Soluble Intercellular Adhesion Molecule-1 (sICAM-1) levels in Neonatal Respiratory Distress Syndrome

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By

Ibrahim Mohamed Mohamed Badran
M.B., B.Ch.

Alexandria University

Supervised by

Prof. Dr. Mohamed Ashraf Abd El-Wahed

Professor of Pediatrics

Faculty of Medicine - Ain Shams University

Ass. prof. Eman Saleh El-Hadidy

Assistant Professor of Clinical Pathology

Faculty of Medicine - Ain Shams University

Dr. Ola Galal Badr El-Deen

Lecturer of Pediatrics

Faculty of Medicine-Ain Shams University

Faculty of Medicine

Ain Shams University

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Introduction

Neonatal respiratory distress syndrome (RDS**)** is the most commonly disease seen in premature infants ***(Lampland, 2007).*** The disease is mainly caused by a lack of a slippery protective substance called surfactant, which helps the lungs to inflate with air and keeps the air sacs from collapsing. This substance normally appears in mature lungs ***(Cole, 2006).***

Bronchopulmonary dysplasia (BPD) is a major complication of premature birth that is associated with younger gestational age and has important long-term consequences for the affected child ***(Ng et al., 2000).***

Inflammation and transepithelial migration of neutrophil in the absence of clinical sepsis have been implicated in the development of RDS and subsequent occurance of BPD in the premature infant ***(Sarafidis et al., 2001).*** The actual movement of neutrophils and monocytes through the vasculature and diapedesis into tissues is mediated by adhesion molecules ***(Parkos, 1997).***

Intercellular adhesion molecule molecule-1 (ICAM-1) is a type of intercellular adhesion molecule that is continuously present in low concentrations in the membranes of leukocytes and endothelial cells. Upon cytokine stimulation, the concentrations greatly increase. ICAM-1 can be induced by interleukin-1(IL-1) and tumor necrosis factor alpha (TNFα) and is expressed by the vascular endothelium, macrophages, and lymphocytes ***(Frijns &Kappelle, 2002).***

Neutrophil migration across endothelial and epithelial cell barriers is dependent on ICAM-1, which is extensively upregulated in inflammatory diseases ***(Becker et al., 1991)*** and detection of a soluble form of ICAM-1 in the circulation has been proposed to be a useful marker of inflammation ***(Seth et al., 1991).***

Aim of the work

The aims of this study are to investigate the role of sICAM-1 in the pathogenesis of neonatal RDS, to asses its relation to severity of RDS and to evaluate its possible participation in subsequent development of BPD.

Respiratory Distress Syndrome

Definition:

Respiratory distress syndrome (RDS) or hyaline membrane disease (HMD), is an acute illness affecting preterm neonates with deficient pulmonary surfactant. It's characterized by manifestations of respiratory distress (working alae nasi, retractions, grunting, cyanosis and auscultatory crepitations) together with a characteristic radiological appearance; representing the single most important cause of mortality and morbidity in preterm neonates ***(Rodriguez et al., 2006).***

Incidence:

RDS occurs in 60-80% of infants less than 28 weeks of gestational age, in 15-30% of those between 32 -36 weeks, in about 5% beyond 37 weeks, and rarely at term **(*Stoll and Chpman, 2007)***. The condition is more common in boys and the incidence is approximately six times higher in infants whose mothers have diabetes because of delayed pulmonary maturity despite macrosomia ***(Cowett, 2002)***.

Risk Factors:

The condition is more common in white than nonwhite infants. There is a strong suggestion that premature rupture of

membrane actually increase the risk of respiratory distress syndrome at a given gestational age ***(Welty et al., 2005)***.

1. **Prematurity:**

   Prematurity remains the single most common risk for RDS. The incidence of RDS is inversely proportionate to gestational age and about 60% of infants born at less than 28 weeks of gestation develop RDS ***(Ward and Beachy, 2003).***

2. **Sex:**

   Boys are more likely to develop RDS than girls and more early to die from the disease ***(Maly and Mauji, 2000).*** In male fetuses, the delayed maturation of lecithin /sphyngomyline (L/S) ratio and the late appearance of phosphatidyl glycerol are androgen induced **(*Greenough et al., 2004).***

3. **Diabetic mother:**

   The infant of diabetic mother has higher insulin levels than normal and insulin has a direct inhibitory effect on lung epithelial cells ***(Whitsett et al., 2000).***

4. **Second-born twin:**

   The second twin is much more likely to develop RDS since it has an increased chance to be asphyxiated ***(Pramanik, 2006).***

5. **Cesarean section delivery:**

   Cesarean section carried out before the onset of labour is considered to increase the risk of RDS ***(Ziadeh & Badria, 2002)***.

6. **Asphyxia:**

   Hypoxia and acidemia reduces the baby's respiratory efforts, resulting in diminished lung fluid removal and less surfactant secretion ***(Greenough et al., 2004).***

7. **Hypothermia:**

   This impairs surfactant synthesis and function via producing hypoxia and acidosis ***(Mathur, 2005).***

8. **Nutrition:**

   Deficiency of fatty acids and inositol in the mother may increase risk of occurrence of RDS ***(Howwlett and Ohlsson, 2003).***

9. **Birth weight:**

   RDS is more in babies < 2500 gram ***(Welty et al., 2005).***

10. **Maternal hypothyroidism:**

    Thyroxin is important for surfactant synthesis ***(Greenough et al., 2004).***

11. **Familial predisposition:**

    The reason is unknown, but it may be inherited abnormality in surfactant synthesis ***(Greenough et al., 2004).***

On the other hand, certain factors may reduce the incidence of RDS such as:

- Use of antenatal steroids,
- Maternal hypertension
- Maternal narcotic addiction especially heroin ***(Pramanik, 2006).***

Pathogenesis:

The progression of RDS begins with bronchial basement membrane edema and sloughing of epithelial cells. Leakage of proteinaceous fluid, from high surface tension forces and increased capillary permeability, occurs into air spaces forming hyaline membrane. After 72 hours, pulmonary macrophages appear and phagocytize the hyaline membranes. Provided that further pulmonary damage has not occurred during treatment, resolution of the disease commonly occurs in 5 to 7 days ***(Nupponen et al., 2002)***.

Circulating polymorphonuclear leukocytes (PMNL) are activated in preterm infants with RDS and this seems to play a role in pathogenesis, with leukocyte activation present only 2 hours after birth. Neverthless, the inflammation is transient, vanishing by day 7-10 unless chronic lung disease is developed ***(Nupponen et al., 2002)***.

This may explain the fact that circulating neutrophil count is lower in infants with RDS than in infant without RDS, and the neutrophil count is inversely correlated with the severity of RDS. Moreover, circulating neutrophils in RDS have more activation markers on their surface, and their oxidation products are much higher in tracheal aspirates from these infants with RDS than from those without RDS. Neutrophil depletion totally abrogates the development of pulmonary edema. These findings indicate that neutrophil activation is a prominent feature in RDS, which then leads to vascular injury and subsequent pulmonary edema observed histologically ***(Welty et al., 2005)***.

The decreased number and increased activation of circulating PMNs and platelets are correlated not only to hypoxia and acidosis, but also to high pressure ventilation ***(Murat et al., 2002)***.

PULMONARY SURFACTANT:

The primary cause of RDS is deficiency of pulmonary surfactant, which is developmentally regulated. The most common cause of surfactant deficiency is preterm delivery and mutations in the genes encoding surfactant proteins B & C (SP-B, SP-C) ***(Jobe, 2006).***

❖ **Composition:**

Pulmonary surfactant is a complex mixture of lipids and proteins that lowers alveolar surface tension:

- **Phospholipids** : (70%-80% of surfactant coposition) Phosphatidylcholine species forms about 70 % of lipid in surfactant . Of this, approximately 60 % is disaturated palmitoylphosphatidyl choline (DPPC); which is the principle surface-active component of surfactant ***(Jobe, 2006).***

- **Protein** : Surfactant contains small proteins. These consist of the hydrophobic surfactant proteins SP-B and SP-C and the hydrophilic proteins SP-A and SP-D. SP-B is required for normal pulmonary function ***(Whitsett et al., 2002)***. SP-C promotes the formation of the phospholipid film lining the alveolus. The hydrophobic SP-B and SP-C are essential for lung function and pulmonary homeostasis after birth. SP-B and SP-C participate in regulating intracellular and

extracellular processes critical for maintaining respiratory structure and function ***(Pramanik, 2006)***.

- **Function:**

Normal lung function requires patent alveoli that are closely situated to appropriately perfused capillaries. Molecular forces of the water molecules in the alveolar lining result in high surface tension and a tendency of the air spaces to collapse, especially at low volumes. The hydrophilic and hydrophobic properties of DPPC result in a head-to-tail orientation in the air-liquid interface inside the alveolus. When the alveolar volume decreases during exhalation and the fluid in the air-liquid interface is compressed, these surface-active molecules in the interface are squeezed together, excluding water molecules. As a result, pulmonary surfactant reduces the surface tension of the liquid lining, decreasing the pressure needed to keep the alveoli inflated and maintaining alveolar stability ***(Pramanik, 2006)***.

Pathophysiology:

The transition from fetus to infant involves many complex adaptations at birth; the most important is the function of the lungs as a gas exchange organ. Figure (1)

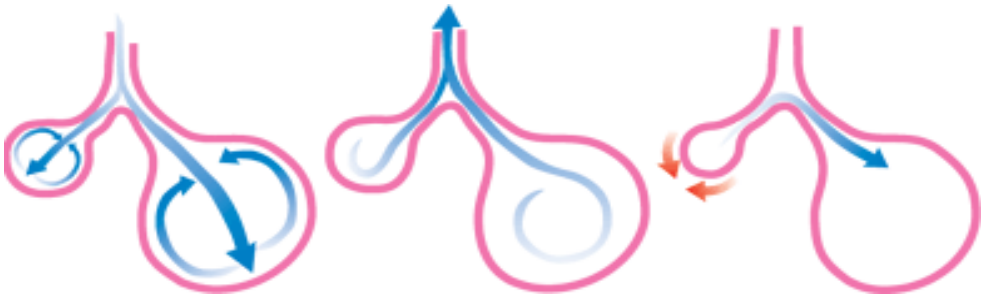

Figure (1): Obeying Laplace's law smaller alveoli would tend to collapse at end expiration forcing air into the larger alveoli that over-inflate. However the film pressure generated by surfactants acts to neutralize the differences and stabilize the lung ***(Bancalari, 2001).***

Preterm surfactant-deficient infants are less well equipped to deal with this transition. Optimum gas exchange is achieved through matching of ventilation and perfusion. Surfactant deficiency (decreased production and secretion) is the primary cause of HMD, The failure of functional residual capacity (FRC) to develop and the tendency of affected lungs to become atelectatic correlate with high surface tension and the absence of pulmonary surfactant. The major constituents of surfactant are dipalmitoyl phosphatidylcholine (lecithin), phosphatidylglycerol, apoproteins (surfactant proteins SP-A -B -C -D) and cholesterol ***(Whitsett and Weaver, 2002).***

With advancing gestational age, increasing amounts of phospholipids are synthesized and stored in type II alveolar cells. These surface-active agents are released into the alveoli, where they reduce surface tension and help maintain alveolar stability by preventing the collapse of small air spaces at end-expiration ***(Bancalari, 2001).***

The amounts produced or released may be insufficient to meet postnatal demands because of immaturity. Surfactant is present in high concentrations in fetal lung homogenates by 20wk of gestation, but it does not reach the surface of the lungs until later. It appears in amniotic fluid between 28 and 32wk. mature levels of pulmonary surfactant are usually present after 35wk. Though rare, genetic disorders may contribute to pulmonary outcome. Abnormalities in surfactant protein genes are associated with severe and/or lethal familial respiratory disease. Synthesis of surfactant depends in part on normal pH, temperature, and perfusion. Asphyxia, hypoxemia, and pulmonary ischemia, particularly in association with hypovolemia may contribute to development of RDS ***(Carol and Porth, 1999).*** (Figure 2)