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Recent Understanding of Pathophysiology, Risk Factors and Treatments of Neonatal Respiratory Distress Syndrome: A review

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Abstract

Neonatal respiratory distress syndrome (NRDS), most regularly seen in preterm babies, is induced by the shortage of surfactant in the lungs. Clinical manifestations of RDS are grunting, tachypnea, retractions, nasal flaring and necessity for complementary oxygen. In the previous three eras, the consequences of RDS have greatly improved by the initiation of antenatal steroids and exogenous surfactant; nevertheless, it still persists as a predominant trouble. In china, respiratory distress typically for late preterm or term newborns is still an ultimate reason for Neonatal Intensive Care Unit (NICU) admissions. Recently found that a growing trend of frequency of NRDS is seen in late preterm infants, which is almost a third of babies with NRDS. The pathophysiological basis of NRDS is surfactant deficit, which is closely related to the gestational age or birth weight. Risk of RDS increases with prematurity. By chest radiography results and acidosis, the diagnosis can be evaluated. Over the past years, mortality from respiratory distress syndrome has fallen significantly due to advances in NICU and better practice of antenatal steroids and surfactant administration. More current clinical trials illustrate that intubation can be avoided either by an initial introduction of continuous positive airway pressure (CPAP) in the labor room to stabilize premature babies and administer selective intratracheal surfactant. This review gives emphasis to the pathophysiology of RDS, risk factors and some of the recent up-to-date approaches for the treatment of RDS in preterm neonates.

Introduction

Neonatal respiratory distress syndrome (NRDS) is the ultimate substantial chief reason for morbidity and mortality in premature newborns [1-3]. The basic abnormality of RDS is surfactant deficiency, hence it is also known as hyaline membrane disease (HMD) [4]. RDS presents with grunting, nasal flaring, chest wall retractions, and increased the effort of inhalation at birth, or in a while subsequently. These infants typically have the progress of warning signs and need supplementary oxygen support. Laboratory findings of the arterial blood gas analysis are characterized initially by hypoxemia and hypercapnia along with variable metabolic and respiratory acidosis. The chest radiograph illustrates air bronchograms and ground-glass opacification in bilateral lung fields with decreased lung volume. A whole "white-out" of the lung fields is frequently seen in more severely affected infants. In the previous three decades, massive advances have been made in interpreting the pathogenesis and management of RDS [5]. The incidence of RDS is reciprocal to advancing gestational age, declines gradually from 60–80% in neonates born between 26–28 weeks gestational age (GA) to 15–30% in those born between 32–36 weeks GA [6, 7].

A multidisciplinary method is vital to attaining greatest outcomes as the management of these babies is difficult. The essential treatment goals are temperature control, nutrition and cardiovascular maintenance and management of early neonatal sepsis. Certainly, the chief respiratory support of RDS infants is surfactant remedy, continuous positive airway pressure (CPAP) and mechanical ventilation (MV). In infants after 36 weeks or at term gestation, RDS may be exist, but is occasional and further diagnostic evaluation must be deliberated [4].

Epidemiology

Though RDS is observed in a lesser amount in developing nations, but mostly due to malnutrition or pregnancy-induced hypertension, premature newborns that are short for the gestational age have extreme intrauterine stress. The overall incidence is 10-15%, but can be as high as 80% in neonates less than 28 weeks. It is most frequently seen in babies born at less than 28 weeks GA and 1/3 of babies born at 28 to 34 weeks GA are affected, but less than 5% are seen in babies born after 34 weeks GA [8]. RDS is more often in male babies [9] and because of lack of lung maturity in spite of macrosomia, RDS has been shown 6 times greater incidence in the mothers with gestational diabetes [10]. One report says that the RDS was 42% in babies of 501-1500g, with 71% observed in babies of 501-750g, 54% observed in babies of 751-1000g, 36% observed in babies of 1001-1250g, and 22% observed in babies of 1251-1500g according to NICHD [11]. White ethnicity, male gender maternal diabetes, cesarean section and chorioamnionitis are related to larger risk and severity of RDS varies from extremely preterm newborns <27 weeks GA whose birth weight is less than 1000g, and very preterm newborns <32 weeks GA whose birth weight is less than 1500g. Term newborns greater than 39 weeks GA have more risk of RDS [12-16]. However, in term and late preterm babies, relations of gender and ethnicity with RDS hazard have not been categorized [17-25]. For the period of the past five years, even though birth rates of premature infants have fallen down in the United States, about 12.3% infants are still delivered, especially 70% of late preterm infants are born less than 37 weeks GA [26].

Diagnostic Criteria

The diagnosis of RDS can be clinically interpreted on the basis of chest roentgenographic findings, respiratory signs, and blood gas values. The ominous signs of RDS requiring immediate intervention usually prominent in the early hours of birth are tachypnea, grunting, retractions, cyanosis and nasal flaring. The diagnostic criteria conferring to the 2013 European Consensus Guidelines are: (1) Arterial oxygen pressure (PaO_2) <50 mm Hg or cyanotic or a need for supplemental oxygen to sustain the level of oxygen saturation SpO_2 >85% within one day of birth and (2) a chest x-ray demonstrates air bronchograms and reticular granularity of parenchyma [27]. Based on chest x-ray features, RDS is categorized into grades: (1) light, slight ground glass opacification; (2) moderate, decreased lung volume and air bronchograms; (3) severe, indistinct cardiac margins

or white lung [28].

Pathophysiology

Preterm babies born <37weeks GA are most likely to develop RDS, as the most pulmonary surfactant is synthesized usually after 30-32 weeks gestation. Deficiency of pulmonary surfactant is due to the catastrophe to reach a sufficient forced residual capacity (FRC) and the lungs tend to collapse due to increased surface tension. Suppression of surfactant production is associated with cold stress, asphyxia, hypoxemia, hypovolemia and pulmonary ischemia. In addition to short gestation, quite a lot of other clinical risk factors have been recognized [29]. In order to indemnify for a reduced tidal volume and increased dead space, tachypnea happens due to an effort to raise minute ventilation. Retractions occur as the infant is obligatory to create a high intrathoracic compression to inflate the poor lung compliance. In order to maintain the alveolar volume grunting take place by the incomplete closure of the glottis. Further clinical signs might be oliguria, hypothermia, hypotension, hypotonia and acidosis. Fetal lung development is affected by maternal nutrition, antenatal glucocorticoids and chorioamnionitis [30]. Pulmonary responses after birth get affected by altering fetal development to consequent postnatal injuries such as high oxygen concentrations or drug reactions [31]. The numerous factors impelling the maturation of the lungs are depicted in Fig. 1.

Avery et al. [5] revealed that the foremost cause of RDS is the lack of surfactant. Pulmonary surfactant is a composition of lipoprotein which is vital for the normal pulmonary function and results in NRDS due to lack of surfactant. The quantity of surfactant secreted is unable to meet postnatal necessities due to immature lungs. Surfactant doesn't reach the external area of the lung, although huge amounts are present by 20 weeks of GA in fetal lungs. Surfactant levels are matured generally later 35 weeks. A number of studies have estimated an inherited association to the pathophysiology of RDS. One of the hydrophobic proteins essential for the ideal surfactant role is surfactant protein B (SP-B), subsequently as a result of respiratory distress syndrome [33, 34]. The pathological process of RDS is intricate with several aspects in Fig. 2. The surfactant is further reduced by the injury of the epithelial lining of the lungs due to the effects and concentrations of respiratory management. Atelectasis is triggered due to diminished production of surfactant, along with minor breathing components and a compliant chest wall which leads to hypoxia. Hypercapnia occurs due to inadequate ventilation, lesser tidal volumes, enlarged physiological dead space. Consequently, atelectasis causes hypoperfusion, pulmonic vascular constriction, and ischemia of lung tissue. Bronchopulmonary dysplasia (BPD) arises due to chronic respiratory distress babies who require oxygen support for a long duration. It has a greater risk for asthma with frequent gasping in children for hospitalization [35].

Risk factors for respiratory distress syndrome

Although the primary risk factor is prematurity, a number of additional factors need to be contemplated. In addition to prematurity, short gestational age, acidosis, asphyxia, maternal diabetes and cesarean section can increase the risk of RDS [36]. The above-mentioned risk factors are well deliberated in detail below.

Maternal risk factors

Advanced maternal age

Dani et al. [12] acknowledged that RDS is associated with progressing age of mothers. Their description was based on due to a greater incidence of pregnancy-induced hypertension, gestational diabetes, abruption placenta and placenta previa in elder women.

Cesarean section

The role of the cesarean section had been controversial in the etiology of RDS. Hansen et al. [37] demonstrated that babies delivered in 37-39 weeks GA by elective caesarean section had shown a rise in respiratory morbidity. Of late, the WHO global survey conveyed the highest cesarean section rate in china was 46.2% among the nine Asian nations [38]. The maximum rate of babies delivered by cesarean section without known indications is seen in China, which might subsequently have an

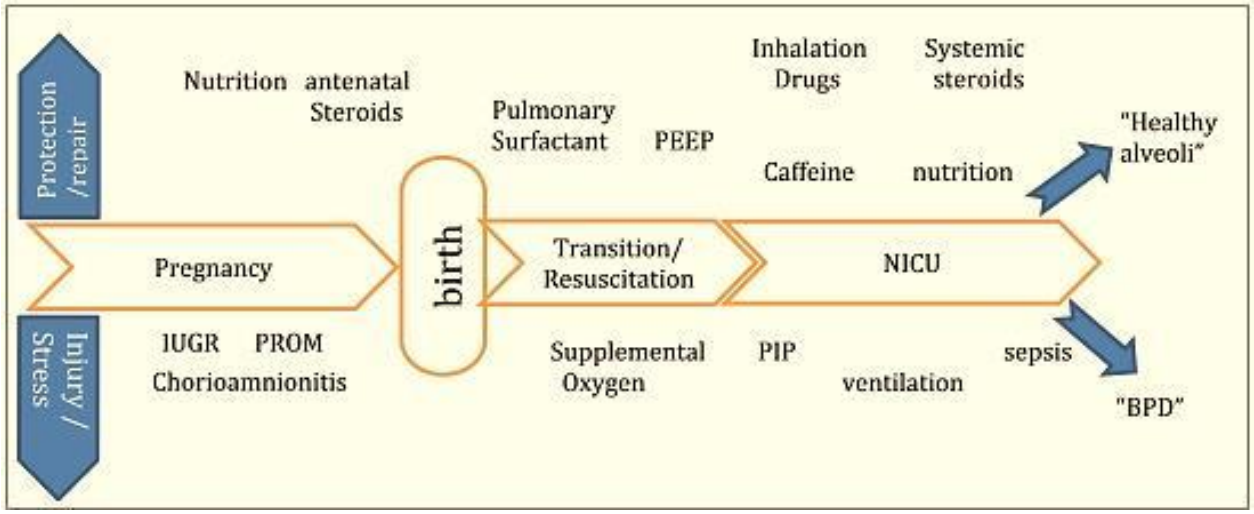

Fig.1 Factors influencing the development of lungs in preterm infants. This information was obtained from reference [32]. IUGR- intrauterine growth retardation, PROM- premature rupture of membranes, PEEP-positive end-expiratory pressure, PIP-positive inspiratory pressure, NICU-neonatal intensive care unit, BPD-bronchopulmonary dysplasia.

inordinate chance of further breathing complications after delivery. The risk of RDS increases possibly due to a combination of delay in exclusion of the lung fluid and deficiency of cortisol reaction related to selective cesarean section and normal labor ominously [39].

Gestational diabetes

A correlation between gestational diabetes and RDS was acknowledged by Robert et al. [40] in 1976. It is mainly due to insulin hormone that prevents the accretion of surfactant protein A and B (SP-A, SP-B) messenger RNA. The surfactant is synthesized in delayed form of phosphatidyl glycerol with a typical arrangement seen in babies of diabetic mothers. On the other hand, there is a conflict of evidence that gestational diabetes is a self-regulating cause for severe RDS beyond 34 weeks.

Infant risk factors

Prematurity

Small gestational age is the ultimate threat for RDS and the progress of disease starts with the relationship of prematurity with reduced production of surfactant. RDS is one of the pivotal complications observed in premature babies rather than several other systemic impairments [41]. In addition, premature babies are at a greater risk of intellectual and developmental disorders compared to other babies. RDS occurs predominantly in preterm infants, its prevalence is in reverse comparative to gestational age and birth weight. RDS will advance in almost 50% of newborns before 30 weeks GA [42], occurs in 60–80% in <26–28 weeks babies, 15–30% between 32–36 weeks and rarely in those >37 weeks babies [6, 7]. Infants who need the support of mechanical ventilation are 90% and almost 80% born at less than 30 weeks GA are cured with surfactant administration [43].

Gender

The male infants have a higher predominance of RDS than female infants (male-to-female ratio ~1.3:1). The surfactant synthesis is possibly delayed due to the action of androgens on type II pneumocytes [36]. An enlarged risk of RDS is associated with male sex due to variances in hormonal regulation of the mechanisms involved in the development of lung [44-48]. It is supposed that the surfactant is produced earlier in female infants than the male fetal lung. The possible explanations may be due to the postponement of fetal lung maturity by androgens, which regulate the factors of growth signaling pathways. Estrogen, which stimulates the production of pulmonary surfactant, surfactant proteins A and B together with phospholipids, lecithin, as well expands lung maturity of fetus by means of enhancing the amount of type II pneumocytes [49, 50].

Race

The occurrence of RDS is highest in premature white newborns compared to black infants. A study showed that the rate of recurrence of RDS in premature babies born after 22-32 weeks GA was 75% in babies of caucasian origin, 54% in Caribbean babies and 40% in babies of African origin [51]. Some researchers found that formerly in infants <32 weeks GA, male gender and white race showed an ethnic disproportion in risk of RDS but also persists in term babies [52-54].

Other risk factors for respiratory distress syndrome

Newborns with pulmonary infections, intrauterine asphyxia, meconium aspiration syndrome and hypoplasia of the lungs cause lack of secondary surfactant. Surfactant synthesis and secretion are diminished by protective aspects such as hypoxia, hypothermia, and acidosis and these by RDS are further aggravated.

Table 1 Maternal and infant risk factors for respiratory distress syndrome.

Maternal factors	Infant factors
Advanced maternal age	Prematurity
Caesarean section	Male gender
Gestational diabetes	Caucasian ethnicity
Multiple pregnancy	Familial inheritance
Gestational hypertension	Birth asphyxia
Intrahepatic cholestasis of pregnancy	Lung infections
Antenatal corticosteroid prophylaxis	Meconium aspiration syndrome

Preventions

Several disputes still exist in spite of modern advances in the perinatal care of RDS. The frequency of RDS in preterm babies might be reduced by prevention of prematurity, avoiding unnecessary c-section deliveries, addiction of narcotics, smoking, and alcohol by mothers. The important preventive strategies are the proper control of high-risk perinatal period and labor, and estimation of lung immaturity with likely *in utero* quickening of development [55, 56].

Corticosteroids

The vivid progress in the outcome of RDS patients is by the initiation of antenatal steroids to mothers among 24 and 34 weeks GA considerably diminishes the incidence of RDS and mortality rate in infants [57]. Prenatal corticosteroids administered before 35 weeks of gestational age has been evidenced to improve the fetal lung maturity and thereby reducing the need for respiratory support and NICU observation. The latest studies journal revealed that the risk of RDS, intracranial hemorrhage, early-onset sepsis, necrotizing enterocolitis (NEC) has been declined by the treatment of antenatal corticosteroids [3, 58-60].

Surfactant therapy

Over the past two eras, the treatment of surfactant for RDS has developed ominously. The most meticulously evaluated therapies presently used in the NICU are inducing the first dose of surfactant for symptomatic premature babies immediately after birth declines leakage of air and RDS mortality rate. A report conveyed the facts on the surfactant deficit related to RDS pathogenesis [5]. Prophylactic or rescue administration of surfactant along with antenatal corticosteroids has made an extreme impact in diminishing the occurrence of RDS, pneumothorax and neonatal mortality. Information on surfactant management gave either prophylactic or early stage of infant hospitalized remained quite debatable. At least 100 mg/kg of surfactant is a prerequisite; however, there are pharmacologic data recommending that 200 mg/kg has an extended half-life and a well moderate reaction. Some studies have revealed that repetitive dosage is more in effect than single-dose treatment in decreasing mortality rate. On the other hand, a rescue course can be administered in women who are at threat of delivery of the preterm baby and less than 33 weeks GA [27]. Modern membrane nebulizers are being revealed for RDS infants along with CPAP for surfactant management [61-63].

Continuous positive airway pressure

The usage of CPAP to reduce the damage of the lungs related with ventilation is a better approach in spite of routine intubation of infants. In the early 1970s, Gregory initially introduced the practice of CPAP, for the management of RDS, has gradually improved and recovered an essential place in the

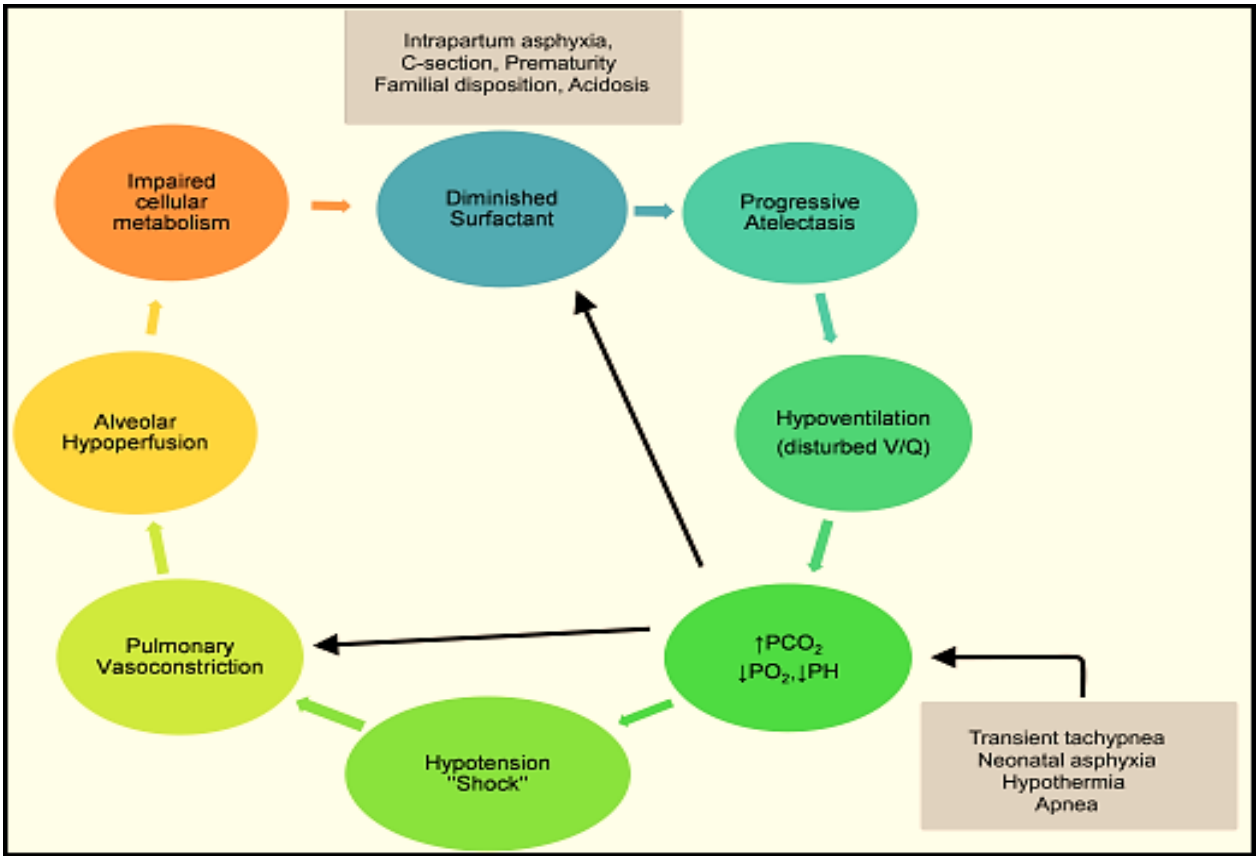

Fig. 2 Factors involved in the pathogenesis of Neonatal respiratory distress syndrome.

RDS treatment. The CPAP has more benefits than mechanical ventilation. An increased occurrence of retinopathy of prematurity and bronchopulmonary dysplasia is related to variations in oxygen saturation [64]. In recent times, a number of huge trials were started to determine safe and effective targeting saturations of 85–89% or 91–95%. Previously, CPAP given at birth cuts the necessity for surfactant treatment and transfer of infants with moderate RDS to tertiary centers and mechanical ventilation (MV) can be avoided. The CPAP used after extubation from MV lessens the necessity for reintubation and at least 5cm H_2O pressure is required. Up to date, no evidence has been conveyed amongst the many maneuvers used to deliver nasal CPAP of any modifications in long-term consequences. A minor study recommended that nasal masks may perhaps be the best to avoid reintubation rather than nasal prongs. Conversely, the outcome on the frequency of BPD is unclear. Dominant variables allied with a greater achievement level are increasing gestational age and prophylactic surfactant. More current clinical trials illustrated that intubation can be avoided either by an initial introduction of CPAP in the labor room to stabilize premature babies and administer selectively intratracheal surfactant thereby mortality rate or chronic lung disease were dropped. The necessity of ventilation and BPD has been substantially reduced by 'INSURE' (Intubate-surfactant-extubate to CPAP) technique. However, the progress of new ventilatory techniques may be essential to come across the challenges [65-68].

Mechanical ventilation (MV)

The objective of MV is to eliminate the levels of carbon dioxide (CO_2) and increase oxygen levels minus affecting lung injury [36]. In the NICU for managing RDS, conventional mechanical ventilation, primarily time cycled, pressure limited ventilation has mostly been used. Yet, there are limited trials to show the data of decreasing the prevalence rate of BPD [69, 70]. The ubiquitous techniques of high-

frequency ventilation (HFV) are high-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation (HFJV) which can be used with less tidal volumes and promote consistent ventilation to the alveoli, when other approaches of respiratory support are futile, MV should be provided with targeted tidal volume ventilation to minimize the duration and reduce BPD. For infants on non-invasive ventilation, caffeine taught to be measured at greater risk of requiring MV. Neonatologists introduced new techniques such as HFOV and HFJV, any of these given as primary approach will not reduce respiratory air leaks. Moreover, predominantly for the reason that of central nervous system complications, the query remains unclear whether HFV should be used as an initial or a rescue method of ventilation [71-73]. Hence, methods most likely to be initiated in the delivery room that might be vital to lessen the lethal outcome of atelectasis and BPD.

Clinical recommendations

As the risk of preterm births is increasing, prior administration of prenatal corticosteroids lessens the risk of respiratory distress syndrome of the neonates. Surfactant deficiency is the principal cause of RDS, prophylactic or rescue surfactant application has made an extreme impact in reducing the incidence of RDS. Proper antenatal care, precautions should be taken to avoid unnecessary cesarean sections, reduce prematurity, choose the ventilator support with appropriate parametric settings to diminish the major outcomes and improve the prognosis of NRDS.

Conclusions

In China, we found that respiratory distress is still a common and recurrent fatal condition in neonates admitted to hospital. The RDS is generally initiated because of the lack of surfactant. Although the primary contributing feature for RDS is prematurity, a number of additional causes need to be contemplated. A multidisciplinary method is vital to attaining greatest outcomes as the management of these babies is difficult. The prenatal steroids given for the maturity of the lungs have become a major throwback to prevent RDS in premature infants. Nevertheless, scarcity of awareness and proficiency among doctors, the stipulation on imported CPAP devices, non-availability of air/oxygen supply, surfactant and standby ventilation and insufficient skillful nursing staff are the foremost challenges. Good antenatal care, well-timed transfer, and optimal delivery and neonatal care practices should be correspondingly done. The aim of the therapeutic remedy of RDS is to abate the anomalous iatrogenic difficulties and to reduce ventilator-induced lung damage, the progress of new ventilatory techniques may be essential to come across the challenges.

Conflict of interests

All the authors declared no conflict of interest.

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