Respiratory Diseases in the Newborn

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Respiratory Physiology

To understand respiratory diseases during this period, knowledge of normal respiratory physiology is helpful. During intrauterine life, the lungs produce liquid and are filled with it. During the last trimester of pregnancy, this lung fluid goes through the trachea and provide all the substances to the amniotic fluid, even surfactant. Lung maturity can be measured using this information in the amniocentesis, as well as the analysis of the lecithin–sphingomyelin ratio (L/E) and phosphatidylglycerol (PG).

The fetus has intermittent respiratory movements, which may work to move this lung fluid out, with the objective to train its postnatal function. During childbirth, lymphatic reabsorption of the lung fluid takes place, probably through cortisol, thyroid hormones, and catecholamines, which are boosted with the air pulmonary expansion when the child has been born. Once the newborn starts to breathe, the first efforts must be very vigorous (around 40 cm H_2O of pressure) to expel lung fluid and establish a residual lung volume. The beginning of breathing facilitates an important reduction in lung vascular resistance caused by the mechanical expansion of the lung as well as the increase in PaO_2 and pH, and

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release of humoral vasodilators. Increase in PaO_2 is also responsible for constraining and functionally closing the patent ductus arteriosus (preterm infants are more resistant to this closure). Besides this, systemic pressure rises when circulation to the placenta is stopped. These changes allow the transition of the blood flow from fetal to neonatal. Pulmonary arterial smooth muscle is proportionately greater in the newborn; therefore, when hypoxemia arises, pulmonary hypertension may easily develop, and thus the lung would go back to a "fetal circulation."

Breathing control is more vulnerable during the neonatal period. Although there is a ventilation response to CO_2 level increase, it is less powerful in the preterm newborn and is further reduced by hypoxemia. Newborns present a paradox response to hypoxemia. For a few seconds, a transient hyperventilation occurs (caused by stimulation of chemoreceptors), which then progresses to a central respiratory depression. In the preterm newborn, the hyperventilation phase is reduced, and it can even be absent in those who are very immature. Respiratory reflexes such as the Hering-Breuer (vagal inhibition) and Head (inspiratory response to lung inflation) are fully functional (Table 36.1).

Distensibility of the rib cage is greater in the newborn, especially in the preterm infant, which makes it difficult to maintain an adequate lung residual capacity, and can also ease alveolar collapse when there is a low lung distension.

Of the resistance forces, 20% correspond to the friction of the lung against the rib cage and 80% correspond to airway resistance. In the newborn, the nostrils are the point of greatest airflow resistance in the airway. This is important, considering that during this period, breathing is done mostly through the nose. Lung airway resistance is greater in the newborn than in the adult. In addition, because of the small size of the airway in the newborn, any obstructive process will noticeably increase lung resistance.

In absolute terms, lung distensibility is less in the newborn than in the adult, but when correction per weight is done the values are similar. Respiratory rate in the newborn is greater than at other ages, and this higher rate may be useful to maintain keep lung volume through the reduction in expiratory time (Table 36.2).

Table 36.1 Respiratory physiology of the newborn

High pressures in the first breaths
Expulsion of lung fluid
Decrease in lung vascular resistance
Constriction and functional closure of the arteriosus ductus
High distensibility of the rib cage
Low functional residual capacity
Increased pulmonary resistance
Low lung distension
High respiratory rate
Nasal breathing
Lower CO_2 ventilatory response in preterm infants
Paradoxical hypoxemia response
High minute ventilation
Increase of dead space in preterm infant
High oxygen consumption
Active Hering-Breuer's and Head's reflexes
Pulmonary arteries with larger muscles

Approaching the Newborn with Respiratory Disease

The respiratory distress syndrome (RDS) symptoms are tachypnea, retraction, grunting, cyanosis, and apnea. Nevertheless, these can present from pulmonary and extrapulmonary causes (Fig. 36.1). A detailed perinatal anamnesis based on risk factor determination and an exhaustive physical examination are essential for determining a precise diagnosis and adequate management.

Excluding hyaline membrane disease, the risk factors related to respiratory diseases are as follows:

- *Conatal pneumonia*: Masculine sex, feverish mother, chorioamnionitis, premature labor, prolonged membrane rupture, prolonged labor, streptococcal maternal colonization, Guillain–Barré syndrome, tracheoesophageal fistula.
- *Meconium aspiration syndrome*: (TTN) Amniotic fluid stained by meconium, fetal distress, post maturity, small for gestational age.

Table 36.2 Comparison of respiratory variables per age

		Newborn	Adult	
Respiratory frequency	(f)	34–45	13	rpm
Tidal volume	(Vt or Vc)	6–8	7	ml/kg
Alveolar volume	(Va)	3.8–5.8	4.8	ml/kg
Anatomical dead space	(VD)	2–2.2	2.2	ml/kg
Minute ventilation	(Ve)	200–260	90	ml/kg/min
Alveolar ventilation	(Va)	100–150	60	ml/kg/min
Functional dead space	(VD)	77–99	30	ml/kg/min
Dead space/tidal volume	(VD/Vt)	0.27–0.37	0.3	
Oxygen consumption	(VO_2)	6–8	3.2	ml/kg/min
Lung resistance	(R)	20–30	3–4	cm H_2O/l/s
Dynamic lung distensibility	(Cd)	4–6	100–150	ml/cm H_2O
Functional residual capacity	(FRC)	20–30	34	ml/kg

BPM breaths per minute
Note: Preterm newborns have a higher dead space/tidal volume ratio (0.5) and greater pulmonary resistance

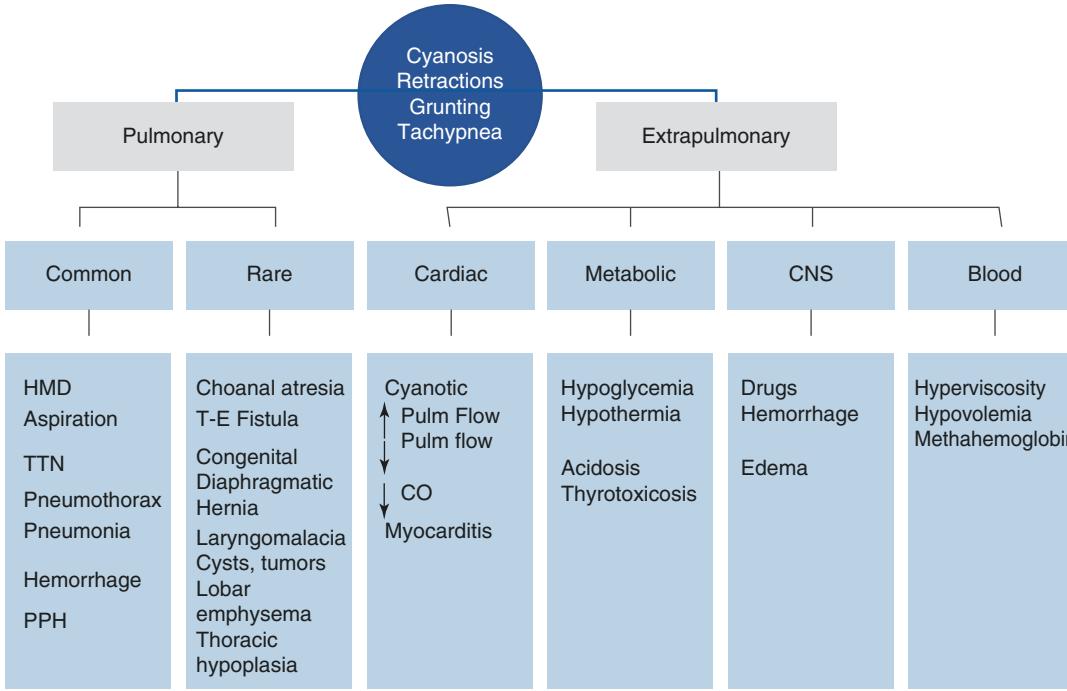

Fig. 36.1 Differential diagnosis for RDS

- *Transient tachypnea of the newborn*: Cesarean section, fast labor, neonatal depression, maternal sedation.
- *Pneumothorax*: History of resuscitation through manual ventilation.
- *Persistent pulmonary hypertension*: (PPH) Meconium aspiration syndrome, neonatal depression, pneumonia, polycythemia, congenital diaphragmatic hernia, ingestion of aspirin or antiinflammatories, hyaline membrane disease, cold stress.

A history of polyhydramnios is related to diaphragmatic hernia and tracheoesophageal fistula. A history of oligohydramnios is related to pulmonary hypoplasia, prolonged membrane rupture, and renal agenesis. In relation to the anamnesis, it is important to consider the following issues:

- *Maternal history*: Health state before pregnancy and during previous pregnancies, prenatal care, prenatal ultrasound, family diseases, pregnancy diseases, drugs and

medications, cause of hospital admittance, labor time, fetal state, amount of amniotic fluid (maturity, infection signs, meconium), bleeding, fetal distress, type of labor, approximate gestational age.

- *Newborn history*: General condition at birth, need for resuscitation, Apgar score, vital signs, evaluation during transition period.
- *Physical examination*: Nutritional state, presence and distribution of cyanosis. Acrocyanosis or distal cyanosis in feet and hands are common findings within the first days of life. However, central cyanosis is always abnormal, and it is evident when deoxygenated hemoglobin exceeds 3 g/dl, and this suggests the presence of hypoxemia. Cyanosis from crying is possible because a short circuit is caused by the Valsalva maneuver through the foramen ovale. Paleness may suggest shock, vasoconstriction, anemia, and obstruction of the cardiac outflow tract. Polycythemia may be suspected if the child looks plethoric; if the child has meconium stains, then meconium aspiration is suspected, and if there is exanthema or a bad smell, it must be considered that the cause of the breathing difficulty is a pneumonia. Nasal flaring shows the newborn's need for air. The shape of a barrel chest suggests a volume increase, and a bell-shaped chest suggests a volume decrease (Table 36.3). Extremely preterm newborns (<1000 g) have a very compliant thoracic wall. During normal breathing a negative interpleural pressure is created, but it goes even further when the lung is sick, causing an evident intercostal and xiphoid retraction, with a tendency to collapse. This collapsing and protruding of the abdominal content, caused by the diaphragm moving downward, are the factors that cause "swing" or paradoxical breathing, which is typical of the severe breathing difficulty syndrome. Tachypnea is considered when the newborn has more than 60 breaths per minute and is the most sensible sign. Normal premature and term newborns will present a respiratory pattern called periodical breathing, which consists of shallow breaths followed by the cease of respiratory efforts or short apneas, which lasts from 5 to 10 s. It is important to notice the height of the tip of the heart, as it will be displaced if there are pulmonary masses, pneumothorax, or pulmonary hypoplasia. A scaphoid abdomen is typical of diaphragmatic hernias, where part of the abdominal content is placed in the thoracic cavity, which does not allow an adequate development of abdominal cavity, but it looks similar to the abdomen of a child who has eliminated meconium in the uterus. Abdomen distension can be seen when there is a tracheoesophageal fistula, especially when positive pressure has been used. If the belly button moves toward one side during inspiration or presents a "belly button dance" sign, it may be a sign of diaphragmatic paralysis in the side to which it is moving. When there is pulmonary hyperinsufflation, the liver and spleen can be easily palpated.

Table 36.3 Causes of changes in thoracic volume

Bilateral	
Volume increase	Transient tachypnea, meconium aspiration syndrome, pulmonary hypertension, cystic lung diseases
Volume reduction	Hyaline membrane disease, pulmonary hypoplasia, thoracic wall restricted
Unilateral	
Low-volume disease	Atelectasis, unilateral pulmonary hypoplasia
High-volume disease	Pneumothorax, unilateral interstitial emphysema, pulmonary cystic disease, Diaphragmatic disease, chylothorax

Considering lung sounds, grunting is the most characteristic. It is caused by the opposition of vocal cords at the end of the expiration phase. Grunting causes positive pressure toward the end of the expiration, which keeps the small airways open and improves ventilation distribution.

- Stridor suggests an obstruction of large airways. If the obstruction is extrathoracic, stridor will be greater at inspiration, although it can be heard in both inspiration and expiration when the obstruction is severe. Pulmonary murmur can be evaluated according to its intensity, length, symmetry,

presence of crepitus, ronchi, or wheezing, although these alterations are less frequent in newborns.

- *Laboratory tests*
  - *Chest X-rays*: Very useful in the differential diagnosis of respiratory and nonrespiratory diseases. Lateral and anteroposterior projections are essential for a good evaluation of pneumothorax, catheter position, and pleural tubes. Bones, soft tissues, and the visible portion of the abdomen must be systemically evaluated before focusing on the heart and lungs. Also, each chest X-ray film must be used to reevaluate the position of tubes and catheters because they usually migrate.

    The trachea is easily curved because of its great flexibility, and it can even seem to have a mass effect, through its compression by other abnormal structures (Table 36.4).
  - *Cell blood count and cultures*: Infections must be actively sought, because of what a prompt treatment involves and also because of the difficulty of making a differential diagnosis, especially when differentiating from hyaline membrane disease.
  - *Pulmonary function test*: Initially it was only performed under investigative conditions, but today many ventilators are equipped with sensors that allow measuring this function. It is very useful to determine tidal volumes (if they are not increased) and pulmonary overdistension signs, which can contribute to neonatal lung damage.
  - *Blood gases*: One of the most useful tests to determine the physiopathology of the disease. It can also be used for treatment, as there are different goals, depending on the gestational age and the type of disease.
  - *Hyperoxy test*: Hypoxemia is considered when extrapulmonary short circuits from right to left are suspected (congenital heart disease and pulmonary hypertension). Oxygen is provided at 100% and gases are controlled. If the disease is pulmonary, PaO_2 increases significantly.
  - *General tests*: Hematocrit must be controlled, because polyglobulic conditions may cause hypoxemia, and acute anemia may cause difficulties in starting spontaneous breathing during resuscitation. In every pathological process glycemia must be controlled because of the immaturity of the regulation systems, which is related to a greater energetic expenditure and reduced intake.

Table 36.4 Common findings and variants in neonatal chest X-ray

Normal findings	Normal variants
Uniform lung fields	Pleural fissures
Less prominence of pulmonary hilums	Tracheal twisting and indentation
8–9 ribs expansion	Mediastinal lines
Tracheal deviation to the right	Pseudohyperlucid lung
Air bronchogram	Apical or intercostal hernia
Cardiac silhouette <60% of thorax	Radiolucency of the suprasternal space

Classification of the Respiratory Problems of the Newborn

I. Respiratory problems caused by perinatal asphyxia.
II. Respiratory problems related to immaturity and lung liquid reabsorption.
III. Respiratory problems related to lung circulation. Respiratory problems conditioned by lung circulation diseases.
IV. Respiratory infections in the newborn: pneumonia.
V. Respiratory problems caused by congenital alterations of the airway and lungs.

Respiratory Problems Related to Perinatal Asphyxia

Cardiorespiratory Depression at Birth

As many as 10% of newborns requires some kind of support to start breathing spontaneously. It is crucial to anticipate this situation by determining which childbirths may produce depression at birth. Because of this, it is important to have at each childbirth at least one qualified person who may provide the initial resuscitation steps, and

another person who may perform advanced resuscitation. The action flowchart is taught at the Neonatal Resuscitation Program, which is regulated by the American Academy of Pediatrics and the American Heart Association.

During childbirth the fetus may be exposed to periods of temporary hypoxia, caused by the decrease of the placenta blood flow. The fetus adapts to these periods by redistributing the blood flow to favor the brain, heart, and adrenal glands. During hypoxic periods, the respiratory system has adaptation mechanisms that are not efficient in either the fetus or the newborn: this is called paradoxical response to hypoxia. It happens when the fetus and newborns who have suffered hypoxia increase their respiratory rate and respiratory effort (tidal and minute volume increase), but this is transitory, and it rapidly progresses into apnea. Therefore, it is not uncommon to face a perinatal hypoxia sign consisting of no respiratory effort at birth, which will require resuscitation techniques to start spontaneous breathing. Depending on how long the fetus has been hypoxic, the apnea may be primary or secondary. Secondary apnea implies a greater time suffering hypoxia, wherein compensatory vascular mechanisms have been overwhelmed, and this is reflected in the fall of arterial pressure. When resuscitating a child with secondary apnea it is crucial to provide ventilation with effective positive pressure, and, less frequently, to use cardiac massage and drugs.

Perinatal Asphyxia and Respiratory Distress Syndrome Caused by Meconium Aspiration

Respiratory distress syndrome caused by aspiration of meconium is a common complication of perinatal asphyxia, and sometimes it is a serious one; this is frequently found in a postterm newborn. Its prevention depends on good control and perinatal management.

Intrauterine asphyxia stimulates gastrointestinal motility and the relaxation of the anal sphincter, which allows the meconium to enter the amniotic fluid, but this is uncommon before 37 weeks of gestation. If the fetus is younger than 34 weeks, the anal sphincter does not relax during asphyxia. Hypoxemia also causes the fetus to initiate deep breathing efforts, and so the fetus aspirates the amniotic fluid containing meconium. During birth the risk of meconium aspiration is greater, as a consequence of the first breaths. Meconium impacts different levels of the thinner airways, which causes an obstructive respiratory disease with entrapped air, and alteration of alveolar stability, along with its inflammatory reaction. Entrapped air is one of the causes of the high rate of pneumothorax in this disease. In almost 50% of the cases, respiratory failure is related and complicated by an important degree of pulmonary hypertension. Ventilatory mechanics are altered: airway resistance is increased, functional residual capacity is also increased because of the entrapped air, pulmonary distensibility is reduced, and there is compromise of the ventilation/perfusion ratio. The result is a respiratory distress situation with hypoxemia and hypercarbia.

Generally, the patient is a term or postterm newborn. Sometimes they are small considering their gestational age, with a history of perinatal asphyxia, which has been certified through the presence of meconium in the amniotic fluid, as well as alteration in the fetal heartbeat and cardiorespiratory depression at birth, which requires resuscitation. There can be meconium in the umbilical cord, and the skin of the newborn may have meconium impregnations. Polypnea and respiratory distress signs appear early: chest retraction, grunting, and nasal flaring. The thorax curves outward, with increased anteroposterior diameter. There is a noticeable cyanosis, which, at the beginning of the clinical presentation, usually responds to an increase in the oxygen inspired fraction, unless there is a serious pulmonary hypertension. During auscultation there can be a reduction of the pulmonary murmur and crackles. Other concomitant complications caused by asphyxia, and which may require specific treatment, must be investigated, such as hypoxic-ischemic encephalopathy, renal impairment, cardiogenic shock, and alterations of the coagulation process.

If the aforementioned clinical history and signs are considered, diagnosis is generally clear. The aim of the laboratory examinations is to corroborate the diagnose of meconium aspiration, evaluate the presence of other complications from asphyxia, and for follow-up.

The following examinations must be done:

- *Anteroposterior and lateral chest X-ray*. X-rays will show irregular opacities as nodules or cords, following the distribution of the bronchial tree next to hyperinsufflation zones. The diaphragm is sometimes flat. It is important to rule out the presence of pneumothorax (Fig. 36.2).
- *Arterial gases*. Arterial gases will show the degree of respiratory failure. These measures must be serially controlled every 48 h, as needed. This information will be key for delivering a prompt and adequate treatment, to evaluate its efficacy as well as the progression of the disease.
- *Cell blood count and blood culture*. These tests are important to obtain hematocrit values and detect a possible infection. Meconium is a good culture medium.

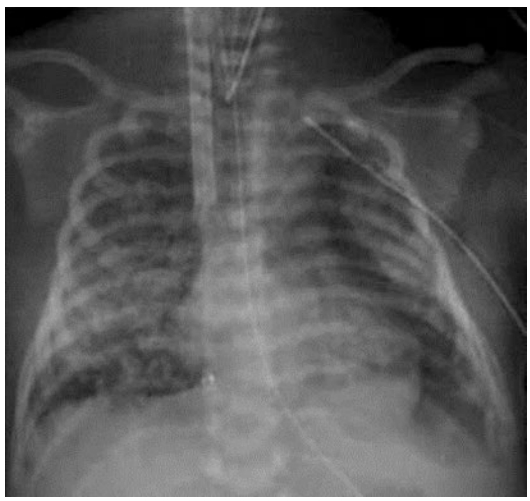

Fig. 36.2 Meconium aspiration syndrome. Chest X-ray of a term newborn combines alveolar interstitial shadows with slightly collapsed areas with pneumothorax to the left side, partially leaking with the insertion of a chest tube. Patient is intubated and connected to venoarterial extracorporeal membrane oxygenation (ECMO)

Depending on the additional problems and the evolution of the patient who has undergone asphyxia and meconium aspiration, other examinations may be necessary if there is suspicion of an important pulmonary hypertension: glycemia, calcemia, cardiac and brain isoenzymes, coagulation tests, brain ultrasound, and echocardiography, when an important pulmonary hypertension is suspected.

Prevention includes good pregnancy control and newborn attention at birth. Meconium aspiration from the trachea, using endotracheal intubation when the newborn is hypotonic, is a common practice, although it has not been validated. Management consists of adequate oxygenation, ventilation support as needed, antibiotics use until an infection is ruled out, and management of complications such as pneumothorax, pulmonary hypertension, and other issues related to asphyxia and sepsis. It has been proven that the administration of diluted surfactant reduces the need of extracorporeal membrane oxygenation and the risk of death.

Respiratory Problems Related to Prematurity and Lung Fluid Reabsorption

Hyaline Membrane Disease

Hyaline membrane disease (or respiratory distress syndrome, RDS) is a respiratory disease characteristic of the premature newborn, caused by pulmonary surfactant deficiency. Surfactant is produced in the type II pneumocytes. It is composed of phospholipids with small quantities of neutral fat, cholesterol, and proteins. The primary active molecule is saturated dipalmitoyl phosphatidylcholine, but phosphatidylglycerol and unsaturated phosphatidylcholine are also present. Surfactant reduces superficial tension, adhering to the alveolar surface and displacing water molecules. It has four proteins: A, B, C, and D. Protein A is more abundant and it is hydrosoluble. It has a key part in the surfactant recycling process and some capacity to protect the lung. Protein B intervenes in the surfactant recycling process. Protein C increases surfactant reabsorption and

production. Protein D has a defensive function in the lungs. Type II pneumocytes appear in the lung from 20 to 24 gestational weeks. Steroids and thyroid hormones increase the transcription and synthesis rate of limiting enzymes. The function of the pulmonary surfactant is to reduce the superficial tension in the alveoli to maintain pulmonary stability and volume during exhalation. It is crucial to have an adequate amount of surfactant in the liquid–air interface to sustain alveolar stability. As a result of surfactant deficiency, there is a tendency to alveolar collapse, which causes a progressive atelectasis, with an intrapulmonary blood flow short circuit that evolves into an increasing hypoxia. Functional alterations characteristic of hyaline membrane disease are reduction of pulmonary distensibility and of the functional residual capacity, accompanied by an alteration of the perfusion–ventilation ratio. This alteration of pulmonary mechanics originates a global respiratory failure with hypoxemia and hypercarbia, which is worsened by the fatigue of the respiratory muscles. Hypoxemia and acidosis increase pulmonary vascular resistance, which worsens the condition.

Hyaline membrane disease is the main cause of respiratory morbidity and mortality in the premature newborn. Its incidence is estimated in about 50% of children who are younger than 29 weeks of gestational age and only about 5% of those older than 34 weeks. In the South American region, an incidence of 74% has been found among newborns whose weight is less than 1500 g at birth. Related risk factors have been described (Table 36.5).

Hyaline membrane disease is characterized by an early-onset progressive respiratory difficulty, usually starting at birth or during the first 6 h of life. It causes a respiratory grunting, usually audible, nasal flaring, retraction, polypnea, and FiO_2 requirements that increase rapidly. Vesicular murmur tends to be reduced during auscultation. Anteroposterior thoracic diameter is reduced. In severe cases, breathing can become paradoxical or in "swings." There is generally edema and reduced diuresis.

Chest X-ray is essential for the diagnosis. The radiological image is characteristic, but not pathognomonic, showing a homogeneous increase of pulmonary density, described as a frosted glass on which air bronchogram images can be seen (Fig. 36.3).

Table 36.5 Risk factors related to hyaline membrane disease (HMD)

Increased risk	Reduced risk
Masculine sex	Female sex
White race	Black race
L/E < 2.0 for premature newborns	L/E > 2.0[a]
Previous brother with HMD	Maternal preeclampsia
Maternal diabetes (A, B, C)	Maternal diabetes (D, F, R)
Maternal hypotension	Maternal drug abuse
Cesarean section without labor	Antenatal steroids
Third-trimester hemorrhage	Chronic abruption
Second twin	Prolonged membrane rupture
Fetal hydrops	Intrauterine growth retardation
Neonatal depression	Vaginal childbirth

[a]Lecithin/sphingomyelin

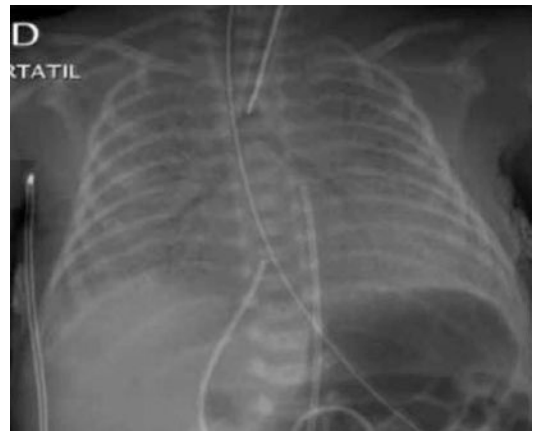

Fig. 36.3 Hyaline membrane disease. Chest X-ray in newborn whose lung volume is lightly reduced (because the newborn has undergone intubation and receives positive pressure), frosted glass sign, and air bronchogram

Blood gases show oxygen requirements that need to be addressed rapidly with fraction of inspired oxygen (FiO_2) above 30–40%. Depending on the seriousness of the case, there may be respiratory or metabolic acidosis.

The most important and difficult differential diagnosis is conatal pneumonia produced by

group B streptococcus. The clinical and radiological findings may be identical. Perinatal history is important for making a differentiation, and in the case of pneumonia, a fast progression with a greater tendency to cardiovascular compromise. During the first hours it can also be confused with transient tachypnea of the newborn. The benign course and good lung volume of this last disease differentiates the two.

Prevention of hyaline membrane disease is essentially perinatal: diversion of risk pregnancies to specialized centers, prevention and management of premature labor, determination of fetal lung maturity depending on the case, and the acceleration of fetal pulmonary maturity.

Following the pioneer study done by Liggins and Howie in 1972, several investigations have confirmed that antenatal steroids are related to a significant reduction in the presentation of hyaline membrane disease. In the same way, it has been demonstrated that antenatal steroids reduce mortality and the incidence of intraventricular hemorrhage. Therefore, beyond traditional usage recommendations for the fetus who is 24–34 weeks of gestational age and at risk of premature birth, in many centers steroids are used before the 24 weeks. Their administration between 34 and 36 weeks is currently under study, given the impact of the currently named "late-term premature newborns." In all cases, the benefits obtained surpass the potential risks of steroid usage, although repeated cycles must only be used for investigation protocols, given the association with a worse neurological outcome. Treatment consists of 2 doses of 12 mg IM betamethasone, with a 24-h difference, or 6 mg dexamethasone IM with a 12-h difference. Optimal benefits start 24 h after initiating therapy and persist up to 7 days after.

These children must be admitted to the intensive care unit. Ideally, they are born in a specialized perinatal center, or at least they are promptly taken to a tertiary neonatal center.

Therapy with exogenous surfactant is, without doubt, the most significant therapeutic advance for hyaline membrane disease. The therapy has changed the natural progression of the disease, making it shorter, and significantly improving the survival rate. There are natural and artificial surfactants: the first are extracted from the amniotic fluid of animals and the second are synthesized, which mainly includes surfactant phospholipids, but not its proteins. A range of studies have shown that both natural and artificial exogenous surfactants significantly reduce morbidity and mortality rate in this disease. Other recent studies do not show significant differences when using different kinds of natural surfactant, which are those most used currently. The most effective approach is the early administration of the surfactant, before 2 h of life. It has also been used as prophylaxis in the higher-risk groups, such as those younger than 30 weeks. Nevertheless, it is becoming increasingly common to use it with nasal continuous positive airway pressure (CPAP) for the initial respiratory stabilization in very low weight premature newborns, which seems to be a more appropriate approach than the prophylactic use of surfactant. The INSURE technique has been widely incorporated into clinical practice: this is INtubation-SURfactant-Extubation, with nasal continuous positive airway pressure. During recent years several studies have administered surfactant to the airway, through a fine tube, but results have not been conclusive.

Respiratory assistance includes the prophylactic or early use of continuous nasal positive pressure, which reduces the need of mechanical ventilation, as well as INSURE. The use of noninvasive nasal ventilation through nasal devices that avoid the use of tracheal intubation is still being studied. Regarding oxygen administration to the premature newborn, current experts recommend to start resuscitating with a FiO_2 of 21–30% to avoid oxidative damage. The saturation goal for respiratory distress syndrome is to keep it between 90% and 95%.

Other diseases have been related to hyaline membrane disease, such as alveolar rupture, infection, persistent arteriosus ductus, intraventricular hemorrhage, and pulmonary hypertension. It is possible that with an adequate treatment or prevention for the hyaline membrane syndrome, all these diseases can be prevented or made less stressful.

The chronic disease most usually related to hyaline membrane disease is bronchopulmonary dysplasia. In the long term, newborns who survive this disease seems to have a greater frequency of respiratory diseases during the first years of life.

We must note that congenital surfactant deficiency does exist. SP-B deficiency is the first known cause of genetic neonatal respiratory distress, and it is usually an autosomal recessive disorder. It is usually presented as a respiratory difficulty syndrome in a term newborn who does not respond to any therapy, with progression is death.

The deficiency of transport protein ABCA3 (ATP-binding cassette member A3) has also been described, which is related to the transcellular transport of surfactant and the assembly of lamellar bodies. ABCA3 gene mutations have an autosomal recessive transmission. SP-C congenital deficiency has also been described. These two can appear during neonatal age, and later during childhood, as chronic respiratory disease.

In these conditions, the diagnosis is through determination of the protein content in the surfactant, which has been collected from the fluid obtained in the bronchoalveolar lavage, DNA genetic testing oriented to identify blood mutations, electron microscopy, and immunohistochemical dying for surfactant proteins on an available tissue sample.

There is no treatment for these congenital surfactant deficits. Lung transplant does not present encouraging results, and the hope for the future may lie in gene therapy.

Newborn Apnea

Newborn apnea consists in the absence of an airflow in the respiratory airway during a period of at least 20 s. It can be fewer than 20 s if bradycardia or cyanosis is present. It must be differentiated from periodic breathing, as already described.

Neonatal apnea especially compromises the premature newborn, and it is present in 50% of children of gestational age less than 32 gestational weeks. According to etiology, the classification is as follows:

- *Primary or idiopathic newborn apnea*. It is the most common one. Its origin is unknown but it is probably related to immaturity in the central and peripheral mechanisms of breathing control. Its onset is usually between the second or third day of life, and it disappears when the newborn is 34–35 weeks of adjusted age, although 2% of premature newborns with very low birth weight at birth can continue to present apneas beyond 40 weeks of gestational-adjusted age.
- *Apnea secondary to other disease*. It can appear in premature and term newborns. The most common triggers are metabolic problems (hypoglycemia, hypocalcemia, hyponatremia), neurological alterations (intracranial hemorrhage, asphyxia, seizures), infections, respiratory distress conditions, bronchopulmonary dysplasia, persistent ductus arteriosus, hypothermia, and anemia. The most important action is to treat the triggering cause.

According to their presentation, apneas are classified as follows:

- *Central apnea:* Absence of airflow and stopping of breathing movements.
- *Obstructive apnea:* There are respiratory movements, but no airflow.

(It must be considered that this type of apnea is not detected by the respiratory monitor. This diagnosis must be suspected in newborns with bradycardia crisis and/or cyanosis with no apparent etiology.)

- *Mixed apnea*. During the same episode, both presentations are mixed. Generally, it appears as an obstructive apnea that stops breathing efforts through hypoxemia.

With the intention of an early diagnosis, it is recommended to routinely monitor every newborn who is younger than 34 weeks, given the high risk of apnea. It is important to consider that newborn hypoxemia, especially if the child is premature, has a depressing effect on the respiratory center.

When the diagnosis of premature newborn idiopathic apnea has been established, the following therapeutic measures must be taken: cardiorespiratory monitoring and permanent O_2 saturation, keep the neck in a neutral position, aspire secretions, keep body temperature as stable as possible, close to the lower point of thermoneutrality, correct hypoxemia, and use methylxanthines, because they stimulate the respiratory center and improve the diaphragm contraction capacity. Theophylline has been the treatment most used for premature newborn apnea, with very good results. As an alternative, caffeine may be used, which has fewer adverse effects, and higher doses can be administrated. In this way, other tools have been used for the treatment of apneas, such as proprioception and olfactory stimuli.

In those cases of serious apnea that do not respond to the previous measures, and that by their intensity produce an important decline in the child's condition, an option is to use nasal continuous positive pressure in higher airflows. If there is no improvement, mechanical ventilation must be started.

Transient Tachypnea of the Newborn

Transient Tachypnea of the Newborn is a clinical condition caused by a temporal alteration of the neonatal breathing adaptation. It presents as a respiratory distress disease, characterized mainly by tachypnea, usually with a benign course, short, and self-limited. It is more frequent in the term or near-term newborns, as well as those delivered by a cesarean section.

It is thought that this disease is caused by a delay in the lung fluid reabsorption that is normally present during fetal life. The relationship to a cesarean delivery, especially when this has been an elective procedure, is caused by the fact that labor would stimulate lung liquid reabsorption, probably mediated by catecholamines secretion.

Even though there are clinical and radiological facts that characterize neonatal transient tachypnea, this entity is an exclusion diagnosis. The main differential diagnosis is hyaline membrane disease, pneumonia, post-asphyxia situations, and cardiovascular problems. If the baby was born through vaginal birth, this diagnosis must be reconsidered, and pneumonia must be suspected.

The respiratory distress clinical presentation mainly consists in tachypnea. Oxygen requirements are usually low, and they are important for the differential diagnosis. When they are higher than 0.40 FiO_2, the diagnosis must be reconsidered; this is a crucial element to differentiate it from a hyaline membrane disease. The chest has an increased or regular anteroposterior diameter. Auscultation may be normal, or the pulmonary murmur may be slightly reduced. Progression usually tends to the improvement of the situation during the first 24–48 h. In some cases, progression may take more time.

The chest X-ray may be normal or show vascular congestion and liquid at the fissures, and sometimes in the pleural space (wet lung) (Fig. 36.4).

Oxygen is administered to maintain a normal PaO_2 according to the requirements determined by the blood gases. pCO_2 is slightly increased. While the FiO_2 is close to 0.40 and the respiratory frequency has a rate of 70/min, there should be no oral intake.

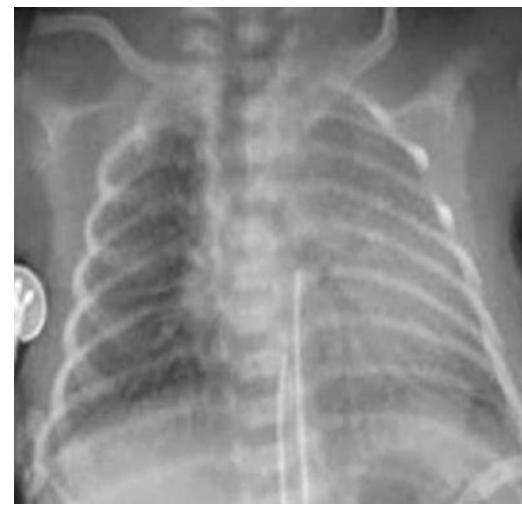

Fig. 36.4 Transient tachypnea of the newborn. Chest X-ray in newborn, where good pulmonary volume is highly visible, with vascular congestion and visible fissure, at the right side

Respiratory Problems Conditioned by Pulmonary Circulation Diseases

Persistent Pulmonary Hypertension

Persistent pulmonary hypertension (PPH) is characterized by an alteration in the evolution from fetal to neonatal blood flow. The pressure of the pulmonary artery and pulmonary vascular resistance are maintained at high values, as happens during the fetal period, which translates in pulmonary hypoperfusion and short circuits from right to left through the ductus and oval foramen. Clinically, this presents through cyanosis and hypoxemia that do not respond to increase of the fraction of inspired oxygen. This problem can present as an isolated condition (idiopathic PPH), but more frequently it is related to other diseases, particularly asphyxia, pneumonia, and meconium aspiration.

Reduction of the resistance and pressure of the pulmonary artery during the hours immediately after birth is central to the conversion from fetal to newborn blood flow. There are predisposing factors for this situation: chronic and acute hypoxia, acidosis and hypercarbia, prenatal maternal use of prostaglandin inhibitors, insufficient anatomical development in the cases of pulmonary hypoplasia, as happens with diaphragmatic hernia or Potter syndrome; and respiratory difficulty syndromes, especially as caused by meconium aspiration.

Pathological analyses of lungs from children with persistent pulmonary hypertension (PPH) show a thickening of the medium muscular layer of the pulmonary arterioles as well as an abnormal extension of the muscular layers in the intra-acinar arteries. This fact has been presented as an explanation for the great lability and sensitivity of the pulmonary vasculature present in these children when faced with hypoxia, acidosis, and other factors that affect it. Some mild hypoxemia episodes can be translated as important changes in the pressure of the pulmonary artery and oxygen requirements (Fig. 36.5).

The cardinal clinical sign is cyanosis that does not improve when oxygen is administrated. Considering parenchymal disease, there is a disproportionate hypoxemia and weak oxygenation. There is an important brittleness in

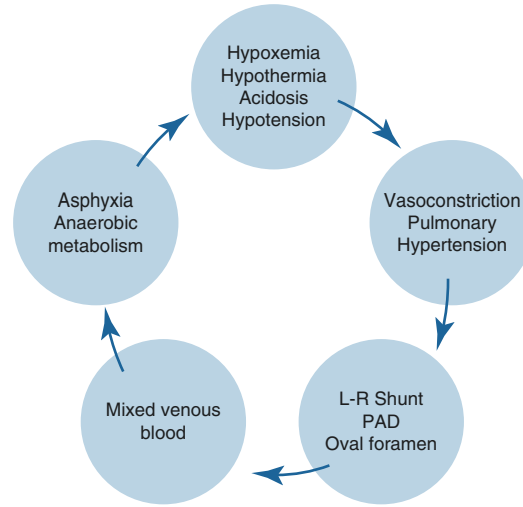

Fig. 36.5 Cycle of events that perpetuate persistent pulmonary hypertension (PPH)

PaO_2, even when FiO_2 has not significantly changed. Small reductions in this may be difficult to recover. Other signs that may be present are those typical of heart failure and a systolic murmur with a reinforcement in the second sound.

Signs are not specific, and it can be difficult to evaluate when there is other related respiratory disease. In some cases, especially in the idiopathic presentation, it is essential to consider the differential diagnosis of congenital heart disease. In 50% of newborns, there will be saturation differences greater than 20% between the preductal territory (left arm) and the post-ductal territory (other limbs).

The chest X-ray will show particular signs of the associated disease. In its idiopathic presentation, free and darker lung fields can be seen because of the pulmonary flow reduction. When there is a left ventricular failure, pulmonary venous congestion will be present.

Doppler echocardiography is the most important diagnostic exam. It shows the short circuits from right to left through the ductus and oval foramen, and in most cases, it will exclude heart structural abnormalities, which is the most important differential diagnosis. If there is a tricuspid failure, the pressure of the pulmonary artery can be estimated.

Prevention must consider all the factors that increase pulmonary resistance and blood flow pressure, before and after the birth. Fetal hypoxia treatment must be avoided, and no anti-prostaglandins should be used when facing early labor symptoms. During the postnatal period, a good resuscitation must be done at birth. Meconium aspiration must also be prevented, as well as hypoxemia and acidosis. Hypoglycemia, hypocalcemia, and polyglobulia must be identified and corrected. Room temperature must be neutral, and an adequate arterial pressure must be maintained. These measures are preventive, but once the persistent pulmonary hypertension state has settled in, they must be considered as part of the treatment.

Further, treatment requires the use of measures that will cause pulmonary vasodilatation. Oxygen is a potent vasodilator, and therefore therapy must try to keep a PaO_2 within the high range of the normal numbers and a pH around 7.40, to have a better oxygen delivery at tissue level, always considering the hemoglobin dissociation curve. Different means of mechanical ventilation have been used with some success. It does not matter which mode is used: the goal is to achieve a sufficient mean airway pressure (MAWP) and adequate ventilation. Often this is achieved with high-frequency ventilation. It is recommended to use inhaled nitric oxygen (iNO), which produces a selective vasodilatation in the pulmonary vascular territory, when the oxygenation index (IO) is greater than 20 ($IO = MAWP \times FiO_2 \times 100/PaO_2$). Transferring the patient to a center with iNO capacity is recommended to avoid any risks for the patient: it is recommended to transfer the patient when IO reaches 15 and does not improve. iNO response is variable when there is a persistent pulmonary hypertension related to malformations, such as a diaphragmatic hernia. Methemoglobin may be present, as this complication has been described when iNO has been used at high ranges during prolonged periods. A recent multi-centric study in Chile proved that mortality rate is reduced through the administration of endotracheal surfactant, in relation to the use of iNO in newborns whose IO was greater than 20 (González et al.).

Sedation has proven to be of great help because the fight against the ventilator, as painful stimuli, affects oxygenation much more than in other disease. It is worth noting that with this treatment we do not have the ability to estimate the compromise related to the underlying disease and the prolonged hypoxia.

It may be necessary to deliver volume or use vasoactive drugs to keep systemic pressure over the estimated pulmonary pressure. Required doses and drugs must be titrated to keep enough systemic pressure to revert the extrapulmonary short circuit without causing vasoconstriction because of drug excess.

Since 1980 the use of extracorporeal membrane oxygenation (ECMO) has been described as being especially efficient in pulmonary conditions related to persistent pulmonary hypertension in newborns. Chile has had this resource since 2003. With this therapy the lungs are left resting during a few days while blood is being oxygenated through an external membrane. By avoiding pulmonary injure during mechanical ventilation, PaO_2 improvement and the underlying disease recovery time, the pulmonary vasoconstriction is reduced by the end of 5 to 10 days, allowing obtaining a survival rate greater than 85% for patients with no related malformations. It is a highly complex procedure, and costly, and it does entail risks. It is indicated for patients with a high probability of death ($IO > 40$ and/or $PaO_2 \leq 40$). This procedure has technical limitations (indicated for children who are past 34 weeks gestational age and weigh more than 2 kg) as well as ethical limitations (neurological conservation). To improve the efficacy of this therapy, it is recommended to transfer the patient 4 to 6 h before the onset of serious persistent pulmonary hypertension.

Persistent Arteriosus Ductus

Persistent arteriosus ductus (PAD) is a blood vessel that is characteristic of fetal blood flow, which communicates the pulmonary trunk with the descending aorta. During fetal life, it allows most of the cardiac output from the left ventricle to go to the aorta, because the pulmonary artery pressure is greater. This function is normal and essential for fetal blood flow.

The finding of a persistent ductus arteriosus in a term newborn is generally related to an anatomical defect, which may or may not be linked to other heart malformations or genetic syndrome.

In the premature newborn, the persistent arteriosus ductus is fundamentally related to immaturity, with an inversely proportional increase in consideration to gestational age. Ductus sensibility to produce a strong contraction when facing PaO_2 is lowered as the gestational age decreases, and its vasodilatation is greater with prostaglandins. Persistent arteriosus ductus alters pulmonary mechanics as well as the gas exchange, which results in a left-sided heart failure.

Generally, the clinical history corresponds to a preterm newborn whose weight is very low. And notably, during the improvement stage in relationship to hyaline membrane disease, when the pulmonary vascular resistance decreased, a systolic ejection murmur appeared. This murmur is rarely continuous, and it can be better auscultated in the left infraclavicular region and the left superior parasternal border, commonly radiating to the side. Its intensity can vary in a short time, and sometimes it is not perceived during auscultation. The onset of the persistent arteriosus ductus may be accompanied by hyperactive precordium, tachycardia, and jumpy pulses in the postductal region. Sometimes the heartbeat can be perceived in the palm of the hand of the newborn. Mean arterial pressure drops at the beginning according to the diastolic pressure, which produces differential pressures (PS-PD) > 25–30 mmHg. Tachypnea is also present, along with an increase in the apnea pattern and general worsening, with an increase of oxygen requirements, ventilation support, and even including the use of vasoactive drugs. Hypoxemia can be seen in the blood gases, and respiratory or metabolic acidosis may be present, if the ductus is present with systemic hypoperfusion.

Chest X-ray can show cardiomegaly and pulmonary congestion signs (Fig. 36.6). Bidimensional Doppler echography is used to confirm the diagnosis and allows calculating approximately the degree of hemodynamic impact, according to the size of the ductus at the pulmonary end, the magnitude of the blood flow through it, and, to a lesser degree, the relationship between the size of the left atrium and the aorta.

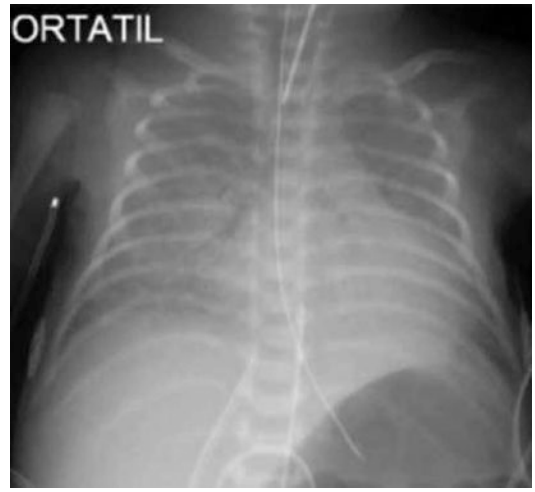

Fig. 36.6 Persistent arterial duct. Chest X-ray of a 31 weeks newborn who, at 10 days of life, presents with respiratory worsening related to a hemodynamically important ductus

In preterm newborns whose weight is less than 1000 g, it is necessary to be careful in ductus detection as it would be easier for this condition to impact the hemodynamic system.

Treatment considers keeping an adequate oxygenation and ventilation support, hematocrit between 40% and 45%, fluid restrictions, a high suspicion of concomitant infection, and pharmacological closure using prostaglandin inhibition, such as indomethacin or ibuprofen. The use of oral or IV paracetamol is still experimental. When these measures fail and hemodynamic compensation persists, surgical closure is performed to avoid secondary pulmonary damage.

Respiratory Infections of the Newborn: Pneumonia

The lung is the organ most frequently affected by infections developed during the first 24 h of life: 90% of fatal infections involve respiratory compromise. Conatal infection is usually ascendant, related to the rupture of membranes, but it tends to happen with intact membranes when they are contaminated by the maternal genital or anal

flora at childbirth, and less frequently, transplacental. The other common cause of infections of the airway is the nosocomial in hospitalized newborns, especially preterm newborns.

Because of their immunity limitations and anatomical features, newborns are greatly susceptible to developing lung infections. The most frequent microbial agents are these:

- *Conatal bacterial infections*: Group B *Streptococcu*s (GBS), *Escherichia coli*, and *Listeria:* also, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Salmonella*, among others.
- *Conatal viral infections*: Herpes simplex, cytomegalovirus, rubella, influenza virus, adenovirus, and echovirus. After the first days, nosocomial bacteria appear, such as *Klebsiella*, *Pseudomonas*, *Enterococcus*, *Staphylococcus*, and *E. coli*. Cytomegalovirus, type II herpes, *Ureaplasma*, and *Pneumocystis jirovecii* (previously known as *P. carinii*) have been identified as causal agents in late pneumopathies, which may produce clinical presentations similar to those of bronchopulmonary dysplasia.

Candida albicans affects premature newborns who receive parenteral feeding and broad-spectrum antibiotics, or who have undergone intestinal surgery.

Chlamydia trachomatis is an organism that can frequently cause neonatal conjunctivitis, and it can also cause a late-onset pneumonia (2–12 weeks of life), in spite of its perinatal acquisition. Its main symptoms are polypnea, grunting, and cyanosis, which rapidly worsen when they are not treated. Early apneas suggest conatal infection. Crackles and abolished pulmonary murmur, which are a particular characteristic of the breastfeeding baby, are not usually found in the newborn. The presence of metabolic acidosis with no clear etiology, as well as a tendency to shock, suggest an infection.

Chest X-ray may reveal areas with pulmonary infiltration, condensations and/or pleural effusions. Nevertheless, it is common to see atelectasis and air bronchogram that cannot be distinguished from hyaline membrane disease.

Culture of airway secretions provides guidance relative to the etiological agent. Cultures must be performed early through tracheal aspiration during the progress of the infection. Positive hemocultures and an altered chest X-ray confirm the diagnosis. A complete blood count (CBC) may show leukocytosis or leucopenia, as well as a deviation to the left. These changes may also appear in cases of perinatal asphyxia or other stressful situations. After the first week of life, changes in the CBC give better signs of infection. C-reactive protein is more useful in nosocomial infection situations. Procalcitonin has also been used as an acute-phase reactant in infections with a good correlation.

These children require treatment in intensive care units. Their treatment includes general control measures of vital signs and internal medium stability: blood gases, glycemia, calcemia, and hematocrit. Many of them require breathing and hemodynamic support with vasoactive drugs. A serious complication is the aforementioned lung hypertension. Specific treatment must be chosen in accordance to the causal agent.

When a conatal bacterial infection is suspected, antibiotic treatment must be implemented early, right after the samples for culture are taken. If the child is referred to a specialized unit, the antibiotic treatment must start immediately after the samples for culture are taken and before the transfer. The scheme used, in accordance to the most frequent infections, is ampicillin and one aminoglycoside, which will be modified if it is necessary when the agent has been identified or depending on the clinical response.

Given the high frequency and severity of the infections caused by group B *Streptococcus* (GBS), some preventive strategies have been developed. The most effective one is to identify mothers who are GBS carriers through perineal culture at 35 to 37 weeks of pregnancy. For them, antibiotic prophylaxis during childbirth is indicated. If this previous information is not known, a prophylaxis treatment is indicated for the pregnant women who are at risk because of their

clinical history, such as previous children with GBS infections, chorioamnionitis, membranes ruptured after 18 h, or preterm birth.

Respiratory Problems Caused by Congenital Alterations of the Airway and Lungs

There are several types of malformations. Because these are extensive, and because this text is only one chapter about the issue, we only mention them (Table 36.6). Regular maternal ultrasound has allowed us to determine or suspect the diagnosis before childbirth, and in some selected cases, these malformations can even be treated during the prenatal phase. Nuclear magnetic resonance has been more frequently used during the past decade to obtain further details, especially about malformations related to the central nervous system, lungs, heart, and kidneys. In these situations, the suggested approach is to refer the mothers to high-volume specialized centers and to diagnostic and fetal therapy centers.

Table 36.6 Malformations that can compromise the respiratory system

Congenital malformations of the upper airway	Choanal atresia, Pierre Robin sequence, macroglossia, velopalatal insufficiency, laryngomalacia, vocal cord paralysis, laryngeal tumors, esophageal atresia combined with tracheoesophageal fistula, tracheal agenesis, congenital tracheal stenosis, tracheobronchomalacia, vascular rings, laryngeal cysts and membranes, laryngeal atresia, cervical tumors causing external compromise (e.g., teratomas).
Congenital malformations related to the lung parenchyma	Congenital lobar emphysema, bronchogenic cyst, neurentenic cyst, cystic adenomatoid malformations, lung sequestration, arteriovenous fistula, congenital pulmonary lymphangiectasia, alveolar capillary dysplasia, pulmonary aplasia or agenesis, pulmonary hypoplasia, congenital diaphragmatic hernia.
Congenital malformations related to the diaphragm and thoracic wall	Congenital diaphragmatic hernia, sternum deformities, thoracic deformations, muscular weakness, skeletal dysplasias.

When there is no prenatal information, the clinical presentation, thoracic radiography, tomography, IRM, and endoscopic studies help us to a precise diagnosis and the actions to be taken. In some cases, only pathological anatomy will give us a precise diagnosis. When a breathing tree malformation is confirmed, it is necessary to determine if this is associated with other malformations or if they are part of a specific syndrome.

Some of these lung and airway malformations can be treated in very specialized university centers for fetal therapy, where successful in utero interventions using fetoscopy tracheal occlusion have been performed to treat diaphragmatic hernias; cystic adenomatoid malformations, when they cause hydrops, with thoracoamniotic shunting or radiofrequency ablation. These therapies are still under evaluation in multicenter research protocols, so they are not yet standard therapies. During childbirth, fetal therapies centers have collaterally developed procedures such as EXIT (ex utero intrapartum treatment), which is currently used in patients suspected of having a non-open airway at birth (cervical teratomas, cystic hygroma, bronchogenic cyst, laryngeal atresia, etc.), whose main principle is to maintain placental blood circulation during the 30 to 45 min while the airway is being secured using intubation assisted through laryngoscopy or tracheostomy.

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