Pathophysiology of respiratory distress syndrome

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Abstract
Respiratory distress syndrome (RDS) is a major cause of neonatal mortality and morbidity, especially in preterm infants. Its aetiology includes developmental immaturity of the lungs, particularly of the surfactant synthesizing system. Surfactant is produced, stored and recycled by type II pneumocytes and is detectable from about 24 weeks’ gestation. It is a mixture of phospholipids, neutral lipids and proteins and is spread as a film over the alveolar surface to lower surface tension and to prevent alveolar collapse. The resulting clinical correlates of RDS can be predicted from the immature lung structure and atelectasis which occur due to surfactant deficiency. Various clinical factors are known to dysregulate surfactant production and function, leading to the development of RDS. Apart from preventing the incidence of prematurity, antenatal steroids and prophylactic surfactant are of proven benefit in reducing the incidence of RDS.

Keywords alveoli; infant; newborn; preterm birth; pulmonary surfactant; respiratory distress syndrome

Introduction
Respiratory distress syndrome (RDS) is the dominant clinical problem faced by preterm infants. It remains a major cause of neonatal mortality and morbidity despite advances in perinatal care. The incidence of RDS decreases with advancing gestational age, from about 60–80% in babies born at 26–28 weeks, to about 15–30% in those born at 32–36 weeks. The syndrome is also more frequent in male infants and infants of diabetic mothers. RDS is caused by developmental insufficiency of surfactant production and function, as well as by structural immaturity of the lungs. It can also result from surfactant protein genetic disorders. This review discusses the pathogenesis of RDS in relation to fetal lung growth and surfactant metabolism. Risk factors for RDS and preventative approaches will also be reviewed.

Lung growth and development
Some understanding of lung growth and development may be useful in understanding why RDS occurs. Normal lung development, which occurs as a series of complex, tightly regulated events, can be divided into five stages (Table 1). During the embryonic stage (fetal weeks 0–7), the lung develops as a ventral diverticulum from the foregut endoderm and, after divisions, the main bronchi and five lobes are formed. The pulmonary arteries develop and accompany the developing airways. The embryonic stage is followed by the pseudo-glandular stage (weeks 7–17). Branching of the airways and vessels continues and by the end of this stage the terminal bronchioles and primitive acini are formed. During the canalicular stage (weeks 17–27), further development of the distal airways into definitive primary acini occurs and the alveolar capillary barrier is formed. Differentiation into type I and II pneumocytes occurs and surfactant components produced by type II cells are detectable in the form of lamellar inclusion bodies by 24 weeks’ gestation. Thus, a possible but immature platform for gas exchange is established. With advances in perinatal medicine and ever increasing survival of extremely preterm infants, this is an important landmark in lung growth and development. However, surfactant deficiency leading to RDS is inevitable if preterm delivery occurs at this stage. In the saccular stage (weeks 28–36), the gas-exchanging surface area increases as the airways wall thins out. Lamellar bodies in type II cells increase and further maturation of type II into type I cells occurs. Capillaries are closely associated with type I cells, thus reducing the distance between the future air–blood interface. The alveolar stage (36 weeks’ gestation–2 years postnatally; although controversy remains regarding the exact timing

<table>
<thead>
<tr>
<th>Stage of lung growth</th>
<th>Time</th>
<th>Structural changes</th>
</tr>
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<tbody>
<tr>
<td>Embryonic</td>
<td>0–7 weeks</td>
<td>Formation of trachea, right and left main bronchi and segmental bronchi. Blood vessels connect to the heart</td>
</tr>
<tr>
<td>Pseudoglandular</td>
<td>7–17 weeks</td>
<td>Differentiation of epithelial cells, formation of conduction airway and terminal bronchioles, formation of pulmonary arteries and veins</td>
</tr>
<tr>
<td>Canalicular</td>
<td>17–27 weeks</td>
<td>Formation of respiratory bronchioles, alveolar ducts and primitive alveoli; differentiation of type I and type II pneumocytes</td>
</tr>
<tr>
<td>Saccular</td>
<td>28–36 weeks</td>
<td>Increment in gas exchange areas; further differentiation of type I and type II cells</td>
</tr>
<tr>
<td>Alveolar</td>
<td>36 weeks–2 years</td>
<td>Septation and multiplication of alveoli</td>
</tr>
</tbody>
</table>

Table 1
of the alveolar phase) is characterized by alveolar formation and maturation. The result is a great increase in gas-exchanging surface area and maturation of cells, which will enable adaptation to the postnatal environment. Other major determinants for lung growth and development include maintenance of an adequate fetal lung fluid volume and fetal breathing movements, which appear to be essential for normal lung growth.²

**Development of type II pneumocytes**

Type II pneumocytes are at the centre of surfactant production and function. Flattening of the acinar epithelium at 22–24 weeks marks the initial differentiation of type II pneumocytes, from which type I pneumocytes will be derived later.³ Type II pneumocytes have a cuboidal shape and comprise 10–15% of the cells of the mature distal lung. They produce surfactant and their characteristic feature is the lamellar bodies which store surfactant. Lamellar bodies are first observed between 22 and 24 weeks’ gestation. Surfactant is secreted from these cells by exocytosis into the lining of the alveoli and appears in the future air spaces at 23–24 weeks’ gestation. Type II pneumocytes mature more rapidly between 32 and 36 weeks’ gestation, thereby promoting functional maturity of the lung.

Type II cells are also important in maintaining structural integrity of the pulmonary alveolus as they proliferate after lung injury and serve as precursors for gas-exchanging type I cells. Type I pneumocytes are flat and elongated and cover the majority of the alveolar surface. Their shape is designed to aid effective gas exchange. These cells are however vulnerable to oxidant damage, that is due to hyperoxia because of their large surface area and reduced anti-oxidant capacity compared to type II alveolar cells which are more resistant to such injury.

**Surfactant**

Surfactant, which is a major determinant of alveolar wall surface tension, is a complex mixture of phospholipids, neutral lipids and proteins. Its major constituents are dipalmitoylphosphatidylcholine (DPPC or lecithin), phosphatidylglycerol, cholesterol and apoproteins (surfactant proteins SP-A, -B, -C and -D). DPPC is the principle component responsible for reducing surface tension. The other phospholipids and proteins aid spreading and re-absorption of surfactant along the alveolar wall.

Four apoproteins have been identified. The hydrophobic SP-B and SP-C play a major role in the surface-active properties of surfactant and are essential for lung function and pulmonary homeostasis after birth. These proteins enhance the spreading, adsorption and stability of surfactant lipids required to reduce surface tension in the alveolus.⁶ Hydrophilic SP-A and SP-D are lectins. Their primary role is in host defence and in surfactant clearance and metabolism.⁷ Despite many commercial attempts, none of the currently available surfactant preparations for treatment of RDS contains either SP-A or SP-D.

The normal alveolar pool size of surfactant phospholipids in a full-term neonate has been estimated at about 100 mg/kg, which is about ten times greater than the amount noted in the lungs of a newborn infant with RDS.⁸ Surfactant deficiency due to decreased production and secretion is the primary cause of RDS and is more severe in the structurally immature lung of the preterm infant.

**Surfactant metabolism**

Surfactant proteins and phospholipids are produced in the smooth endoplasmatic reticulum of type II pneumocytes then transported via the Golgi apparatus to the lamellar bodies which are the intracellular stores for surfactant (Figure 1). From these, surfactant is secreted by exocytosis into the liquid lining of the alveoli. In the alveolus, the phospholipids undergo transition to an extracellular form, tubular myelin, in association with SP-A and SP-B. SP-B and SP-C are responsible for liberating the phospholipids from this structure and ordering them into a monolayer at the air–liquid interface. Subsequently, most of the phospholipid and protein components of surfactant are recycled by endocytosis from the alveolar lumen in the form of small vesicles by the type II pneumocytes. Alternatively, a small proportion (~10%) is phagocytosed and degraded by alveolar macrophages. A single transit of the phospholipid components of surfactant through the alveolar lumen normally takes only a few hours. The phospholipids in the lumen are recycled by type II cells and reutilized approximately ten times before being degraded.

The cycle of surfactant synthesis and metabolism is tightly regulated to ensure maximal economy and function, especially in the neonatal period. There is negative feedback of surfactant production mediated by SP-A binding to type II cells. Surfactant secretion, at least to some extent, is triggered by stretch receptors and by β-adrenergic receptors on type II pneumocytes, with receptor numbers increasing towards the end of gestation. Several other mechanisms which stimulate the synthesis and release of surfactant into the alveolar space have been also identified.⁹ Some of these pathways involve catecholamines, cyclic adenosine monophosphate (cAMP), adenosine triphosphate (ATP), calcium and prostaglandins.

![Figure 1](Image)

**Figure 1** Surfactant recycling. The location and movement of surfactant from the type II pneumocyte to the alveolus is shown. Surfactant is synthesized from precursors in the endoplasmatic reticulum (ER) and transported via the Golgi apparatus (G) to lamellar bodies (LB) where it is stored. From there it is secreted into the liquid lining of the alveolus where it forms tubular myelin (TM), which generates the surface tension reducing monolayer. Subsequently, surfactant components are taken up by the type II pneumocytes again in the form of small vesicles. A small proportion of surfactant is also taken up by alveolar macrophages. (Redrawn with permission from McCabe et al.²⁹)
Pathophysiology of surfactant deficiency

Surfactant is spread as a thin film at the air–liquid interface of the alveolar surface, lowering its surface tension and thereby preventing alveolar collapse, especially at the low alveolar volumes reached at end-expiration. It also reduces the pressure required for subsequent alveolar inflation and maintains a satisfactory functional residual capacity.

It is therefore clear that in the absence of an adequate amount of mature pulmonary surfactant, infants with RDS will progressively develop atelectasis and abnormalities of lung function. The alveoli tend to collapse at end-expiration, resulting in a low functional residual capacity. The pressure needed to inflate the lungs will be high, the lung compliance will be decreased and the work of breathing greatly increased. Infants with RDS have a low tidal volume and a large physiological dead space. Minute ventilation may be increased due to an increased respiratory rate in an attempt to sustain alveolar ventilation, but alveolar ventilation remains inadequate.

Atelectasis with other areas of over inflation may co-exist, especially in an infant receiving mechanical ventilation and thus leading to ventilation–perfusion mismatching and right-to-left intrapulmonary shunting. This limits the excretion of carbon dioxide and oxygen saturation of pulmonary venous blood, leading to respiratory acidosis and hypoxaemia. Persistent hypoxaemia leads to metabolic acidosis, reduced cardiac output and hypotension. Arterial blood gases in severe RDS thus reflect a mixed metabolic and respiratory acidosis. Acidosis will further reduce surfactant production and may also increase pulmonary vascular resistance.

The increased work of breathing is manifested by intercostal and substernal retractions as the infant generates higher negative pleural pressure to maintain alveolar ventilation. Most preterm babies are born with poor reserves of surfactant and the characteristic deterioration in the early phase of RDS is in part due to the disappearance of these small quantities together with fatigue as the neonate struggles to sustain adequate ventilation. Proteins leak into the alveolar spaces during the early stages of acute lung injury and will further inhibit the small amount of surfactant present. Hypoxaemia and acidemia will also affect surfactant function and synthesis.

In the untreated infant, endogenous surfactant production commences from 2–3 days of age and heralds clinical recovery from respiratory distress. By reducing surface tension, surfactant allows the alveoli to re-expand with inspiration. Therefore, optimum gas exchange is achieved through matching of ventilation and perfusion. Clinically, the functional residual capacity improves and the work of breathing decreases markedly due to the decreased airway resistance and improved lung compliance.

Pathological findings: on macroscopic examination a surfactant deficient lung appears poorly inflated, has the consistency of liver and does not float in water. Microscopically, the initial finding is of alveolar epithelial cell necrosis, which can develop within half an hour of birth. The epithelial cells become detached from the basement membrane and small patches of hyaline membrane form on the denuded areas. Hyaline membranes are composed of fibrin, cellular debris, red blood cells, neutrophils and macrophages. They appear as an eosinophilic, amorphous material, lining or filling the alveolar spaces and thus adversely affecting gas exchange. In the initial stages, these changes are rather patchy, but by about 24 hours of age more generalized hyaline membrane formation occurs. After 24 hours, the repair phase begins and cells of resolution, mainly macrophages, appear within the airway lumen. After 5–7 days, the hyaline membranes start to disappear and the remnants are phagocytosed by the macrophages. The architecture of the lung returns to normal. In the prolonged inflammatory processes of many preterm infants, the disease may progress to chronic lung disease of prematurity (CLD).

Risk factors for the development of respiratory distress syndrome

Many risk factors of RDS have been described (Table 2). Some of the common ones are described below.

Prematurity

The greatest risk factor for RDS is low gestational age and the development of the disease begins with the impaired synthesis of surfactant associated with prematurity. About 50% of infants born before 30 weeks’ gestation will develop RDS and the incidence decreases with advancing gestational age, from about 60–80% in babies born at 26–28 weeks, to about 15–30% of those born at 32–36 weeks. As described above, RDS is the result of both surfactant deficiency and structural immaturity of the lungs.

Gender

Boys are more likely than girls to develop RDS (male-to-female ratio ∼1.3:1). These differences are thought to be partly due to androgenic actions on type II pneumocytes delaying the production of mature surfactant.

Race

There are ethnic differences in the incidence of RDS with higher rates observed in Caucasian compared to black infants. In a study of preterm infants born between 23 and 32 weeks’ gestation, the incidence of RDS was 75% in Caucasian infants, 54% in infants of Caribbean origin and 40% in infants of African origin.

<table>
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<tr>
<th>Risk factors for respiratory distress syndrome</th>
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<td>Multiple pregnancy</td>
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<tr>
<td>Elective caesarean section</td>
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<td>Gestational diabetes</td>
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<tr>
<td>Intrahepatic cholestasis of pregnancy</td>
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<td><strong>Infant factors</strong></td>
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<tr>
<td>Prematurity</td>
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<td>Hypothermia</td>
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<td>Caucasian ethnicity</td>
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<tr>
<td>Intrapartum asphyxia</td>
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<td>Pulmonary infections</td>
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<td>Pulmonary haemorrhage</td>
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<tr>
<td>Meconium aspiration syndrome</td>
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<td>Congenital diaphragmatic hernia</td>
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<td>Pulmonary hypoplasia</td>
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Table 2
Multiple pregnancy
In twin pregnancies, the second twin is usually at greater risk of developing RDS. This risk of developing RDS in the second twin increases with gestation and is most significant after 29 weeks. It is not clear whether this increased risk is due to delayed maturation of the lungs or an increased risk of hypoxia/acidosis in the second twin.

Caesarean section
At any given gestational age the incidence of RDS is greater for infants born by caesarean section, especially without established labour, than for those born by vaginal delivery. The combination of elective caesarean section and delivery before term significantly increases the risk of RDS. The reasons for the increased risk of respiratory morbidity are probably a combination of delayed removal of lung fluid and a lack of cortisol response associated with spontaneous labour.

Maternal diabetes
Infants of diabetic mothers are more likely to develop RDS compared to infants of non-diabetic mothers of equivalent gestational age. These babies have an abnormal pattern of surfactant synthesis with delayed appearance of phosphatidylglycerol. Insulin has been shown to delay the maturation of type II pneumocytes and decreases the proportion of saturated phosphatidylcholine in surfactant. However, delivery at term rather than at 36–37 weeks reduces the risk of severe RDS in infants of diabetic mothers.

Genetic disposition
Cases of familial RDS in term babies have been reported and it is now clear that some of these are due to genetic reasons, such as partial or complete deficiency of SP-B. In cases where SP-B is completely absent, death is inevitable despite intensive care and surfactant treatment. Partial deficiency of SP-B has also been reported and this may be compatible with survival. Similar genetic defects of other components of surfactant are increasingly being described.

Intrahepatic cholestasis of pregnancy
It has recently been shown that maternal intrahepatic cholestasis of pregnancy is significantly associated with the occurrence of RDS in the newborn. It has been hypothesized that bile acids can cause surfactant depletion in the alveoli.

Other risk factors
Secondary surfactant deficiency may occur in infants with intrapartum asphyxia, pulmonary infections (e.g. Group B β-haemolytic streptococcal pneumonia), pulmonary haemorrhage, meconium aspiration syndrome, congenital diaphragmatic hernia or pulmonary hypoplasia. RDS is further exacerbated by treatable and preventable factors, including hypothermia, hypoxia and acidosis, which impair surfactant production and secretion.

Prevention
Most important in decreasing the incidence of RDS is prevention of prematurity, including avoidance of unnecessary and poorly timed caesarean sections. Maternal narcotic addiction, smoking and alcohol intake all reduce the incidence of RDS in preterm babies. The mechanism is probably due to stimulation of surfactant production, but the significant adverse effects of these drugs clearly prohibit their use in pregnancy.

The two major management approaches to prevent the development of RDS are the use of antenatal treatment of women in preterm labour with glucocorticoid hormone to accelerate fetal lung maturation and the early use of surfactant replacement therapy.

Antenatal glucocorticoids
Several randomized controlled clinical trials have been performed on the efficacy of antenatal corticosteroids in preterm birth to decrease the rates of RDS and the first structured review on corticosteroids in preterm birth was published in 1990. A recent Cochrane review showed that treatment with antenatal corticosteroids reduces the risk of neonatal death, RDS, intraventricular haemorrhage, necrotizing enterocolitis, infectious morbidity, need for respiratory support and neonatal intensive care unit admission. Antenatal administration of corticosteroids accelerates lung growth by several mechanisms, including maturation of type II pneumocytes and production of surfactant. However, repeated doses to the mother in threatened preterm labour may affect the final numbers of alveoli and somatic growth; this has been shown at least in animal models.

Thyrotropin-releasing hormone
Thyroxine increases surfactant production and lung maturation. However, unlike T3 and T4, thyrotropin-releasing hormone (TRH) readily crosses the placenta and increases the amount of surfactant phospholipid. TRH in combination with corticosteroids has been used in the past. However, some studies have shown that receiving surfactant in addition to TRH does not decrease the incidence of RDS in infants. In follow-up studies, there was an increased risk of motor delay in surviving infants. Therefore, antenatal administration of TRH to women in preterm labour is not routinely used in practice.

Prophylactic surfactant administration
Prophylactic, or preventive, surfactant administration is defined as endotracheal intubation and surfactant administration to infants at high risk of developing RDS. For infants at high risk for RDS, prophylactic surfactant replacement therapy is preferable to later rescue therapy for established RDS as survival, CLD or death and air leak are significantly decreased. Together with antenatal corticosteroid treatment, the use of prophylactic surfactant has made the greatest contribution to decreasing the incidence of RDS and its associated morbidity and morbidity.

Summary
RDS is caused by developmental insufficiency of surfactant production and structural immaturity of the lungs. The incidence is therefore inversely related to the gestational age and RDS remains the leading cause of death in premature infants. The lack of surfactant, which is produced in type II pneumocytes from 24 weeks’ gestation, leads to a reduction in lung compliance. The alveoli tend to collapse, giving rise to atelectasis and a reduced functional residual capacity. Apart from prematurity, several factors contribute to the development of RDS. The risk of
developing RDS is markedly reduced with the administration of antenatal steroids and prophylactic surfactant.

REFERENCES


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Practice points

- RDS is caused by developmental immaturity of the lung, particularly the surfactant-producing type II pneumocytes
- Surfactant reduces surface tension at the alveolar surface and its lack leads to atelectasis
- The greatest risk factor for RDS is prematurity but there are many others
- Antenatal steroids and prophylactic surfactant administration have been shown to be of the greatest benefit in reducing the incidence of RDS