Mother in Fetal Growth Regulation

Fetal growth and development are influenced by genetic as well as environmental factors. Maternal genes have an important specific influence on fetal growth; for example, maternal height is a major determinant of fetal size, representing uterine capacity and the potential for growth.

In fact, the individual characteristic based on the race, obstetric history, and constitutional characteristics of the parents, especially of the mother, could be taken into account to improve diagnostic accuracy construction of customized fetal growth and for antenatal detection of the true small fetuses, whose risk of adverse perinatal outcomes is substantially increased (Ghi et al. 2016).

Although the birth weights of siblings are similar and correlate, environmental influences are also important in determining growth. Maternal constraint refers to the limited capacity of the uterus to support fetal growth and is important in limiting fetal overgrowth and subsequent dystocia, to ensure the mother's capacity for future successful pregnancies (Picciano 2003).

Maternal Nutrient Intake

The mother is the supplier of oxygen and essential nutrients to the fetus via the placenta. Maternal diet, caloric intake, and metabolic function have an important role in supplying nutrients to the fetus. Increased caloric intake is necessary during the second and third trimesters to allow for fetal and placental growth (Christian et al. 2003). A Cochrane systematic review of six randomized controlled trials found that balanced protein-energy supplementation reduced the risk of small for gestational age (SGA) neonates by approximately 30% (Kramer and Kakuma 2003). Glucose is an important nutrient in the control of fetal growth. Studies of diabetic women have shown that low blood glucose levels during pregnancy as a result of excessively tight glycemic control lead to a greater incidence of SGA neonates, whereas high blood glucose levels increase the likelihood of macrosomia (Leguizamon and von Stecher 2003).

Maternal Uterine Artery Blood Flow

Increased uterine blood flow is essential to meet the metabolic demands of the growing uterus as well those of the placenta and fetus (Kliman 2000). Uterine artery blood flow increases by more than threefold during pregnancy, partly influenced by an increased artery diameter and reduced resistance to flow. In addition to increased uterine blood flow during normal pregnancy, new blood vessels develop in the uterus, promoted by the placental hormones human chorionic gonadotropin (hCG) (Zygmunt et al. 2002) and IGF-II (Zygmunt et al. 2003). Using Doppler assessment of uterine arterial flow at 23 weeks' gestation, Albaiges et al. (2000) found that increased uterine artery blood flow resistance was associated with an increased risk of an SGA baby. In the clinical practice, women with an abnormal uterine artery Doppler at 20–24 weeks (defined as a pulsatility index >95th centile) and women who have one major risk factor for SGA (maternal age > 40 years; chronic hypertension; diabetes with vascular disease; renal impairment; antiphospholipid syndrome; smoker >11cigarettes per day; cocaine; maternal or paternal SGA; previous SGA baby; previous still-birth; intensive exercise; previous pre-eclampsia; pregnancy interval <6 months; pregnancy interval >60 months; heavy bleeding similar to menses; PAPP-A < 0,4 MoM on first trimester screening) should be referred for serial ultrasound measurement of fetal size and

assessment of well-being with umbilical artery Doppler commencing at 26–28 weeks of pregnancy (RCOG 2014).

Maternal Smoking and Drug Use

Maternal cigarette smoking is associated with reduced birth weight. Early reports suggested a doubling of the rate of low birth weight in babies of smokers compared with those of nonsmokers and a dose-dependent effect with increasing number of cigarettes smoked. More recent studies demonstrated a 3.5-fold increased risk of SGA infants in women who smoked during pregnancy (Bamberg and Kalache 2004; Rich-Edwards et al. 2003), with a greater effect on low birth weight with increasing maternal age (Krampl et al. 2000). Growth restriction is usually symmetrical with reduced weight, head circumference, and abdominal circumference. The use of drugs, such as cocaine and marijuana, also has significant negative effects on fetal growth. Cocaine use contributes to an increased rate of low birth weight and a reduction in mean birth weight of at least 100 g.

Maternal Hypoxia

Maternal hypoxia influences fetal growth. Its effect is independent of socioeconomic status, prematurity, maternal smoking, pregnancy-induced hypertension, and parity. The combination of hypoxia and pregnancy appears to be important in altering maternal physiology, including changes in immune pathways (Clapp 2003). Maternal hypoxia affects placental and uterine blood flow, which contribute to reduced nutrient transport to the fetus (Skomsvoll et al. 2002).

Maternal Inflammatory Diseases

The presence of maternal inflammatory disease may contribute to reduced fetal growth. Several inflammatory diseases are associated with reduced fetal growth, including rheumatoid arthritis (McGaw 2002), inflammatory bowel disease, systemic lupus erythematosus, and periodontal disease (Bowden et al. 2001). Women with active inflammatory arthritis during pregnancy have smaller babies compared with healthy women or women whose disease is in remission (Xiao et al. 2003), suggesting that active inflammation during pregnancy may contribute to reduced fetal growth. Maternal health influences the maternal state during pregnancy with implications for fetal growth. In addition to inflammatory diseases, many other maternal factors, including preeclampsia (Allen 2001), anemia (Fowden and Forhead 2004), infections, and alcohol consumption, influence fetal growth via changes in placental function.

Role of the Placenta in Fetal Growth Regulation

The placenta receives and transmits endocrine signals between the mother and fetus and is the site of nutrient and waste exchange.

During human pregnancy, the placenta is an important endocrine organ. It produces hormones, including estrogens and progesterone, hCG, human growth hormone (GH) variant, and human placental lactogen. Some of these play a role in the regulation of fetal growth. Fetal insulin promotes growth of the fetus, acting as a signal of nutrient availability (Ferrazzi et al. 2000). Insulin deficiency results in reduced fetal growth, as the fetal tissues decrease their uptake and utilization of nutrients. There is also a relationship between increased insulin production and increased fetal growth. It has been proposed that the fetus increases its own production of insulin in response to maternal hyperglycemia and that this increase in fetal insulin is responsible for the increased growth and macrosomia observed in diabetic pregnancies.

Adequate placental growth is essential for adequate fetal growth. Several aspects of placental function are critical for human fetal growth and development, including adequate trophoblast invasion, an increase in uteroplacental blood flow during gestation, transport of nutrients such as glucose and amino acids from mother to fetus, and the production and transfer of growth-regulating hormones. Increased blood flow during pregnancy increases the flow of nutrients from mother to fetus, and uteroplacental blood flow has been shown to be reduced by up to 50% in women with preeclampsia (ACOG 2012). Doppler velocimetry is used to detect increased vascular resistance in the uterine arteries, which occurs

as a result of abnormal trophoblast invasion of the spiral arteries. In addition, examination of the fetal circulation, particularly umbilical artery waveforms, may reflect placental insufficiency (ACOG 2012). Umbilical vein blood flow, measured by Doppler ultrasound, is decreased in IUGR fetuses, representing reduced perfusion of the fetal tissues.

1.2.3 Diagnosis of Fetal Well-being

During pregnancy, women are generally offered noninvasive screening tests, such as blood tests, ultrasound, and cardiotocography (CTG) to evaluate the baby's health. Alternatively, more invasive tests, such as chorionic villous sampling (CVS) or amniocentesis, may be performed.

1.2.3.1 Ultrasound

Obstetric ultrasound is usually used to:

- Diagnose pregnancy
- Assess possible risks to the mother (miscarriage or molar pregnancy)
- Check for fetal malformation
- Determine intrauterine growth restriction
- Note the development of fetal body parts
- Check the amniotic fluid and the umbilical cord

Generally an ultrasound examination is ordered whenever an abnormality is suspected or following a schedule similar to that outlined below:

7 weeks: Confirm pregnancy
11–13 weeks: Determine expected date of delivery and screening for aneuploidy
20–22 weeks: Perform a scan to assess anatomic integrity
32 weeks: Evaluate fetal growth, verify the position of the placenta, and perform the Doppler study to establish fetal well-being

Three-dimensional (3-D) and four-dimensional (4-D) ultrasound techniques are used to provide additional imaging of fetal structures. Today 3-D ultrasound is most commonly performed for the visualization of the baby's face (Fig. 1). However, it has the potential to become part of routine care and many hospitals use the 3-D ultrasound to detect fetal anomalies, especially of the heart and of the CNS (Figs. 2 and 3).

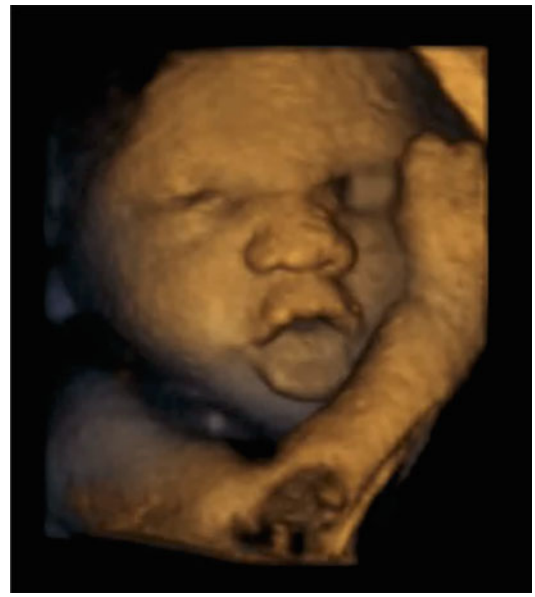

Fig. 1 Reconstructed 3-D imaging of fetal face (Image courtesy of G. Rizzo)

1.2.3.2 Screening Tests for Aneuploidy

Women should be offered prenatal assessment for aneuploidy by screening or diagnostic testing regardless of maternal age or other risk factors (Practice Bulletin No. 162 2016).

Prenatal genetic diagnostic testing is intended to determine, with as much certainty as possible, whether a specific genetic disorder or condition is present in the fetus. In contrast, prenatal genetic screening is designed to assess whether a patient is at increased risk of having a fetus affected by a genetic disorder (Spencer et al. 1999).

Two methods are currently available in the screening for aneuploidy:

1. At 11–13 weeks' gestation, combination of maternal age, fetal nuchal translucency

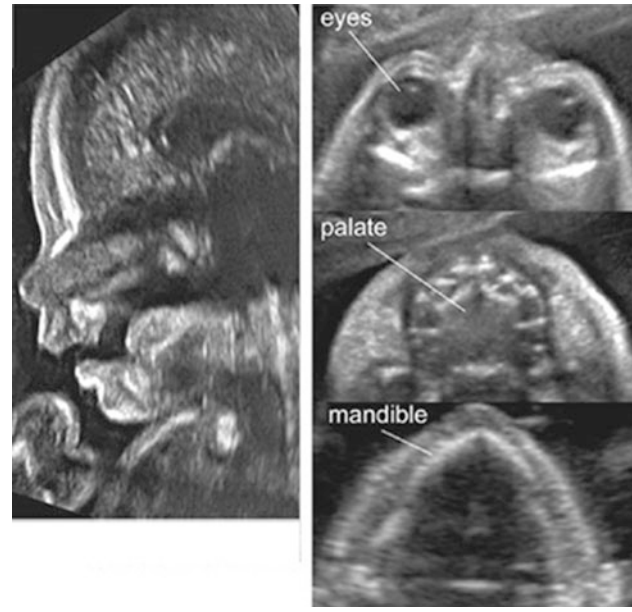

Fig. 2 Reconstructed 3-D imaging of the eyes, palate, and mandible from the fetal profile

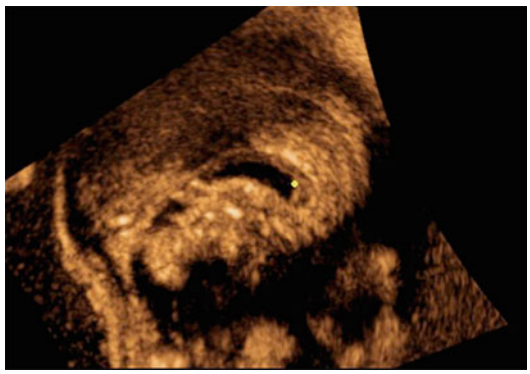

Fig. 3 Reconstructed 3-D imaging of the corpus callosum (Image courtesy of G. Rizzo)

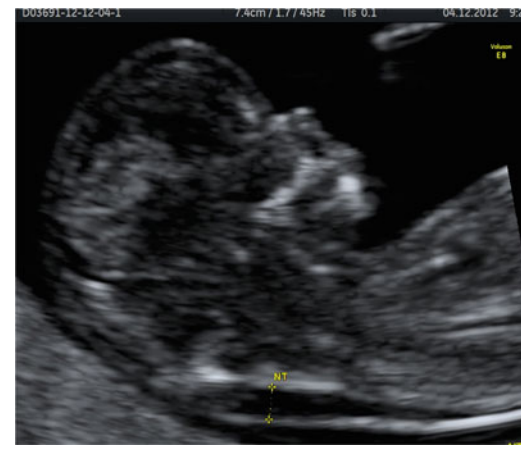

Fig. 4 Fetal profile at 12 weeks of gestation showing nuchal translucency (Image courtesy of G. Rizzo)

thickness measured by ultrasound (Fig. 4) and maternal serum concentration of free β-human chorionic gonadotropin and pregnancy-associated plasma protein-A could assess the risk for trisomy 21, trisomy 18, and trisomy 13 (Nicolaides 2004; Palomaki et al. 2011).

The incidence of fetal trisomies is directly related to maternal age. The risk of having a child with Down syndrome increases in a gradual, linear trend until about age 30 and increases exponentially thereafter.

Nuchal translucency (NT) is the sonographic appearance of a collection of fluid under the skin behind the fetal neck in the first-trimester of pregnancy. NT normally increases with gestation. Increased NT thickness over the normal range for gestational age is related to chromosomal defects, especially trisomy 21, but is also associated with major abnormalities of the heart and great arteries and a wide range of genetic syndromes.

The level of free b-hCG in maternal blood normally decreases with gestation. In trisomy 21

pregnancies, free b-hCG is increased. The level of PAPP-A in maternal blood normally increases with gestation, and in trisomy 21 pregnancies the level is decreased.

Some studies demonstrated that the detection rate of this test can increase to about 95% by also examining the nasal bone (absent or hypoplastic in a high proportion of fetuses with trisomy 21 and other chromosomal abnormalities), ductus venosus flow (a-wave absent or reversed in fetal aneuploidies or in fetal cardiac defects), and tricuspid flow (tricuspid regurgitation is a common finding in fetuses with trisomy 21, 18, and 13 and in those with major cardiac defects).

2. From the 10th week of gestation, analysis of cell-free DNA in maternal blood. Circulating cell-free DNA in the plasma of pregnant women is a mixture of genomic DNA fragments of maternal and fetal (placental) origin that could be extracted and analyzed (Sparks et al. 2012; Zimmermann et al. 2012; Canick et al. 2013; Botto et al. 1996). Screening for fetal aneuploidy in pregnant women using cell-free DNA has demonstrated high sensitivity and specificity to screen for common aneuploidies in high-risk populations. Recently, this method started to include microdeletion screening and whole genome screening.

1.2.3.3 Invasive Tests

After an abnormal first-trimester ultrasound examination or screening test, it is necessary to confirm the diagnosis with an invasive procedure, chorionic villous sampling, or amniocentesis. The earlier CVS results allow for more management options, although amniocentesis also is an option for diagnosis (Spencer et al. 1999).

Chorionic Villous Sampling

Chorionic villus sampling for prenatal genetic diagnosis generally is performed between 10 and 13 weeks of gestation. In fact, before 10 weeks there is a risk of limb-reduction defects (Akolekar et al. 2015).

The primary advantage of CVS over amniocentesis is that the procedure can be performed earlier in pregnancy and the viable cells obtained by CVS for analysis allow for shorter specimen processing time (5–7 days versus 7–14 days), so the results are available earlier in pregnancy.

The most recent meta-analysis of studies calculated a procedure-related loss rate of 0.22% (Alfirevic et al. 2003).

The incidence of culture failure, amniotic fluid leakage, or infection after CVS is less than 0.5% (Winsor et al. 1999).

Amniocentesis

Amniocentesis for the purpose of genetic diagnosis usually is performed between 15 weeks and 20 weeks of gestation, but it can be performed at any later gestational age. An amniotic fluid sample of 20–30 ml is obtained from a pocket free of fetal parts and umbilical cord.

The most recent meta-analysis of studies calculated a procedure-related loss rate of 0.11% (Alfirevic et al. 2003).

The incidence of culture failure is approximately 0.1% of samples (Winsor et al. 1999).

1.2.3.4 Cardiotocography

Cardiotocography is a technique of surveillance of fetal well-being useful first of all during labor to identify the fetus compromise. When the risk of antepartum fetal demise is increased (e.g., pregestational and gestational diabetes mellitus; hypertension; gestational hypertension; preeclampsia; systemic lupus erythematosus; chronic renal disease; antiphospholipid syndrome; hyperthyroidism; hemoglobinopathies; heart disease; decreased fetal movement; oligohydramnios; fetal growth restriction; late-term or postterm pregnancy; isoimmunization; previous fetal demise; monochorionic multiple gestation), it may be necessary to monitor fetal activity during pregnancy with a nonstress test (NST) to identify some degree of uteroplacental compromise (Liston et al. 2007). The NST is based on the premise that the heart rate of a fetus that is not acidotic or neurologically depressed will temporarily accelerate with fetal movement. Heart rate reactivity is thought to be a good indicator of normal fetal autonomic function. Loss of reactivity may result from any cause of central nervous system depression, including fetal acidemia. Attention is required for the preterm fetuses; in

fact, the NST of the normal preterm fetus is frequently nonreactive: from 24 weeks to 28 weeks of gestation, up to 50% of NSTs may not be reactive (Bishop 1981), and from 28 weeks to 32 weeks of gestation, 15% of NSTs are not reactive (Macones et al. 2008). For this reason, starting fetal monitoring after 32 weeks of gestation is appropriate for most at-risk patients. However, in pregnancies with very high-risk conditions, testing might begin at a gestational age when delivery would be considered for perinatal benefit (ACOG 2014).

1.2.4 Fetal Injuries

It is important during fetal development to maintain good fetal oxygen delivery to avoid irreversible fetal compromise. Fetal hypoxia from any cause leads to conversion from aerobic to anaerobic metabolism, which produces less energy and more acid. If the oxygen supply is not restored, the fetus dies. Hypoxia may be classified as follows:

- *Hypoxemic hypoxia*: reduced placental perfusion with maternal blood and consequent decrease in fetal arterial blood oxygen content due to low pO_2
- *Anemic hypoxia*: reduced arterial blood oxygen content due to low fetal hemoglobin concentration
- *Ischemic hypoxia*: reduced blood flow to the fetal tissues

Making this diagnose can be difficult, and some episodes of hypoxia before and during birth may pass unnoticed at the time but may affect the central nervous system and not become evident until much later in life.

1.2.4.1 Causes of Hypoxia

Two major categories of neurological injury can be observed in the full-term infant: (1) hypoxic-ischemic encephalopathy (HIE) and (2) intracranial hemorrhage (ICH). Brain hypoxia and ischemia due to systemic hypoxemia, reduced cerebral blood flow (CBF), or both are the primary pathophysiological processes that lead to a hypoxic-ischemic encephalopathy.

The first compensatory adjustment to a hypoxic-ischemic (asphyxic) event is an increase in CBF due to hypoxia and hypercapnia. This is associated with a redistribution of cardiac output so that the brain receives an increased proportion of the cardiac output. This is followed by a slight increase in systemic blood pressure (BP) due to increased release of epinephrine. In the fetus suffering from acute asphyxia (hypoxic ischemia), if early compensatory adjustments fail, cerebral blood flow (CBF) may become pressure passive, and brain perfusion becomes dependent on systemic BP. As BP falls, CBF falls below critical levels, and a diminished blood supply in the brain leads to insufficient oxygen to meet its needs and intracellular energy failure.

Neuronal injury in hypoxic ischemia is an evolving process. During the early phases of brain injury, brain temperature drops, and there is local release of neurotransmitters, such as g-aminobutyric acid transaminase (GABA). The magnitude of the final neuronal damage depends on both the severity of the initial insult and damage due to energy failure, injury during reperfusion, and apoptosis. The extent, nature, severity, and duration of the primary injury are all important in determining the magnitude of the residual neurological damage.

Intracranial hemorrhage in the full-term infant can be intraventricular, subarachnoid, subdural, or intracerebellar. There is often ventilatory disturbance and hypoxia because of varying neurological depression. Intraventricular hemorrhage (IVH), which is unusual in term infants, may be associated with evidence of intrapartum asphyxia but may also be clinically silent and underdiagnosed, causing later deficits or hydrocephalus (Rohan and Golombek 2009).

Approximately 20% of neonatal HIE is primarily related to antepartum events that lead to hypoxic ischemia. Maternal conditions such as hypotension, placental vasculopathy, and insulin-dependent diabetes mellitus may predispose the fetus to intrapartum hypoxic ischemia because there is little reserve to compensate for the stresses of labor (Volpe 2008). Intrapartum events such as

prolapsed cord, abruptio placentae, and traumatic delivery have been linked to 35% of cases of HIE. Because of the limitations in determining the actual timing of the insult, it may be difficult to identify the antepartum contribution separately from the intrapartum. Other events besides intrapartum hypoxia may be responsible for HIE or CP, as less than 25% of these infants have symptoms of hypoxic ischemia at birth (Task Force on Neonatal Encephalopathy and Cerebral Palsy Staff American College of Obstetricians and Gynecologists with American Academy of Pediatrics Staff 2014).

The true incidence of intracranial hemorrhage (ICH) in utero has not been determined. Significant subarachnoid hemorrhage can occur with intrapartum hypoxia or may result from trauma at delivery. It can be isolated or associated with subdural bleeding and cerebral contusion. The presentation is variable but generally includes CNS depression, irritability, and seizures. When subarachnoid hemorrhage is associated with other signs of physical injury and is caused by a difficult delivery, outcome is frequently poor.

1.2.5 Fetal Response to Injury

During normal development, cardiovascular and circulatory functions progress from fetal life, which is characterized by low PaO_2 (20–24 mmHg; 2.66–3.19 kPa) through transition at birth, to normoxemia after birth (PaO_2 70–80 mmHg; 9.31–10.64 kPa); the fetus and newborn are clearly able to thrive despite their "hypoxic" environment. Adaptive responses by the cardiovascular, metabolic, and endocrine systems allow fairly severe intrauterine hypoxic stress to be tolerated, with the fetus having relatively normal growth and development. However, severe acute or chronic intrauterine hypoxic stress in utero can cause compromised circulation, organ dysfunction, and threaten survival or intact survival. At the time of transition to extrauterine life, signs of a depressed circulatory system because of intrauterine hypoxia may become apparent because of the increased metabolic demands at birth and loss of placental gas exchange (Anderson et al. 2004).

The fetal heart also has a greater capacity for anaerobic metabolism than the adult heart (Philipps 2004).

Renal impairment is commonly reported following a generalized hypoxic-ischemic insult at birth. The degree of insult varies in effect from oliguria with minor electrolyte abnormality and minimally elevated creatinine to complete renal failure requiring dialysis.

An elevated blood concentration of liver enzymes, as a marker of hepatocellular injury due to perinatal hypoxia, is also common after acute hypoxia, but irreversible liver damage is rare.

Fetal cardiovascular and endocrine responses may be altered, both in acute and in chronic hypoxia. Recurrence of mild hypoxia may occur in pregnancies where the blood flow to placenta, uterus, and fetus is repeatedly compromised by physiological and environmental influences. In chronic hypoxia, fetal growth restriction is not uncommon, and depression of growth factors during hypoxia has an important protective effect in conserving fetal substrate for energy as opposed to growth needs (Noori et al. 2004; Seri and Evens 2001). The full-term infant, while more likely to survive a severe hypoxic-ischemic insult at birth than a preterm infant (approximately 70% vs. 30%), is also more likely to have significant long-term morbidity (Cressens and Huppi 2006). In umbilical venous blood, mild hypoxemia may be manifest through an absence of hypercapnia or acidemia. In severe uteroplacental insufficiency, the fetus cannot compensate hemodynamically, and hypercapnia and acidemia increase exponentially (Bastek et al. 2008). Hypoxemic growth-restricted fetuses also demonstrate a range of hematological and metabolic abnormalities, including erythroblastosis, thrombocytopenia, hypoglycemia, deficiency in essential amino acids, hypertriglyceridemia, hypoinsulinemia, and hypothyroidism. Low birth weight increases the risk for perinatal mortality (death shortly after birth), asphyxia, hypothermia, polycythemia, hypocalcemia, immune dysfunction, neurologic abnormalities, and other long-term health problems (Petrini et al. 2009).

1.2.5.1 Fetal Hemodynamic Aspects

Acute hypoxemia produces various circulatory adaptations in the fetus that enhance fetal survival, including the development of tachycardia, hypertension, redistribution of blood flow toward the brain, myocardium and adrenals, and depression of fetal breathing and skeletal muscle activity.

This results in an increased blood supply to the brain, myocardium, and adrenal glands and reduced perfusion of the kidneys, gastrointestinal tract, and the lower extremities. There is preferential delivery of nutrients and oxygen to vital organs, compensating for a diminished placental supply (Sheridan 2005).

This compensation is manifest as cerebral vasodilatation and there is a decrease in the pulsatility index (PI) in cerebral vessels (Figs. 5 and 6). The PI index is an arterial blood-flow velocity waveform index designed to quantify the pulsatility or oscillations of the waveform. It is calculated by the formula PI = (Vmax − Vmin)/Vmax mean, where Vmax is the peak systolic velocity, Vmin is the minimum forward diastolic velocity in unidirectional flow or the maximum negative velocity in diastolic flow reversal, and Vmax mean is the maximum velocity averaged over one cardiac cycle. Cerebral vasodilatation produces a decrease in left ventricular afterload, while increased placental and systemic resistance result in an increased right ventricular afterload.

In severe hypoxemia, there is also redistribution of umbilical venous blood towards the ductus venosus. Consequently, blood flow in the umbilical vein, which contributes to the fetal cardiac output, is increased. In contrast, a reduced afterload is associated with an increase in peak diastolic forward flow, indicating that fetal systemic vascular resistance has a major influence on venous return and filling patterns of the right heart. Increased placental resistance and peripheral vasoconstriction cause an increase in right ventricular afterload, and thus ventricular end-diastolic pressure increases. This may result in highly pulsatile venous blood flow waveforms and umbilical venous pulsations due to the transmission of atrial pressure waves through the ductus venosus.

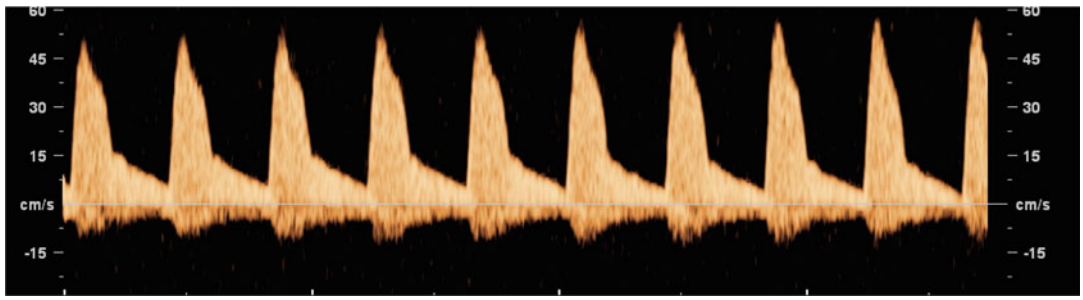

Fig. 5 Flow velocity waveforms from the middle cerebral artery in a normal fetus (Image courtesy of G. Rizzo)

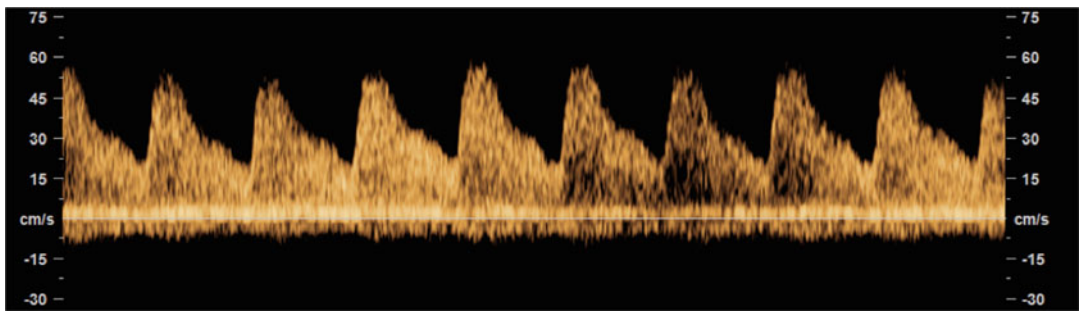

Fig. 6 Flow velocity waveforms from the middle cerebral artery in a growth-restricted fetus (Image courtesy of G. Rizzo)

Investigations of the venous vascular system have become increasingly important in the assessment of fetal myocardial function, and different indices are used to evaluate the blood flow velocity during the different phases of the cardiac cycle in the ductus venosus. Reference values for ductus venosus flow velocities are represented by ventricular systole (S wave) and diastole (D wave), the lowest forward velocity during atrial contraction (A wave) (Fig. 7). Different indices are calculated, e.g., the S/A ratio. The most important parameter which represents the final stage of disease is the abnormal reversal of blood flow velocities in the ductus venosus, inducing an increase in the S/A ratio, mainly due to a reduced A component of the velocity waveforms (Fig. 8). Reference values should be used for ductus venosus flow velocities during ventricular systole (S wave) and diastole (D wave), the lowest forward velocity during atrial contraction (A wave) and different calculated indices as the S/A.

In the inferior vena cava, there is an increase of reverse flow during atrial contraction with progressive fetal deterioration, suggesting a higher pressure gradient in the right atrium. (Figs. 9 and 10). A high venous pressure induces a reduced velocity at end-diastole in the umbilical vein, causing typical end-diastolic pulsations. The development of these pulsations is close to the onset of abnormal fetal heart rate patterns and is frequently associated with acidemia and fetal endocrine changes. At this stage, there may be an increased coronary blood flow velocity compared with that seen in normally grown third-trimester fetuses and, if the affected fetus is not delivered, intrauterine death may occur within a few days.

1.2.5.2 Fetal Growing Aspects

Accurate detection of suboptimal fetal growth is among the objectives of modern obstetrics. To achieve this result, sonography plays a critical role in providing a reliable estimate of fetal biometry, thus confirming the clinical suspicion of growth restriction and substantially influencing pregnancy management. An approach based on customized charts has proved to be more accurate than traditional population-based charts for antenatal detection of the true small fetuses, whose risk of adverse perinatal outcomes is substantially increased (Ghi et al. 2016).

The term small for gestational age (SGA) describes a condition in which the fetus is smaller than expected for the number of weeks of pregnancy (below the tenth percentile) and is unable to achieve its genetically determined potential size; when a SGA fetus shows also signs of placental insufficiency, it is defined an intrauterine growth restriction (IUGR) fetus. IUGR is not synonymous with SGA. Some, but not all, growth-restricted fetuses/infants are SGA, while 50–70% of SGA fetuses are constitutionally small, with fetal growth appropriate for maternal size and ethnicity.

This functional definition is useful to identify a population of fetuses at risk of poor outcome. The clinician's challenge is to distinguish between these two conditions and identify IUGR fetuses whose health is endangered in utero because of a hostile intrauterine environment and consequently to monitor and intervene appropriately.

In fact, data support the notion that long-term consequences of IUGR last well into adulthood. These individuals are predisposed to the development of a metabolic syndrome later in life, manifesting as obesity, hypertension, hypercholesterolemia, cardiovascular disease, and type 2 diabetes. Several hypotheses suggest that intrauterine malnutrition results in insulin resistance, loss of pancreatic beta-cell mass, and an adult predisposition to type 2 diabetes. Although the causative pathophysiology is uncertain, the risk of a metabolic syndrome in adulthood is increased among individuals who were IUGR at birth (Engle et al. 2007). In addition to an increased risk for physical sequelae, mental health problems have been found more commonly in children with growth restriction.

1.2.5.3 Diagnosis

Fetal arterial Doppler studies are useful in the differential diagnosis of SGA and IUGR fetuses. In normal pregnancies, umbilical artery (UA) resistance shows a continuous decline as the pregnancy progresses (Fig. 11), but this does not occur in fetuses with uteroplacental insufficiency.

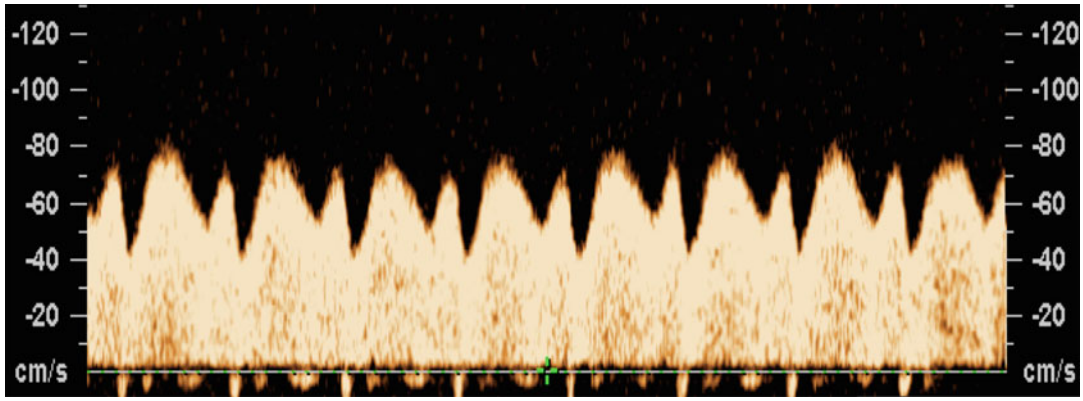

Fig. 7 Color Doppler examination of the ductus venosus with normal flow velocity waveforms (Image courtesy of G. Rizzo)

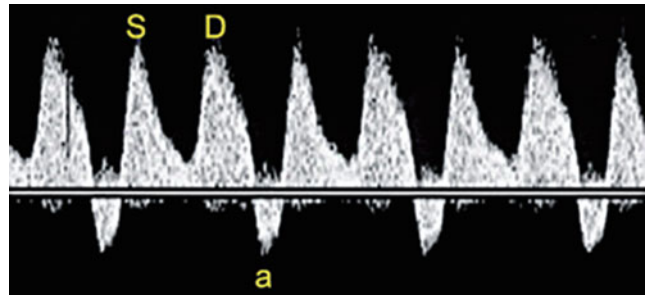

Fig. 8 Abnormal DV waveform with reversal of flow during atrial contraction and markedly increased pulsatility systole (*S*), diastole (*D*), atrial contraction (*a*)

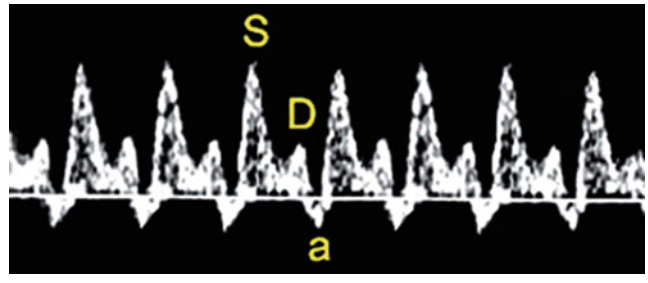

Fig. 9 Doppler examination of the inferior vena cava with normal flow velocity waveforms

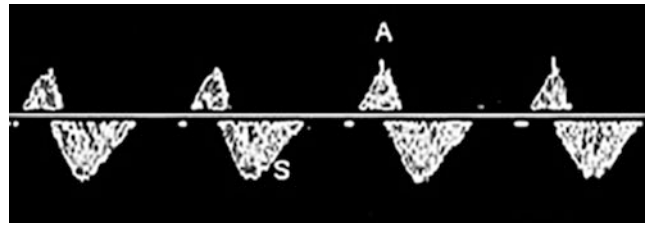

Fig. 10 Abnormal waveform with increase in reversed flow during atrial contraction in a growth-restricted fetus

The most commonly used measure of gestational age-specific UA resistance is the systolic-to-diastolic ratio of flow, the Pulsatility Index (PI), which increases with worsening disease. As the insufficiency progresses, end-diastolic velocity is lost and eventually reversed (Fig. 12). The status of UA blood flow supports the diagnosis of IUGR and provides early evidence of circulatory abnormalities in the fetus, helping clinicians to identify these high-risk fetuses. UA Doppler measurements may help the clinician decide whether a small fetus is truly growth restricted and to identify a small fetus at risk of chronic hypoxemia, but IUGR diagnosis is challenging and cannot only be based only on umbilical artery Doppler (Cruz-Martínez et al. 2011).

In hypoxemic fetuses with impaired placental perfusion, the PI in the umbilical artery is increased and the fetal middle cerebral artery PI is decreased; consequently, the PI ratio of the middle cerebral artery to umbilical artery (MCA/UA), defined as cerebroplacental ratio, (CPR) is decreased.

The CPR is emerging as an important predictor of adverse outcome not only for IUGR fetuses but also for SGA and appropriate for gestational age (AGA) fetuses close to term (DeVore 2015).

Recent evidence suggests that a proportion of these SGA fetuses have milder forms of late-onset intrauterine growth restriction as suggested by an increased risk of adverse perinatal outcome (McCowan et al. 2000; Doctor et al. 2001; Figueras et al. 2008a), abnormal neonatal neurobehavioral performance (Figueras et al. 2009), and suboptimal neurodevelopment in childhood (McCowan et al. 2002; Figueras et al. 2008b). These findings add to the body of evidence suggesting that the diagnostic category of SGA includes a proportion of cases with true growth restriction and mild placental insufficiency, which is not reflected in the umbilical artery Doppler. Recent studies suggest that the risk of adverse outcome in these fetuses is best established by means of brain Doppler examination. Thus, brain sparing as measured by the middle cerebral artery Doppler is associated with poorer perinatal outcome, higher risk of cesarean delivery for nonreassuring fetal status (Severi et al. 2002), and increased risk of abnormal neurodevelopmental tests at birth (Oros et al. 2010) and at 2 years of age (Eixarch et al. 2008).

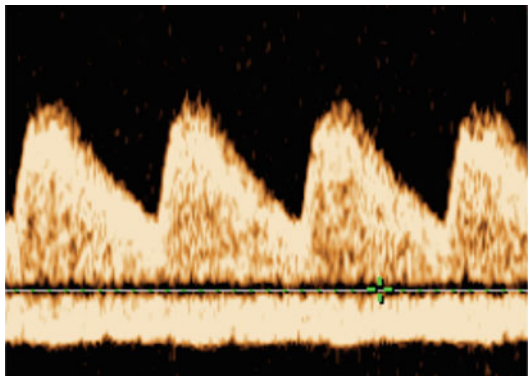

Fig. 11 Color Doppler of the umbilical artery with normal flow velocity waveforms (Image courtesy of G. Rizzo)

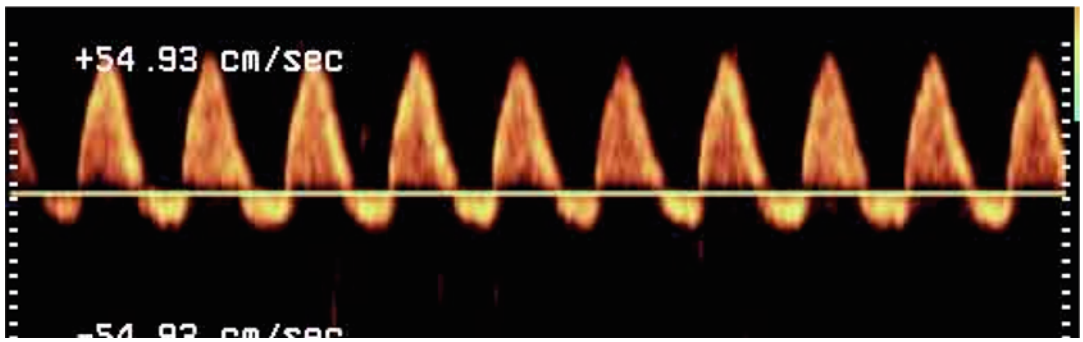

Fig. 12 Color Doppler of the umbilical artery with reversed flow (Image courtesy of G. Rizzo)

1.2.5.4 Timing of Delivery and Management

In the past, the period from 3 weeks before until 2 weeks after the estimated date of delivery was considered "term," with the expectation that neonatal outcomes from deliveries in this interval were uniform and good. Increasingly, however, research has shown that neonatal outcomes, especially respiratory morbidity, vary depending on the timing of delivery within this 5-week gestational age range. To address this lack of uniformity, The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommended that the label "term" be replaced with the designations below (ACOG 2013):

- Early term (37 0/7 weeks of gestation through 38 6/7 weeks of gestation)
- Full term (39 0/7 weeks of gestation through 40 6/7 weeks of gestation)
- Late term (41 0/7 weeks of gestation through 41 6/7 weeks of gestation)
- Postterm (42 0/7 weeks of gestation and beyond)

Preterm birth, defined as birth at less than 37 + 0 weeks of gestation, is the most important single determinant of adverse infant outcome in terms of both survival and quality of life (Saigal and Doyle 2008).

An useful pragmatic definition for a "premature" infant is one who has not yet reached the level of fetal development that generally allows life outside the womb. In the normal human fetus, several organ systems mature between 34 and 37 weeks, and the fetus reaches adequate maturity by the end of this period. One of the main organs greatly affected by premature birth is the lung.

In Europe and many developed countries, the preterm birth rate is generally 5–9%, and in the USA, it has risen to 12–13% in the last decades. There are three categories of preterm birth: (1) spontaneous preterm births are the 40–45% preterm births that follow preterm labor of spontaneous (i.e., idiopathic) onset; (2) 25–30% preterm births occur after premature rupture of the membranes; (3) the remaining 30–35% are preterm births that are induced for obstetric reasons.

Babies born just a few weeks earlier than full-term usually do not experience any problems related to their slight prematurity. However, the more premature these infants are, the more serious are the complications.

Although there are recommendations that term IUGR fetuses should be monitored during delivery as high-risk pregnancies (Royal College of Obstetricians and Gynaecologists 2002), there is no consensus about the best strategy for delivery.

The Lancet published data on brain development in survivors of the multicenter Growth Restriction Intervention Trial (GRIT) (Thornton et al. 2004). The aim of this study was to identify compromised fetuses between 24 and 36 weeks' gestation and answer the question of whether it was safer to deliver them immediately or to delay until there was no clinical doubt that delivery was necessary. In the GRIT study, the 24 week gestation babies were very different from those at 36 weeks. In the absence of severe congenital abnormalities, the current infant mortality after 32 weeks' gestation is low: the causes of this rare event include asphyxia, necrotising enterocolitis, and infection; respiratory distress syndrome is rare in this group. By contrast, before 32 weeks, and particularly in the extreme preterm fetus, there is a much higher mortality, and the levels of morbidity were also emphasized by the EPICure Study, in which 49% of surviving infants born at less than 26 weeks' gestation had some disability at 30 months of age and 19% were severely disabled (Wood et al. 2000). The EPICure study reached some important conclusions. It demonstrated that 44% of infants born at 25 weeks' gestation survived to discharge, whereas delivery at 22 weeks almost invariably resulted in neonatal death.

Neonatologists, obstetricians, and parents must increasingly recognize that infants born less than 25 weeks' gestation who survive are at risk of disability at school age. In the EPICure study, only 20% were totally free of disability at school age and so the prognosis must be guarded. Disability was classified as follows:

1. *Severe*: The child was likely to be highly dependent on care-givers, e.g., non-ambulant cerebral palsy, profound hearing loss, or blindness.

2. *Moderate*: Children who were likely to be reasonably independent, e.g., ambulant cerebral palsy, some hearing loss, or some visual impairment.
3. *Mild*: Children with neurological signs with minimal functional consequences.

In the EPICure study, over half of the survivors had moderate disability or no disability at school age. In addition, some of the 24% with moderate disability were improved with spectacles and hearing aids.

There is uncertainty about whether iatrogenic delivery of the very preterm (before 33 weeks of gestation) growth-restricted fetus should be undertaken before the development of signs of severe hypoxemia, with a consequent risk of prematurity-related neonatal complications, or whether delivery should be delayed, incurring risks of prolonged exposure to hypoxia and malnutrition imposed by the hostile intrauterine environment (Walter et al. 2009). With every week that passes, there is a decreasing risk of complications including intraventricular hemorrhage, retinopathy of prematurity, and sepsis. However, delay may expose the growth-restricted fetus to ischemic injury of the brain, resulting in asphyxia, periventricular leukomalacia, and intraventricular hemorrhage, as well as a significant risk of intrauterine death. It is important to weigh the risks and benefits of early interventions. This is a dynamic process, in which advancements in both fetal and neonatal medicine are of crucial importance for the appropriate counseling of parents and the management of these pregnancies.

The GRIT study showed a small increase in fetal death if the obstetrician delayed delivery, and a small increase in neonatal death if early delivery was chosen. Thus the monitoring of fetal health is particularly important if there is growth restriction. Such fetuses have few metabolic reserves, and sudden death during pregnancy may occur. Labor is an intermittently hypoxic event, and anaerobic metabolism may not be an option when there are inadequate stores of fat and glycogen.

In recent years, placental and fetal arterial Doppler flow-velocity waveforms have guided the timing of delivery. Doppler has been particularly effective in assessing the growth-restricted pregnancy and has been a useful adjunct for the assessment of the very preterm fetus, when cardiotocographical monitoring is unhelpful. However, in the growth-restricted hypoxemic fetus, redistribution of well-oxygenated blood to vital organs, such as the brain, heart, and adrenals, represents a compensatory mechanism to prevent fetal damage, and when the reserve capacities of the circulatory redistribution reach their limits, fetal deterioration may occur rapidly. In clinical practice, serial Doppler investigations estimate the duration and degree of fetal blood flow redistribution. The onset of an abnormal venous Doppler recording indicates deterioration in the fetal condition and iatrogenic delivery should be considered.

Delivery of IUGR fetuses remain a challenging problem for clinicians not only for preterm but also for fetuses near term. In practice, term pregnancies are often delivered, and the delivery of the late preterm (34 + 0–36 + 6 weeks) or early term (37 weeks) growth-restricted fetus is also recommended if there are additional risk factors for adverse outcome, such as maternal medical/obstetrical disorders, arrest of growth over a 3–4 week interval, and/ or absence or reversal Doppler flow in the umbilical artery (Spong et al. 2011).

A recent multicenter clinical trial, the Disproportionate Intrauterine Growth Intervention Trial At Term (DIGITAT), failed to demonstrate differences in perinatal outcome between expectant management compared with induction of labor in fetuses beyond 36 weeks' gestation (Boers et al. 2010; Tajik et al. 2014).

The study confirms that the relatively favorable neonatal outcomes in both study groups could reflect the fact that participants and clinicians were more alert to possible complications and monitoring was intensified.

In conclusion, the goal in the management of the preterm fetus is to deliver the most mature fetus possible, at least at 32–34 weeks, in the best condition possible increasing fetal and maternal monitoring (Table 1).

Table 1 Suggested management of the preterm fetus

What to do	Perform parental counseling
	Share any type of decisions with the neonatologist, the anesthesiologist, and the couple, personalizing the specific situation
	Fill the informed consent as much detailed as it is possible
Considering	Short-term consequences: RDS, NEC, IVH, PVL, pulmonary dysplasia, sepsis
	Long-term consequences: cerebral palsy, mental impairment, attention disorders
	Pregnancy age and prognosis age
	Etiology of the preterm labor (maternal causes, fetal causes)
	Maternal mortality related to the type of delivery
	Fetal presentation
	Obstetric anamnesis of the patient
	Combination of the multiple factors
When	Better after 26 weeks
	Using corticosteroids between 48 h and 7 days before delivery
Where	Any hospital with NICU
How	Trying to reduce the effects of the hypoxia
	Balance maternal and fetal morbidity
	Preterm delivery is not itself an indication of cesarean section unless associated with maternal or fetal consequences

1.3 Part 2 General Characteristics of Preterm and Term Newborn

1.3.1 History

A full family history is essential. This should include a full medical and social history. Note should be taken of alcohol ingestion and of any drugs (prescribed or recreational). It should enquire about the possibility of consanguinity – the question, "Are your families related?" to both parents is one way of approaching this often delicate subject. Enquiry should be made about the presence of possible transmissible and inheritable diseases in the families of both parents. Tall or short stature can generate a search for specific undiagnosed diseases in the parents (e.g., Marfan syndrome, gluten intolerance, achondroplasia). Anemia in the parents can be a marker of a hematological defect (e.g., thalassemia), as well as the place of origin and ethnicity of the parents (e.g., G6PD deficiency).

1.3.1.1 History of the Pregnancy and Delivery

A baby's well-being is determined by periconceptional events. The mother's medical history is important, including the possibility of maternal diabetes mellitus and other illnesses and her immune status (HBV, HCV, HIV, CMV, toxoplasmosis, rubella, HSV-HZV, and syphilis). The possibility of seroconversion during pregnancy should be considered. Enquiry should be made about the course of the pregnancy. Account should be taken of the time of booking for antenatal care (late booking may be a sign of a disorganized life style and associated problems).

The results of antenatal checks should be noted: fetal growth and ultrasound results, amniotic fluid volume, maternal anemia, urine results and maternal diabetes mellitus, and pregnancy-induced hypertension or pre-eclampsia. The results of vaginal and anal bacterial swabs within the month before delivery should be noted (group B streptococci or *Listeria monocytogenes*) and whether the mother was given appropriate intrapartum antibiotic prophylaxis.

A history of the pregnancy should include note of drugs taken during the pregnancy and their indications. Consider evidence of infectious illnesses or fever close to the time of delivery and take note of the timing of membrane rupturing and the quantity and color (blood or meconium staining) of the amniotic fluid.

Details of the delivery should be noted, i.e., whether vaginal, operative (forceps of vacuum extraction), cesarean section (planned or emergency, before or during the labor), and evidence of fetal distress.

The baby's presentation should be noted because abnormal limb position may be due to a breech presentation. The possibility of birth trauma (e.g., cephalohematoma, fracture of the clavicle) should be considered.

Adaptation to postnatal life should be considered, bearing in mind that during the first hours after birth the baby is in a transitional period, passing from intra- to extrauterine life.

A baby's condition during the minutes just after birth is described by the Apgar score, usually recorded at 1 and 5 min (see Table 2). Although the Apgar score may be criticized (it is subjective on the part of the observer, often recorded some time after delivery), in its favor, it is almost universally recorded. The score was described in 1953 by Dr. Virginia Apgar, a North American pediatric anesthetist. She intended it to indicate whether or not resuscitation was needed. Although imperfect, there is no doubt that a low score (0 or 1, signifying an absent or slowly beating heart) indicates a baby who is barely alive at the time of birth, and a score of 8 or more indicates an individual whose general condition is good. However, the Apgar score is an imperfect indicator of subsequent progress or outcome. A baby who has a high initial score may develop difficulties with gas exchange in the minutes that follow, even if these problems are transient.

More recent researches have shown that the great majority of normal term infants reach transcutaneous pre-ductal values of oxygen saturation $\geq$90% after 10 min from birth and that premature infants <32 weeks' gestation can require a longer time to reach the same target (Wychoff et al. 2015; Parmigiani and Corona 2016).

Table 2 Apgar score

Sign	0	1	2
Appearance (color)	Blue or pale	Pink body with blue extremities	Completely pink
Pulse (heart rate)	Absent or <60 beats/min	$\geq$60– <100 beats/min	>100 beats/min
Grimace (reflex irritability)	No response	Grimace	Cough or sneeze
Activity (muscle tone)	Limp	Some flexion	Active movements
Respiration	Absent	Slow, irregular	Good, crying

Another new approach is to start the resuscitation of term babies with room air, adding oxygen after 30–60 s preferably under pulsoximeter guidance. In fact, it has been shown that asphyxiated infants resuscitated with room air started regular breathing significantly before than those resuscitated with 100% oxygen (Rabi et al. 2011).

Another important topic related to assistance at birth is if delayed cord clamping can improve cardio-circulatory adaptation after birth. Some data seem in favor of retarded cord clamping after 1 min or after first breath in term infants; however, this is still controversial and not yet well understood under the physiopathologic aspect (Parmigiani and Corona 2016; Hooper et al. 2016).

Most healthy babies are inclined to breastfeed during the first hour of life, and babies recognize their mother's smell. This is the best moment to favor mother-infant bonding and breastfeeding.

A baby's size is an indicator of intrauterine development and nutrition. Intrauterine growth restriction can be a consequence of poor placental function (e.g., due to diseases such as pregnancy-induced hypertension, systemic lupus erythematosus, cocaine ingestion, or infection) and congenital disease, chromosomopathy, or fetal alcohol syndrome.

Observation of a baby's movements, when undressed and preferably in the presence of one or both parents, allows for observation of the quality of movements (whether symmetrical, coordinate, and smooth).

Eyes may be difficult to examine at birth because there is often some eyelid edema, but they must be checked later to note the presence of a red reflex. In the case of babies who are discharged early from hospital, this may need to be done at home by the family doctor or community midwifery team.

Lips, gums, and palate must be examined to exclude the presence of a cleft or other malformation.

The hips should be examined to exclude congenital dislocation. During the immediate neonatal period, the ability to achieve full abduction is a useful sign. It may only be possible to elicit a positive Ortolani sign, an index of hip luxation/subluxation, later during the first week.

Arms, legs, fingers, and toes should be examined to identify any abnormality (e.g., webbing, number, length). Examination of the chest should note any asymmetry during respiration, subcostal or intercostal retraction, and ancillary nipples. The skin may show areas of hypo- or hyperpigmentation, scars, blisters, pustules, petechiae, or evidence of birth trauma (cuts, bruises). The diaper area should be examined to look for anomalies of the external genitalia, an imperforate or anterior anus, and hairy tufts or dimples over the sacrum.

1.3.1.2 Clinical Aspects of CNS Development

Motor and sensory functions mature during pregnancy and are already in great part developed by the middle of the second trimester of pregnancy and the process continues after birth. Ultrasound, particularly so-called 4D ultrasound, allows for the identification and classification of fetal movements, and natural fetal behavior has been studied. Sporadic, irregular ("vermiform") movements are seen between 6 and 7 weeks' gestation, involving the whole body. Generalized, brief movements from the legs to the neck and head (such as "startle") are observed at 8 weeks' gestation. At 9 weeks, flexor movements of the cranial and caudal poles towards the centre appear, interspersed with jerks that allow small movements within the amniotic liquid and partial rotation of the head. At the tenth week, hand-to-head movements, mouth opening with tongue protrusion, swallowing, rotation along the longitudinal axis, and independent movements of limb flexion and extension can be observed (Ianniruberto and Tajani 1981; Kurjak et al. 2008).

The maturation of the central nervous system (CNS) determines an infant's response and tolerance to various sensory inputs. A premature infant may demonstrate signs of immaturity (Holditch-Davis et al. 2003) such as:

Diffuse and indeterminate sleep or waking states with frequent whimpering, facial twitches, or apparent smiling

Abrupt transitions between states

Periods of fussiness or crying

Low-level alertness, characterized by a dull, glassy-eyed look

Hyperalertness, characterized by wide-open eyes with a panicked, worried look; an appearance of extreme vigilance

Uncoordinated eye movements: roving or floating eyes

Immature tone, posture, and general coordination

The five senses can be altered by prematurity:

1. The earliest response to auditory stimulation has been recorded at 19 weeks' gestation but consistent responsiveness is established by 25 weeks. Deafness is a complication of intraventricular hemorrhage or periventricular leukomalacia affecting 5–10% of preterm infants. It may also be the result of a cytomegalovirus infection, which may have caused preterm delivery. The ambient noise of a NICU is rarely less than 40 dB (as in the womb), and more often around 70–100 dB (American Academy of Pediatrics. Committee on Environmental Health 1997).
2. Functional maturation of the visual system starts at around 5 months and it is still immature at term (Graven 2004). Retinopathy of prematurity (ROP), formerly known as retrolental fibroplasia and affecting premature babies exposed to excessive oxygen, is nowadays largely preventable: oxygen delivery is monitored carefully and all infants below 32 weeks' gestation have regular examination of the retina following a generally accepted international protocol. Advanced stages of ROP are treated by cryo- or laser therapy. However, decreased visual acuity or strabismus may follow. Nowadays, total blindness is infrequent.
3. Taste develops under the influence of amniotic fluid flavonoids and odorants transmitted from the maternal diet from as early as 14 weeks' gestation. Taste after birth can be disturbed by drugs, by the late introduction of oral feeding, or by the impaired development of taste centers.
4. The sensory system starts to develop at 8 weeks and is functional by 12 weeks' gestation. Being touched may be uncomfortable

even for full-term infants who have not developed all the receptors and pathways, and perception may also be disturbed by drugs, e.g., maternal cocaine use. In the preterm infant, touch may be a powerful stressor. Touch should be gentle and combined with the stimulation of other senses, for example, speaking to the baby. Touching for no good reason should similarly be avoided. Parents should be taught to touch gently and about "kangaroo care".

5. The olfactory tract is part of the primitive encephalon and a baby at term is able to recognize its mother's odor. The olfactory system is fully functional by 14 weeks' gestation. Strong odors can be stressful for preterm babies who are unable to communicate this to their carer.

These signs of immaturity should be recognized and a favorable environment should be created, avoiding overstimulation. Woolf (1959, 1966), Brazelton (1984), and Prechtl (1974) described different states of behavior. The Brazelton scale assesses neonatal behavior in six states: quiet sleep, active sleep, drowsiness, alert inactivity, active awake, and crying (Table 3). The baby should be observed in a state of quiet wakefulness.

Table 3 Neonatal states classification scale

State	Characteristics
Quiet sleep	Regular breathing, eyes closed. Spontaneous activity confined to startle and jerky movements at regular intervals.
	Responses to external stimuli are partially inhibited, and any response is likely to be delayed. No eye movements, and state changes are less likely after stimuli or startles than in other states.
Active sleep	Irregular breathing patterns, sucking movements, eyes closed but rapid eye movements can be detected underneath the closed lids. Infants also have some low-level and irregular motor activity. Startles occur in response to external stimuli and can produce a change in state.
Drowsiness	While the newborn is semi-dosing, eyes may be open or closed; eyelids often flutter; activity level variable and interspersed with mild startles. Drowsy newborns are responsive to sensory stimuli but with some delay, and state change frequently follows stimulation.
Alert inactivity	A bright alert look, with attention focused on sources of auditory or visual stimuli; motor activity is inhibited while attending to stimuli.
Active awake	Eyes open, considerable motor activity, thrusting movements of extremities, and occasional startles set off by activity; reactive to external stimulation with an increase in startles or motor activity. Discrete responses are difficult to distinguish due to general high activity level.
Crying	Intense irritability in the form of sustained crying and jerky limb movement. This state is difficult to break through with stimulation.

Data from (Brazelton 1984)

1.3.1.3 The Preterm Infant

Maturity is determined by the length of gestation, and the severity of problems related to prematurity is directly related to gestation.

Weeks of gestation are generally considered as completed weeks. The World Health Organization has defined preterm infants as those with gestational age less than 37 weeks. Recently, the term "late preterm infants" (instead of "near-term") has been used for those infants that are born at a gestational age between 34 weeks and 36 weeks and 6 days. These infants have a rather higher morbidity and mortality than term infants (gestational age $\geq$37 weeks), even though they are of similar size (Woolf 1959, 1966; Brazelton 1984; Prechtl 1974). Some North American authors have also used the terms "premies" and "micropremies" to describe very immature babies.

Classification by birth weight is as follows:

- *Low birth weight* (LBW), 1501–2500 g
- *Very low birth weight* (VLBW), 1001–1500 g
- *Extremely low birth weight* (ELBW), $\leq$1000 g

Because of the survival of very light and premature babies, the term "incredibly low birth weight" has been used to refer to babies weighing less than 750 g.

A fundamental problem for all preterm infants is their poor ability to maintain body temperature because of reduced glycogen stores (depending on gestational age) and thinner skin, with the most

immature lacking the ability to shiver. Thus a primary aim is to avoid heat loss (and insensible water losses) by drying, heating, and covering the baby. This also decreases glucose consumption, reducing the risk of hypoglycemia. Plastic wrapping of body and head (apart the face) immediately after birth is advisable for babies <32 weeks' gestation to maintain temperature between 36.5 °C and 37.5 °C (Wychoff et al. 2015).

The preterm baby often experiences delayed respiratory adaptation. Depending on the degree of immaturity, the lungs are morphologically immature and lack surfactant. Such babies may require the endotracheal administration of exogenous surfactant and mechanical ventilation. Bronchopulmonary dysplasia (chronic lung disease with O_2 dependency) is a complication of severe prematurity, which may continue to cause problems during subsequent years.

Premature infants have reduced immune defenses. Furthermore, infection may be the primary cause of preterm delivery, sometimes affecting the baby before birth. Such infections, in combination with lung and brain immaturity, increase the risk of later disability (see ▶ Chap. 14, "Follow-Up Outcomes of High-Risk Infants").

The gastrointestinal tract is not yet adapted to enteral feeds, posing considerable challenges to those responsible for their care. Early nonnutritive feeding should be considered. Milk, preferably from the mother or a human milk bank, may be started early but cautiously, particularly for the most immature infant. Careful note should be taken of early signs of gastrointestinal intolerance, e.g., increased volume or bile-staining of gastric aspirates or abdominal swelling. The most immature infants require parenteral nutrition (partial or total) to provide adequate nutrients and calories for growth, and this may need to be continued for several weeks. This practice requires a central, indwelling catheter, increasing the risk of infection.

Because of advances in the care of these very vulnerable infants, survival at the earliest gestation is improving.

Survival at early gestation and the associated risks of neurodevelopmental impairment are considered elsewhere (see ▶ Chap. 17, "Cerebral Plasticity and Functional Reorganization in Children with Congenital Brain Lesions").

Not only babies at extremely low gestation but also those born late preterm are at risk.

Various evidence points to the environment being of major importance for appropriate development. Although neonatologists strive to recreate an extrauterine environment that is similar to that of the womb, there are many differences.

Light, painful interventions, development in air instead of surrounded by amniotic fluid, noise, stress, sleep-wake cycles interrupted by nursing procedures, continuous intravenous nutrition (without the intermittent glycemic peaks of normal feeding and maternal ingestion), fluctuations in oxygen delivery, carbon dioxide, pH levels, and blood pressure may all interfere with normal brain development. A high tech/soft touch approach may be beneficial and a mother's touch and breastfeeding should be encouraged even for very tiny babies.

In some units, parents are supported by a psychologist to help with attachment. In spite of the best endeavors of staff, having a baby in a neonatal unit, often for several months, is undoubtedly stressful, giving rise to feelings of inadequacy on the part of the mother, who may feel a biological failure, and anxiety on the part of the father, who is no longer in control of the situation.

References

ACOG (2012) Committee Opinion 545 Noninvasive Prenatal Testing for Fetal Aneuploidy

ACOG (2013) Committee Opinion No 579: definition of term pregnancy. Obstet Gynecol 122(5):1139–1140

ACOG (2014) Antepartum fetal surveillance. Obstet Gynecol 124:1

Akolekar R et al (2015) Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. Ultrasound Obstet Gynecol 45:16–26

Albaiges G, Missfelder-Lobos H, Lees C et al (2000) One-stage screening for pregnancy complications by color Doppler assessment of the uterine arteries at 23 weeks' gestation. Obstet Gynecol 96:559–564

Alfirevic Z, Mujezinovic F, Sundberg K (2003) Amniocentesis and chorionic villus sampling for prenatal diagnosis. Cochrane Database Syst Rev Issue 3. Art. No.: CD003252.

Allen LH (2001) Biological mechanisms that might underlie iron's effects on fetal growth and preterm birth. J Nutr 131:S581–S589

American Academy of Pediatrics. Committee on Environmental Health (1997) Noise: a hazard for the fetus and the newborn. Pediatrics 100:724–727

Anderson P, Kleiman C, Lister G, Telner N (2004) Cardiovascular function during development and response to hypoxia. In: Polin R, Fox W, Abman S (eds) Fetal and neonatal physiology. Saunders, Philadelphia, pp 645–669

Bamberg C, Kalache KD (2004) Prenatal diagnosis of fetal growth restriction. Semin Fetal Neonatal Med 9:387–394

Bastek LA, Sammel MD, Paré E et al (2008) Adverse neonatal outcomes: examining the risk between preterm, late preterm, and term infants. Am J Obstet Gynecol 199:367.e1–367.e8

Bishop EH (1981) Fetal acceleration test. Am J Obstet Gynecol 141:905–909

Boers KE et al (2010) Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). BMJ 341:c7087

Botto LD, Olney RS et al (1996) Chorionic villus sampling and transverse digital deficiencies: evidence for anatomic and gestational-age specificity of the digital deficiencies in two studies. Am J Med Genet 62:173–178

Bowden AP, Barrett JH, Fallow W, Silman AJ (2001) Women with inflammatory polyarthritis have babies of lower birth weight. J Rheumatol 28:355–359

Brazelton TB (1984) Neonatal behavioral assesment scale, 2nd edn. Heinemann, London

Canick JA et al (2013) The impact of maternal plasma DNA fetal fraction on next generation sequencing tests for common fetal aneuploidies. Prenatal Diagnosis 33:667–674

Christian P, Khatry SK, Katz J et al (2003) Effects of alternative maternal micronutrient supplements on low birth weight in rural Nepal: double blind randomised community trial. BMJ 326:571

Clapp JF (2003) The effects of maternal exercise on fetal oxygenation and feto-placental growth. Eur J Obstet Gynecol Reprod Biol 110(Suppl 1):S80–S85

Cressens P, Huppi PS (2006) The CNS: hypoxic ischemic encephalopathy. In: Fanaroff AA, Martin R, Walsh MC (eds) Neonatal-perinatal medicine. Mosby, St Louis

Cruz-Martínez R et al. (2011) Fetal brain doppler to predict cesarean delivery for nonreassuring fetal status in term small-for-gestational-age fetuses. Obstet Gynecol 117(3):618–26

DeVore GR (2015) The importance of the cerebroplacental ratio in the evaluation of fetal well-being in SGA and AGA foetuses. Am J Obstet Gynecol 213(1):5–15

Doctor BA et al (2001) Perinatal correlates and neonatal outcomes of small for gestational age infants born at term gestation. Am J Obstet Gynecol 185:652–659

Eixarch E et al (2008) Neurodevelopmental outcome in 2-year-old infants who were small-for-gestational age term fetuses with cerebral blood flow redistribution. Ultrasound Obstet Gynecol 32:894–899

Engle A, Tomashek KM, Wallman C, Committee on Fetus and Newborn (2007) 'Late preterm' infants: a population at risk. Pediatrics 120:1390–1401

Ferrazzi E, Rigano S, Bozzo M et al (2000) Umbilical vein blood flow in growth-restricted fetuses. Ultrasound Obstet Gynecol 16:432–438

Figueras F, Eixarch E, Gratacos E, Gardosi J (2008a) Predictiveness of antenatal umbilical artery Doppler for adverse pregnancy outcome in small-for-gestational-age babies according to customised birthweight centiles: population-based study. BJOG 115:590–594

Figueras F et al (2008b) Small-for-gestational-age fetuses with normal umbilical artery Doppler have suboptimal perinatal and neurodevelopmental outcome. Eur J Obstet Gynecol Reprod Biol 136:34–38

Figueras F et al (2009) Neurobehavior in term, small-forgestational age infants with normal placental function. Pediatrics 124:e934–e941

Fowden AL, Forhead AJ (2004) Endocrine mechanisms of intrauterine programming. Reproduction 127:515–526

Ghi T et al (2016) Customized fetal growth charts for parents' characteristics, race, and parity by quantile regression analysis. J Ultrasound Med 35:e35–e44

Graven SN (2004) Early neurosensory visual development of the fetus and newborn. Clin Perinatol 31:199–216

Holditch-Davis D, Blackburn ST, Vandenberg K (2003) Newborn and infant neurobehavioural development. In: Kenner C, Wright Lott J (eds) Comprehensive neonatal nursing: a physiological perspective, 3rd edn. WB Saunders, St Louis, pp 236–284

Hooper SB, Binder-Heschl C, Polglase GR et al (2016) The timing of umbilical cord clamping at birth: physiological considerations. Maternal Health Neonatol Perinatol 2:4

Ianniruberto A, Tajani E (1981) Ultrasonographic study of fetal movements. Semin perinatol 5:175–181

Kliman HJ (2000) Uteroplacental blood flow. The story of decidualization, menstruation, and trophoblast invasion. Am J Pathol 157:1759–1768

Kramer MS, Kakuma R (2003) Energy and protein intake in pregnancy. Cochrane Database Syst Rev CD000032

Krampl E, Lees C, Bland JM et al (2000) Fetal biometry at 4300 m compared to sea level in Peru. Ultrasound Obstet Gynecol 16:9–18

Kurjak A, Tikvica A, Stanojevic M et al (2008) The assessment of fetal neurobehavior by three-dimensional and four-dimensional ultrasound. J Matern Fetal Neonatal Med 21:675–684

Leguizamon G, von Stecher F (2003) Third trimester glycemic profiles and fetal growth. Curr Diab Rep 3:323–326

Liston R, Sawchuck D, Young D (2007) Fetal health surveillance: antepartum and intrapartum consensus guideline. J Obstet Gynaecol Can 29:909

Macones GA, Hankins GD, Spong CY, Hauth J, Moore T (2008) The 2008 National Institute of Child Health and Human Development workshop report on electronic

fetal monitoring: update on definitions, interpretation, and research guidelines. Obstet Gynecol 112:661–666
McCowan LM, Harding JE, Stewart AW (2000) Umbilical artery Doppler studies in small for gestational age babies reflect disease severity. BJOG 107:916–925
McCowan LM, Pryor J, Harding JE (2002) Perinatal predictors of neurodevelopmental outcome in small-for-gestational-age children at 18 months of age. Am J Obstet Gynecol 186:1069–1075
McGaw T (2002) Periodontal disease and preterm delivery of low-birth-weight infants. J Can Dent Assoc 68:165–169
Nicolaides KH (2004) Nuchal translucency and other first-trimester sonographic markers of chromosomal abnormalities. Am J Obstet Gynecol 191:45–67
Noori S, Friedlich P, Seri I (2004) Pathophysiology of shock in the fetus and newborn. In: Polin R, Fox W, Abman S (eds) Fetal and neonatal physiology. Saunders, Philadelphia, pp 772–781
Oros D et al (2010) Middle versus anterior cerebral artery Doppler for the prediction of perinatal outcome and neonatal neurobehavior in term small-for-gestational-age fetuses with normal umbilical artery Doppler. Ultrasound Obstet Gynecol 35:456–461
Palomaki GE et al (2011) DNA sequencing of maternal plasma to detect down syndrome: an international clinical validation study. Genet Med 13:913–920
Parmigiani S, Corona MF (2016) Capitolo 28. Promozione dell'allattamento al seno. In: Felis S, Parmigiani S (eds) Il parto. Edi-Ermes Publisher, Milan, pp 359–372
Petrini JR, Dias T, Mc Cormick MC et al (2009) Increased risk of adverse neurological development for late preterm infants. J Pediatr 154:169–176
Philipps A (2004) Oxygen consumption and general carbohydrate metabolism of the fetus. In: Polin R, Fox W, Abman S (eds) Fetal and neonatal physiology. Saunders, Philadelphia, pp 465–478
Picciano MF (2003) Pregnancy and lactation: physiological adjustments, nutritional requirements and the role of dietary supplements. J Nutr 133:1997S–2002S
Practice Bulletin No. 162 (2016 May) Prenatal diagnostic testing for genetic disorders. Obstet Gynecol 127(5): e108–e122
Prechtl HFR (1974) The behavioral states of the newborn infant: a review. Brain Res 76:1304–1311
Rabi Y, Singhal N, Nettel-Aguirre A (2011) Room-air versus oxygen administration for resuscitation of preterm infants: the ROAR study. Pediatrics 128: e374–e381
RCOG (2014) The investigation and management of the small-for-gestational-age fetus. Green top guideline 31-Jan 2014
Rich-Edwards JW, Buka SL, Brennan RT, Earls F (2003) Diverging associations of maternal age with low birthweight for black and white mothers. Int J Epidemiol 32:83–90
Rohan AJ, Golombek SG (2009) Hypoxia in the term newborn: part three – sepsis and hypotension, neurologic, metabolic and hematologic disorders. MCN Am J Matern Child Nurs 34:224–233
Royal College of Obstetricians and Gynaecologists (2002) The investigation and management of the small-for-gestational-age fetus. Evidence-based clinical guideline no. 31. RCOG, London, pp 1–16
Saigal S, Doyle LW (2008) An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 371:261–269
Seri I, Evens J (2001) Controversies in the diagnosis and management of hypotension in the newborn infant. Curr Opin Pediatr 13:116–123
Severi FM et al (2002) Uterine and fetal cerebral Doppler predict the outcome of third-trimester small-for-gestational age fetuses with normal umbilical artery Doppler. Ultrasound Obstet Gynecol 19:225–228
Sheridan C (2005) Intrauterine growth restriction. Aust Fam Physic 34:717–723
Skomsvoll JF, Baste V, Irgens LM, Ostensen M (2002) The recurrence risk of adverse outcome in the second pregnancy in women with rheumatic disease. Obstet Gynecol 100:1196–1202
Sparks AB et al (2012) Noninvasive prenatal detection and selective analysis of cell-free DNA obtained from maternal blood: evaluation for trisomy 21 and trisomy 18. Am J Obstet Gynecol 206:319 e311–319 e319
Spencer K, Souter V, Tul N, Snijders R, Nicolaides KH (1999) A screening program for trisomy 21 at 10–14 weeks using fetal nuchal translucency, maternal serum free b-human chorionic gonadotropin and pregnancy-associated plasma protein-A. Ultrasound Obstet Gynecol 13:231–237
Spong CY, Mercer BM, D'alton M, Kilpatrick S, Blackwell S, Saade G (2011) Timing of indicated late-preterm and early-term birth. Obstet Gynecol 118:323–333
Tajik P et al (2014) Which intrauterine growth restricted fetuses at term benefit from early labour induction? A secondary analysis of the DIGITAT randomised trial. Eur J Obstet Gynecol Reprod Biol 172:20–25
Task Force on Neonatal Encephalopathy and Cerebral Palsy Staff American College of Obstetricians and Gynecologists with American Academy of Pediatrics Staff (2014) Neonatal Encephalopathy and Neurologic Outcome, Second Edition. Obstetrics & Gynecology 123(4): 896–901
Thornton JG, Hornbuckle J, Vail A et al (2004) Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomized controlled trial. Lancet 364:513–520
Volpe JJ (2008) Hypoxic-ischemic encephalopathy: clinical aspects. In: Volpe JJ (ed) Neurology of the newborn. Elsevier Saunders, Philadelphia, pp 400–480
Walter EC, Ehlenbach WJ, Hotchkin DL et al (2009) Low birth weight and respiratory disease in adulthood. A population-based case-control study. Am J Respir Crit Care Med 180:176–180
Way W (2006) Recent observations on the regulation of the fetal metabolism of glucose. J Physiol 572:17–24
Winsor EJ et al (1999) Cytogenetic aspects of the Canadian early and mid-trimester amniotic fluid trial (CEMAT). Prenat Diagn 19:620–627

Wolff PH (1959) Observations on newborn infants. Psychosom Med 21:110–118

Wolff PH (1966) The causes, controls and organization of behaviour in the neonate. Psychol Issues 5:1–105

Wood NS, Marlow N, Costeloe K et al (2000) Neurologic and developmental disability after extremely preterm birth. N Engl J Med 343:378–384. comment 343:429–430

Wychoff MH, Aziz K, Escobedo M et al (2015) Part 13: neonatal resuscitation. 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 132(Suppl 2):S543–S560

Xiao R, Sorensen TK, Williams MA, Luthy DA (2003) Influence of pre-eclampsia on fetal growth. J Matern Fetal Neonatal Med 13:157–162

Zimmermann B et al (2012) Noninvasive prenatal aneuploidy testing of chromosomes 13, 18, 21, X, and Y, using targeted sequencing of polymorphic loci. Prenat Diagn 32:1233–1241

Zygmunt M, Herr F, Keller-Schoenwetter S et al (2002) Characterization of human chorionic gonadotropin as a novel angiogenic factor. J Clin Endocrinol Metab 87:5290–5296

Zygmunt M, Herr F, Munstedt K et al (2003) Angiogenesis and vasculogenesis in pregnancy. Eur J Obstet Gynecol Reprod Biol 110(Suppl 1):S10–S18