Respiratory Development and Respiratory Distress Syndrome

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The purpose of this article is to review fetal lung development and respiratory distress syndrome.

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Abstract

Respiratory development is crucial for all newborn infants. Premature infants may be born at an early stage of development and lack sufficient surfactant production. This results in respiratory distress syndrome. This article reviews the normal fetal development of the lung as well as the disorder that develops because of an early birth.

Keywords: respiratory distress; respiratory distress syndrome (RDS); surfactant

The lungs of the fetus begin development at about 22–25 days after conception with the formation of the lung bud from the foregut of the embryo, followed by successive branching of the bronchial tree.[1,2] There are five periods of lung development: embryonic, pseudoglandular, canalicular, saccular (terminal sac), and alveolar (Table 1). There is overlapping of these time periods because, as the lung matures, there may be varying structures developing in different parts of the lung at the same time. As the more immature structures are present, the more mature structures are starting to develop throughout the lung.

The lung is made up of both endoderm and mesoderm: the endoderm from the foregut and the mesoderm from the splanchnopleuric mesoderm.[1] The blood vessels within the lung are derived from nearby blood vessels as the lungs develop.

The first period of lung development, or the *embryonic* stage, begins during the fourth week of fetal life (Figure 1). There is a small bulging of the foregut at the pharynx. This lung bud elongates and forms the trachea, larynx, and the initial bronchi. At about the fifth week, the main bronchus develops three bronchial buds on the right and two bronchial buds on the left (which will develop into the lobes of the lungs; Figure 2). The laryngeal epithelium multiplies rapidly during this time period, causing an occlusion of the laryngeal lumen. As the tracheoesophageal folds develop, they divide the foregut into the ventral trachea and the dorsal esophagus. If there is incomplete separation of these two areas, a tracheoesophageal fistula will occur. Pulmonary agenesis will occur if the branching of the bronchi is halted during this stage.

Further branching of the bronchi occurs during the second period of lung development, the *pseudoglandular* stage. The pleuroperitoneal canal closes by the seventh week of fetal life, separating the thorax from the abdominal cavity (which prevents congenital diaphragmatic hernia). Around the tenth week of fetal life, a recanalization occurs that opens the larynx, forming the vocal cords.[2] If recanalization does not occur at this time, the lumen of the larynx may remain blocked, causing tracheal atresia. During this stage, there is significant development of the bronchioles until the bronchial divisions are completed at about 16 weeks' gestation.[2] At this time, there is still no possibility of gas exchange.

During the third period, the *canalicular* stage, the terminal bronchioles give rise to the respiratory bronchioles, which then develop several tubules called *alveolar ducts*, leading to the future primitive alveoli. As the

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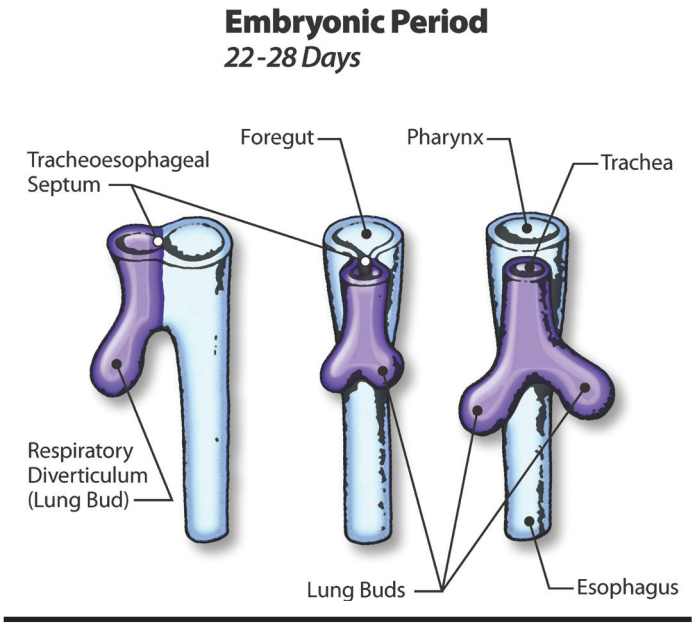
TABLE 1 ■ Stages of Lung Development and Possible Defects[1,2]

Stage of Development	Fetal Time Period	Events Occurring	Defects Possible with Maldevelopment
Embryonic	3–7 wk	Respiratory bud forms. Initial branching Trachea and larynx forms.	TEF Pulmonary agenesis
Pseudoglandular	6–16 wk	Branching continues. Terminal bronchials Closure of pleuroperitoneal folds	CDH Tracheal atresia Pulmonary hypoplasia
Canalicular	16–28 wk	Development of respiratory bronchials ⇒ some alveolar ducts ⇒ terminal sacs Lung tissue vascularized Gas exchange at ~24 wk	Respiratory insufficiency
Saccular (terminal sac)	24–38 wk	Many terminal sacs Epithelium thins. Type I and II pneumocytes	Surfactant deficiency (RDS)
Alveolar	36 wk–3 y	True alveoli develop. Alveolar ducts and alveoli increase in number. Secondary septation Increase in number and size into childhood (possibly up to 8 y of age)	BPD (lack of secondary septation)

Abbreviations: TEF = tracheoesophageal fistula; CDH = congenital diaphragmatic hernia; RDS = respiratory distress syndrome; BPD = bronchopulmonary dysplasia.

bronchioles continue to grow and branch, the vascular system is also developing. The blood vessels of the lungs develop at the same time as the bronchioles develop, but, initially, the blood vessels are relatively far away from the respiratory or alveolar ducts. Respiration with gas exchange is possible at the end of the canalicular period because some of these alveolar ducts have developed terminal saccules, and the lung tissue is well-vascularized at this point with a network of blood vessels coming much closer to the terminal saccules or primitive alveoli (Figure 3).[2] Premature births that occur during the late canalicular period produce infants who have immature structure of their airways as well as surfactant deficiency, from Type II cells that are just beginning to develop. By the end of the canalicular period, all 23 conducting airways are present.[2]

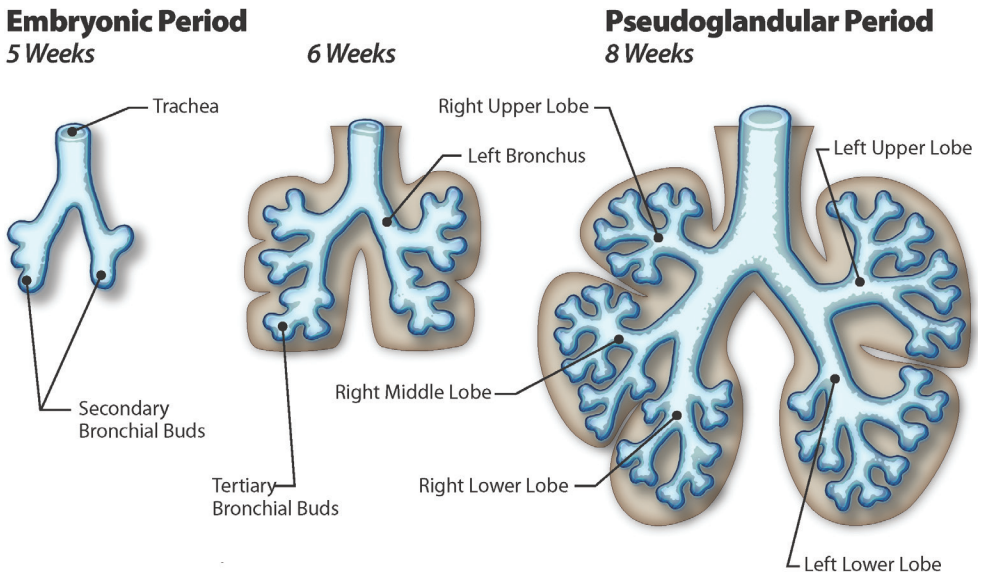
FIGURE 1 ■ Initial formation of lung buds from foregut in the embryonic period.



The fourth period is called the *saccular* or *terminal sac* period. During this stage, the alveolar ducts are producing primitive alveoli called *terminal saccules.* These sacs are immature but can provide limited gas exchange via the Type I alveolar cells, which are flat and thin, to move oxygen and carbon dioxide across the capillary-air interface (see Figure 3). Many of the Type II cuboidal pneumocytes are producing surfactant throughout this period, but the levels would be less than at term.

The fifth period is called the *alveolar* stage, where the true alveoli are formed. Alveoli mature, grow, and septate, forming secondary alveoli during this stage. This stage continues after birth through about the first three to five years of life.[2] Bronchopulmonary dysplasia (BPD) occurs as a result of damage to the airways because of premature birth. It was found that many babies with BPD have a lack of secondary septation during this alveoli stage when the numbers of alveoli increase significantly. After birth, alveolarization increases the number of alveoli from somewhere between 0 and 50 million at birth to more than 300 million in adults.[2] Therefore, the maturation and septation of these alveoli into secondary alveoli is necessary for infants who are born prematurely to recover from respiratory distress syndrome (RDS) and for less severe BPD development.

FIGURE 2 ■ Embryonic to pseudoglandular period.



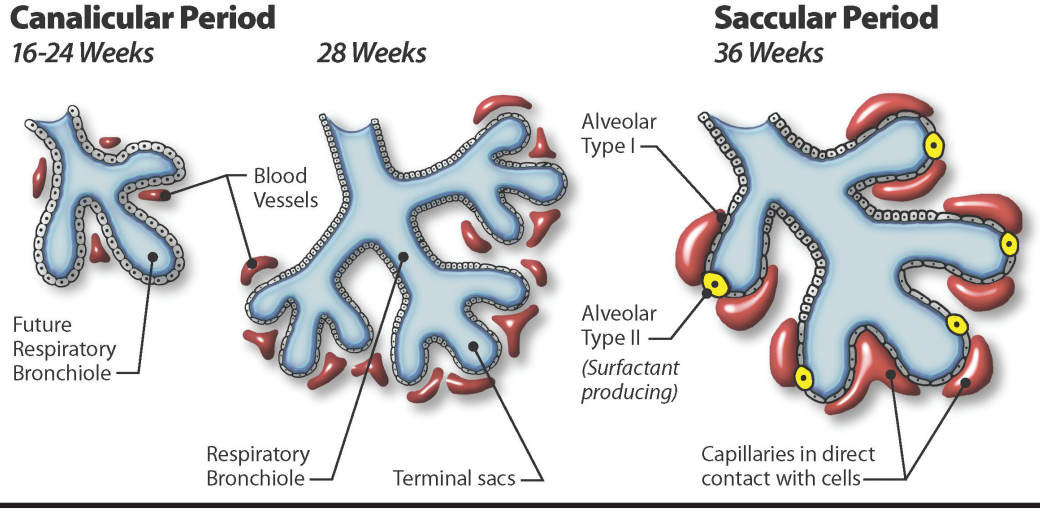
INCIDENCE

RDS affects approximately 40,000 infants annually in the United States.[3] RDS is a disease that affects mostly premature infants. The relationship of RDS is inversely proportional to gestational age; thus, the more premature infants are at higher risk for developing RDS.[4] The incidence of RDS has decreased over the past 50–60 years with the introduction of continuous positive airway pressure (CPAP), conventional ventilation, high-frequency ventilation, and surfactant replacement for neonates. But according to the March of Dimes Foundation, 825 premature infants still die each year secondary to RDS.[5]

PATHOPHYSIOLOGY

RDS is primarily caused by surfactant deficiency. Surfactant is a lipoprotein molecule composed of phospholipids, neutral lipids (cholesterol), and surfactant proteins (SPs), which are SP-A, SP-B, SP-C, and SP-D.[6] The main phospholipid is dipalmitoyl phosphatidylcholine (DPPC), also called *lecithin*. Phosphatidylglycerol and DPPC are two of the markers for lung maturity obtained from amniotic fluid testing. During the canalicular phase of respiratory development, Type II pneumocytes in the epithelial lining of alveoli produce and store surfactant beginning around 22 weeks of gestation.

FIGURE 3 ■ Canalicular to saccular period.



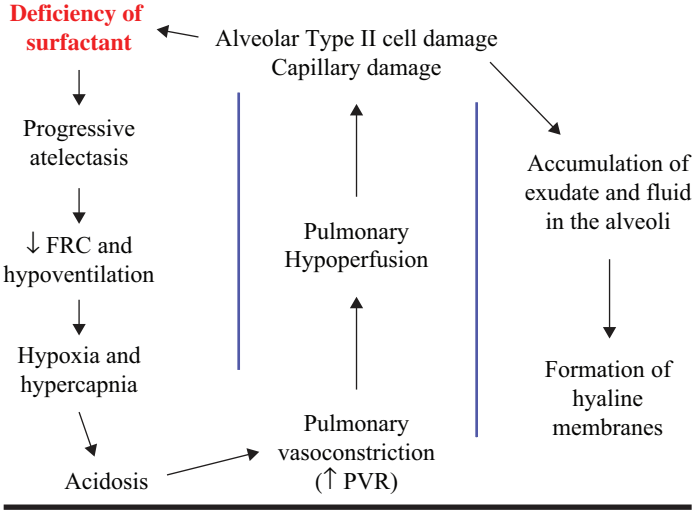
Surfactant creates a soapy-like texture that reduces the surface tension within the alveoli, enhancing alveolar expansion, which then allows optimal gas exchange to occur. Surfactant plays a role in maintaining functional residual capacity (FRC) by decreasing the amount of pressure that is needed to open and expand alveoli and prevents alveolar collapse upon expiration. In infants with RDS, surfactant deficiency reduces lung compliance and increases the incidence of alveolar atelectasis.

Other consequences of surfactant deficiency include intrapulmonary shunting, which leads to hypoxemia, hypercarbia, and acidosis. Under normal circumstances, the relationship of ventilation and perfusion (V/Q) within the alveoli and lung are evenly matched; pulmonary capillaries surround alveolar sacs, and, as deoxygenated blood circulates through the capillaries, carbon dioxide diffuses through the capillaries into the alveoli and oxygen is exchanged. When alveoli are either overdistended or overcollapsed, pulmonary blood flow bypasses the alveolar unit(s). This is referred to as intrapulmonary shunting, and it further reduces the carbon dioxide and oxygen gas exchange between the pulmonary capillaries and alveoli. V/Q mismatching ensues, which exacerbates the exchange of carbon dioxide and oxygen, resulting in hypoxemia and hypercarbia. As hypoxemia worsens and oxygen supply diminishes, metabolic acidosis may be seen secondary to anaerobic metabolism. As the disease progressively worsens, hypoxemia and acidosis may result in pulmonary vasoconstriction and increased pulmonary vascular resistance, causing right-to-left intracardiac shunting through the foramen ovale and ductus arteriosus. This cascade of events intensifies V/Q mismatching in the lungs, and an infant may become quite cyanotic and hypotensive (Figure 4).

For infants on mechanical ventilation, additional sequelae may occur, including the need for higher amounts of ventilator pressure. Increased mean airway pressure is required to open the alveoli that have collapsed and to maintain alveolar expansion within the lung. Because of this increased pressure, volume and barotrauma can result, inducing release of inflammatory cytokines, which impairs surfactant production. In addition, the increased pressure damages the endothelial lining of alveoli, causing proteins to leak out and creating a fibrous matrix (hyaline membrane), which further exacerbates the disease.

RDS can occur because of inadequate amounts of surfactant present at birth or an inability to regenerate surfactant at a fast enough rate to compensate for its use. Other disease processes can cause RDS as experienced in infants of diabetic mothers secondary to inhibition of the release of surfactant. Furthermore, meconium aspiration syndrome may inactivate surfactant, leading to RDS.

FIGURE 4 ■ Cycle of respiratory distress syndrome pathophysiology.



Abbreviations: FRC = functional residual capacity; PVR = pulmonary vascular resistance.

CLINICAL MANIFESTATIONS

The clinical manifestations of RDS begin at birth or shortly afterward, are generally progressive, and may be followed by respiratory failure because of ongoing atelectasis.[7] Clinical symptoms will appear as the infant attempts to compensate for the increasing atelectasis. Some clinical signs of RDS include tachypnea, retractions, nasal flaring, diminished breath sounds, inspiratory crackles, cyanosis, and pallor. Tachypnea is defined as a respiratory rate >60 breaths/minute and occurs as the infant attempts to increase the exchange of oxygen and carbon dioxide; however, as the infant tires and atelectasis increases, the infant is at risk for respiratory failure. Tachypnea usually worsens after the first one to two hours until about 48 hours, but improvement often occurs by about 72 hours with normal production of endogenous surfactant.

Because of decreased lung compliance and increased rib cage compliance, the infant exhibits retractions as he attempts to create high intrathoracic pressure to open the lungs. Another compensatory mechanism is nasal flaring, which is an attempt to reduce airway resistance by opening the nasal passages wider. In an effort to maintain FRC, expiratory grunting may be audible secondary to partial closure of the glottis during expiration. FRC is the amount of air left in the lungs after expiration and is necessary to prevent alveolar collapse. Grunting is not usually heard in the very preterm infant but may be heard in infants closer to term.

Premature infants with RDS also present with diminished breath sounds and rales or "crackles" noted upon auscultation. The decreased breath sounds are because of atelectasis with no air movement within those alveoli. Fine crackles or rales are heard as the alveoli pops opens with inspiration.

Chest x-rays of infants with RDS will have a reticulogranular appearance, commonly called a "ground-glass" appearance with air bronchograms and hypoaeration. This fine granular appearance is because of the atelectasis of some alveoli and other alveoli that remain expanded. This grainy appearance of the x-ray may not show up immediately after birth but can develop within the first 24 to 48 hours of life.

FIGURE 5 ■ Reticulogranular densities of respiratory distress syndrome chest x-ray.

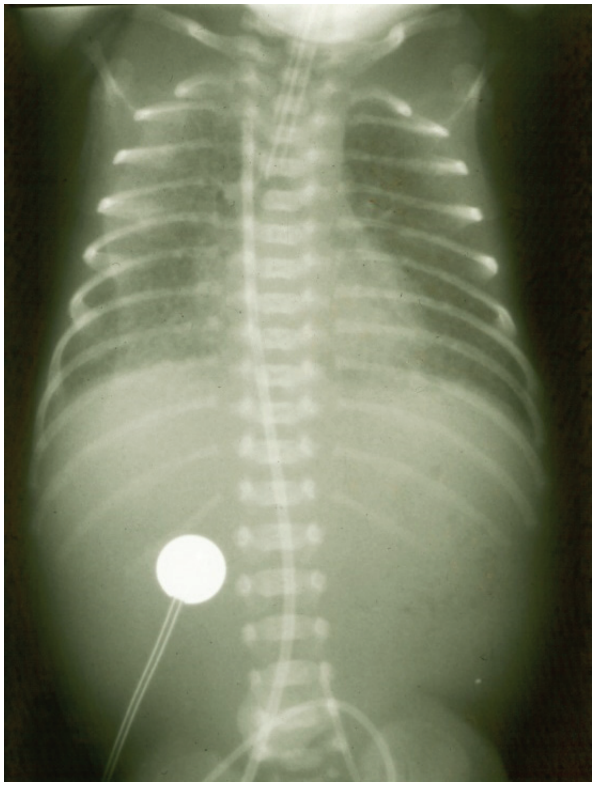
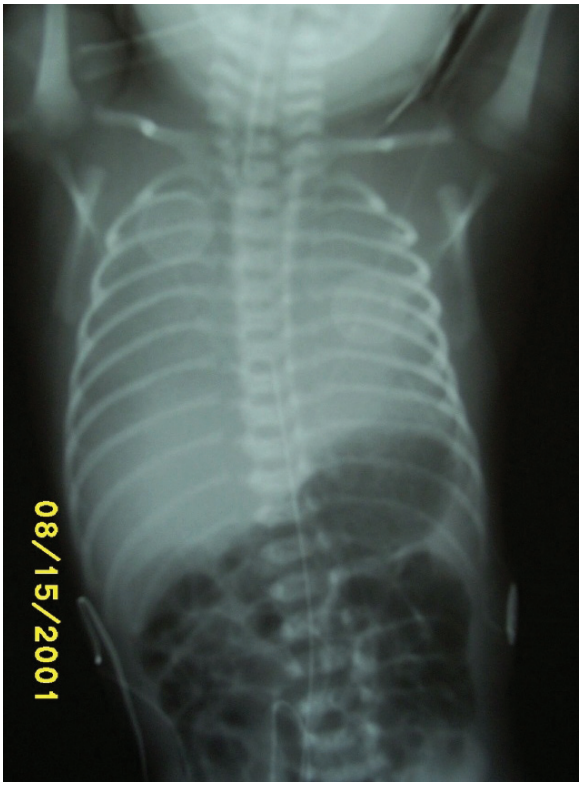


FIGURE 6 ■ "White-out" chest x-ray of respiratory distress syndrome.



The granular densities are usually symmetric throughout the lung fields (Figure 5). A "white-out" chest x-ray will occur if there are very few expanded alveoli and/or a large amount of infiltrate from pulmonary edema or the hyaline membranes/exudate in the alveoli (Figure 6). With a "white-out" chest x-ray, the heart borders are no longer visible because of the extreme atelectasis. Air bronchograms are visualizations of open bronchi (black) over collapsed alveoli (white; Figure 7).

Without surfactant treatment, the infant who can no longer compensate will become flaccid, inactive, and hypotensive, with lowered oxygen saturations and retention of carbon dioxide. Respiratory acidosis and metabolic acidosis will result in abnormal blood gases.

MANAGEMENT

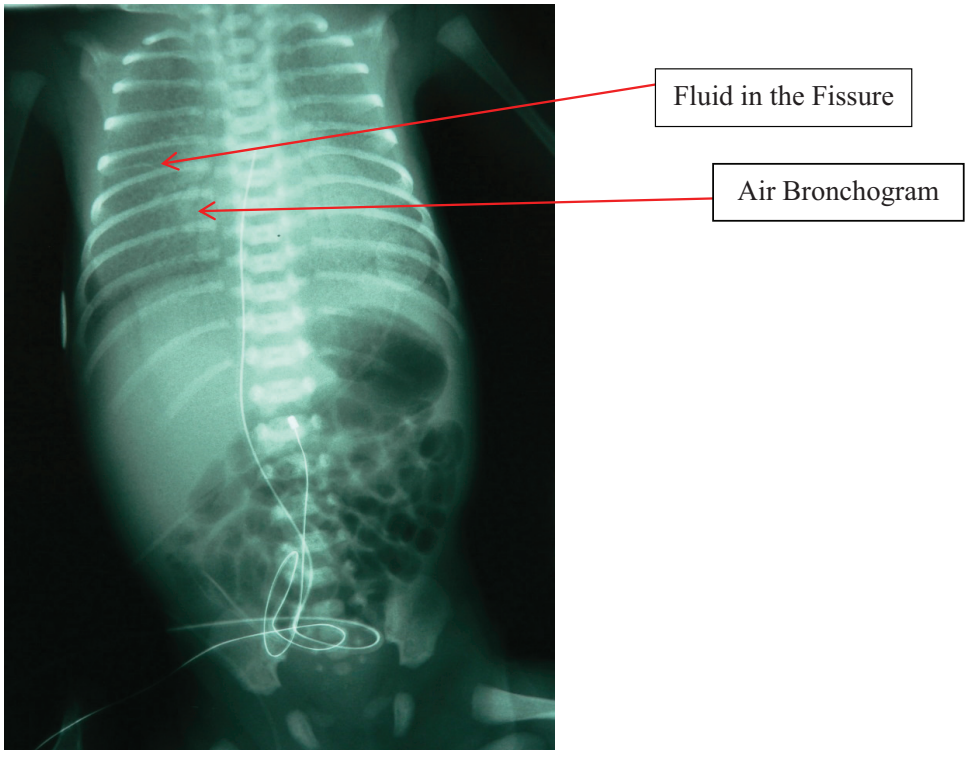
The optimal management for reducing the risk of an infant developing RDS is to prevent preterm deliveries. Preliminary 2013 data from the March of Dimes indicate that 11.4 percent of all deliveries in the United States result in a preterm infant (<37 weeks gestation). Although there has been a steady decline in the last several years, there is still much work to be done to meet the March of Dimes goal to reduce the rate of preterm deliveries to 9.6 percent or less by 2020.[8]

Administration of antenatal corticosteroid to a pregnant woman accelerates fetal lung maturation and helps reduce the incidence and severity of RDS in the newborn.[9,10] Antenatal corticosteroid accelerates lung maturation by enhancing production of Type I pneumocytes, which increases lung volume and compliance, and Type II pneumocytes, which produces surfactant and reduces alveolar surface tension, to help prevent atelectasis and optimize gas exchange.[10] If a pregnant woman is <34 weeks gestation and has premature labor, treatment of the mother is indicated. Optimal benefits are seen if delivery occurs within seven days of initial administration; however, if delivery is imminent (i.e., within 1 to 2 hours), antenatal corticosteroids should still be considered as there may be some benefit for the infant.[9]

The two antenatal corticosteroids that can be given are betamethasone or dexamethasone. Although there are more studies using betamethasone with more efficacious short- and long-term results, both are acceptable for antenatal administration.[10] Betamethasone is given every 24 hours for two doses, and dexamethasone is given every 12 hours for four doses.

One of the most substantive discoveries in neonatal medicine was the development of exogenous surfactant; the greatest benefit occurs when combined with antenatal corticosteroid administration.[11,12] There are three animal-derived exogenous surfactants available in the United States and one synthetic surfactant (Table 2). In 2012, the U.S. Food and Drug Administration approved Surfaxin (lucinactant),

FIGURE 7 ■ Chest x-ray of air bronchogram with granular lung fields and "fluid in the fissure."



a peptide-containing synthetic surfactant, which is the first synthetic surfactant to be used in the United States. This synthetic surfactant appears to have the highest surface tension activity (Table 3). Although the benefits of exogenous surfactant are well studied, timing of administration is variable depending on prenatal factors, such as maternal antenatal corticosteroid administration, and postnatal factors such as infant's gestational age and severity of the disease. However, clinical trials have shown that the earlier surfactant is given in the course of the disease, regardless of administration of antenatal corticosteroids, the more effective it is.[12,13] There are two distinguishing time frames for surfactant

TABLE 2 ■ Types of Surfactant for Replacement

Surfactant Type	Origin	Content	Dose	Name/Manufacturer
Human	Human amniotic fluid	SP-A, B, and C Protein 10%	NA	Not commercially available (because of risk of infections and difficult process to purify)
Natural (animal-derived)	Calf (minced bovine lung)	DPPC PG SP-B and C	4 mL/kg	Beractant (Survanta) by AbbVie Inc.
	Calf (lavage of bovine lung)	DPPC PG SP-B and C	3 mL/kg	Calfactant (Infasurf) by ONY, Inc.
	Pig (minced porcine lung)	DPPC PG SP-B and C	2.5 mL/kg, then 1.25 mL/kg	Poractant alfa (Curosurf) by Chiesi USA, Inc.
Synthetic	NA	DPPC	5 mL/kg	Colfosceril (Exosurf) by GlaxoSmithKline (not available in United States)
	NA	DPPC POPG	5.8 ml/kg	Lucinactant (Surfaxin) by Discovery Laboratories, Inc. (FDA approval 2012; available 2013)

Abbreviations: SP = surfactant protein; DPPC = dipalmitoyl phosphatidylcholine; PG = phosphatidylglycerol; POPG = palmitoyl-oleoyl-phosphatidylglycerol; FDA = U.S. Food and Drug Administration.

TABLE 3 ■ Comparison of Surface Tension–Lowering Activity of Surfactants

Surfactant Type	Surface Tension Activity
Lucinactant	(HIGH)
Beractant	
Calfactant	
Poractant	
Colfosceril	(LOW)

administration: prophylactic and rescue therapy. Prophylactic therapy includes intubation and administration of exogenous surfactant to prevent the development of RDS in infants who are considered high risk. Prophylactic surfactant is given after initial stabilization but within the first 10–30 minutes of life.[12] Rescue therapy occurs when an infant is given surfactant within the first 12 hours of life based on specific criteria (i.e., radiographic evidence of RDS, increasing oxygen requirements or respiratory support, and blood gas derangements such as respiratory and/or metabolic acidosis); early rescue therapy is considered less than two hours from birth.[12]

There are many published studies looking at the timing of exogenous surfactant administration and initial respiratory support (INSURE—intubation, surfactant, early extubation; COIN—CPAP or intubation; SUPPORT—surfactant positive pressure and pulse oximetry randomized trial). The American Academy of Pediatrics has published a clinical report on surfactant replacement therapy[12] and a policy statement pertaining to respiratory support[13] in preterm infants at birth. The American Academy of Pediatrics recommends "using CPAP immediately after birth with subsequent selective surfactant administration . . . as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants. If it is likely that respiratory support with a ventilator will be needed, early administration of surfactant followed by rapid extubation is preferable to prolonged ventilation."[13(p173)]

Other supportive management includes optimizing the infant's metabolic and cardiopulmonary status. Thermoregulation is important to monitor because infant temperatures that are too high or too low increase metabolic demand and thus increase the use of oxygen. This can quickly deplete any oxygen reserves, especially for an infant in respiratory distress, who is likely experiencing hypoxemia. Fluid management is necessary to avoid pulmonary edema that can worsen V/Q mismatch and also increase the infant's need for oxygen and respiratory support. Optimizing nutrition is also important to provide energy for metabolic needs and growth.[14]

CONCLUSION

In conclusion, it's imperative for the bedside nurse to be able to identify an infant who is at risk for developing RDS, understand the basic pathophysiology of the disease, and provide appropriate nursing management. Prompt recognition of circumstances that can further worsen the disease is vital in mitigating sequela of RDS.

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