INTRODUCTION

Neonatal respiratory distress syndrome (RDS) was previously called hyaline membrane disease. It is a disease mainly caused lack of slippery substance in the lung called surfactant. This substance helps the lung fill with air and keeps the air sacs from deflacting. Surfactant is present when the lungs are fully develop ***(Martin and Fanaroff, 2013).***

RDS is the leading cause of mortality and mortality in premature babies ***(Jackson, 2012).***

The pulmonary surfactant is produced by the alveolar type 2 (AT-2C) cells of the lung. It is essential for efficient exchange of gases and maintain the structural integrity of alveoli. Surfactant is a secretory product composed of lipids and proteins ***(Akella and Deshpande, 2013).***

Surfactant synthesis is regulated by many hormones, growth factor, and cytokines. It is already known that corticosteroids play a role in surfactant synthesis and lung maturation. In animal studies, it has been demonstrated that another steroid hormone, 25-hydroxyvitamin D (25(OH)D), affects fetal lung development ***(Fettah et al., 2015).***

Early preterm infants (EPTIs) are likely at risk of low vitamin D status because of high prevalence of vitamin D deficiency in pregnancy, lack of sunlight exposure during hospitalization and difficulty in ensuring adequate enteral nutrition ***(Monangi et al., 2014).***

The impact of vitamin D on early lung development and maturation and lung diseases of early life is an emerging field of research ***(Lykkedegn et al., 2015).***

Moreover, vitamin D is suggested to play a role in the embryogenesis and in cellular growth and differentiation, including lung development and regulation of lung maturation in the fetus, where by hypovitaminosis D could be hypothesized to aggravate premature neonatal lung diseases ***(Lykkedegn et al., 2015).***

Vitamin D has anti-inflammatory properties and modulates lung growth. Vitamin D directly increase fetal alveolar type 2 cell (AT2C) growth by 26% ***(Mandell et al., 2013).***

Animal experiments have demonstrated that 25(OH)D plays an important role in pulmonary maturation and also enhances steroid activity***(Ataseven et al., 2013).***

AIM OF THE WORK

This study aimed at investigating serum level of vitamin D (25(OH)D) as risk factor for development of RDS in preterm neonates.

PREMATURITY

Premature birth is a significant cause of infant morbidity and mortality. In the United States, the premature birth rate, which had steadily increased during the 1990s and early 2000s, has decreased annually for four years and is now approximately 11.5% ***(Glass et al., 2015)***.

Prematurity remains a global health problem. In addition, prematurity is associated with learning and motor disabilities and with visual and hearing impairment, contributing to approximately half of disabilities in children. Although preterm birth has actually decreased in the United States over the past five years, worldwide rates have increased over the last decade ***(Hamilton et al., 2013).***

"Preterm birth" is defined as any birth prior to 37 weeks' completed gestation or fewer than 259 days since the first day of the mother's last menstrual period ***(Spong, 2013).***

Recently, the premature birthrate has decreased. Preliminary data for 2012 show a preterm birth rate of 11.5%, compared to a maximum of 12.5% in 2009 ***(Hamilton et al., 2013).***

Risk factors for preterm birth:

Risk factors associated with preterm labor and deliveries include the following socio-demographic and obstetric factors (Table 1):

Table (1): Causes of preterm birth ***(Robinson, 2016).***

Identifiable causes of preterm birth
Fetal:
▪ Fetal distress. ▪ Multiple gestations. ▪ Erythroblastosis. ▪ Nonimmune hydrops.
Placental:
▪ Placental dysfunction. ▪ Placenta previa. ▪ Abruptio placentae.
Uterine:
▪ Bicornuate uterus. ▪ Incompetent cervix (premature dilatation).
Maternal:
▪ Preeclampsia. ▪ Chronic medical illness (cyanotic heart disease, renal disease) infection (Listeria monocytogenes, group B streptococcus, urinary tract infection, bacterial vaginosis, chorioamnionitis). ▪ Drug abuse (cocaine).
Other:
▪ Premature rupture of membranes. ▪ Polyhydramnios. ▪ Iatrogenic. ▪ Trauma.

Normal lung development:-

A simplified sequence of development includes several stages: embryonic, pseudoglandular (8–17 weeks), canalicular (16–23 weeks), saccular (23–32 weeks), and alveolar (overlaps saccular-postnatal) ***(Glass et al., 2015).***

Complications of prematurity:

Respiratory-related concerns, specifically apnea of prematurity and accompanying intermittent hypoxemia, are universal in extremely preterm infants and are one of the predominant reasons for extended hospital care. Even with aggressive intervention including supplemental oxygen, mechanical ventilation and pharmacological therapies, cardiorespiratory events not only continue to occur but also increase during early postnatal life ***(Di Fiore et al., 2015).***

Studies in neonates have shown an association between early exposure to apnea and intermittent hypoxia and both short- and long-term consequences including retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), sleep-disordered breathing and neurodevelopmental impairment ***(Di Fiore et al., 2015).***

a) <u>Apnea of prematurity:</u>

Although apnea of prematurity (AOP) is a developmental and thus self-resolving disorder, it may result in extremely frequent or prolonged episodes of intermittent hypoxemia/ bradycardia ***(Di Fiore et al., 2015).***

Apnea of prematurity is most widely defined as a cessation of breathing lasting more than 15 to 20 s or more than 10 s if associated with oxygen desaturation (SpO2 ⩽ 80 to 85%) and/or bradycardia (heart rate <80 b.p.m. or ⩽2/3 of baseline) in infants born less <37 weeks gestation ***(Finer et al., 2006).***

b) Retinopathy of prematurity:

ROP is a vasoproliferative disorder of the retina that can result in significant visual loss. It is a consequence of perturbations in retinal vascular development triggered by multiple factors, including oxygenation level ***(Chen and Smith, 2007).***

Two studies have documented a significant association between intermittent hypoxic episodes and the development of severe ROP in preterm infants ***(Di Fiore et al., 2010).***

c) Neurological outcomes:

The neurologic sequelae of prematurity and its treatment impart life-long structural and functional impairments. Similar to the response of the lung, injury to the brain correlates highly with gestational age. Even with the dramatic changes in management over the last two decades (e.g., prenatal steroids, avoiding postnatal steroids, easy access to surfactant), the rates of neuro-developmental abnormalities among ex-preterm infants remain high ***(Hutchinson, 2013).***

The most frequent injuries noted in the premature brain are periventricular-intraventricular hemorrhage (PV-IVH) including periventricular hemorrhagic infarction and periventricular leukomalacia (PVL) ***(Steven and Sunil, 2006).***

d) Patent ductus arteriosus (PDA):

Patent ductus areteriosus (PDA) -typically presents as pulmonary vascular pressures begin to fall. If untreated, it may result in increasing left-to-right shunt and ultimately cause heart failure, manifested by respiratory decompensation and cardiomegaly ***(Honrubia and Stark, 2004).***

e) Neonatal sepsis:

Preterm infants, however, remain at high risk of early onset sepsis and its sequelae. They are also at risk for hospital-acquired sepsis. Neonatal survivors of sepsis can have sever neurologic sequelae due to central nervous system infection, as well as from secondary hypoxemia resulting from septic shock, persistent pulmonary hypertension, and sever parenchymal lung disease ***(Puopolo, 2008).***

RESPIRATORY DISTRESS SYNDROME

RDS, also known as hyaline membrane disease, is caused by pulmonary surfactant deficiency in the lungs of neonates, most commonly in those born at<37 weeks gestation. The risk of developing into RDS increased with decreasing of gestational age and birth weight; the incidence rate is 80% in infants <28 weeks gestation, 60% at 29 weeks, and 15-30% at 32-34 weeks, but declined with maturity to 5% at 35-36weeks and is almost 0% by 39 weeks gestation ***(Liu et al., 2010).***

Causes of RDS:

RDS of prematurity is a major cause of morbidity and mortality is preterm infants. Primarily, respiratory distress syndrome is caused by deficiency of pulmonary surfactant. As most alveolar surfactant is produced after about 30-32 weeks gestation, preterm infants born before then will probably develop RDS ***(Farser et al., 2004).***

Further study on infant RDS found that the deficiency of surfactant was a consequence of either insufficient production by the immature lungs or a genetic from of the disease is not associated with premature birth and occurs in full-term babies ***(Nkadi et al., 2009).***

Surfactant formation and physiology:

Surfactant is a complex lipoprotein composed of 6 phospholipids and 4 apoproteins. Surfactant recovered by alveolar wash from most mammals contains 70-80% phospholipids, 8-10% protein, and 10% neutral lipids, primarily cholesterol. Although it is a marker for lung maturity, it is not necessary for normal lung function ***(Sun et al., 2015).***

Pulmonary surfactant is a lipoprotein complex located on the surface of the lung alveoli. Surfactant reduces surface tension and participates in host defense and the control of inflammation in the lung ***(Phokela et al., 2005).***

The pulmonary surfactant is produced by the AT-2C of the lung. It is essential for efficient exchange of gases and maintain the structural integrity of alveoli. Surfactant is a secretory product composed of lipids and proteins ***(Akella and Deshpande, 2013).***

The major phospholipid component dipalmitoyl phosphatidylcholin reduces the surface tension in the alveoli and maintains alveolar expansion at the end of expiration. The proteins are mainly the four apoproteins, surfactant protein A, B, C, and D (SP-A, SP-B, SP-C, and SP-D). The hydrophilic SP-A and SP-D apoproteins are a defense against infections and inflammation ***(Akella and Deshpande, 2013).***

SP-A and SP-B (and, to a lesser extent, SP-C) promote the formation of the surfactant monolayer, which is the functionally active form of surfactant and possesses the surface-active properties ***(Akella and Deshpande, 2013).***

Whereas mutations in the SP-C-gene have been associated with neonatal RDS and interstitial lung disease, the absence of SP-B has led to respiratory failure and death shortly after birth ***(Bersani et al., 2012).***

In humans, premature birth before the 34th gestational week is associated with RDS, a disease characterized by structural lung immaturity and inadequate surfactant production. RDS is a major cause of death in extremely premature neonates, where birth before the 24th gestational week is at the limit of survival despite modern intensive care. In humans, premature infants born before 32 week of gestation have low concentrations of SP-A and SP-B and barely detectable levels of SP-C ***(Bersani et al., 2012).***

After birth, the concentration of SP-A increases rapidly, whereas SP-B and particularly SP-C increase more slowly ***(Ballard et al., 2003).***

Antenatal corticosteroids protect to some degree against RDS when given to mothers with potential preterm labor from 24–34 week of gestation ***(Samtani et al., 2005).***

The corticosteroids stimulate fetal lung maturation, including AT-2C differentiation and pulmonary surfactant synthesis ***(Halliday, 2008).***

Risk factors of RDS:

1. **Prematurity:** Prematurity is the most important risk factor predisposing to neonatal RDS ***(Goraya et al., 2001).***

2. **Sex:** Boys are more likely to develop RDS than girls and more likely to die from the disease ***(Maly et al., 2000).***

3. **Race:** RDS has been reported in all races worldwide occurring most often in preterm infants of Caucasian ancestry ***(Hintz et al., 2007).***

4. **Apgar score:** The incidence of RDS increases in neonates with apgar scores less than or equal to 3 at one and five minutes ***(Rubatelli et al., 1998).***

5. **Birth weight:** The incidence of neonatal RDS is higher in babies with low birth weight (LBW) (<2500grams), than those with normal birth weight (2500-3999grams) according to ***(Welty et al., 2005).***

6. **Genetic:** Genetic disorders of surfactant production and metabolism include surfactant protein B and surfactant protein C gene mutations, and mutations of the ABCA3, whose product is an adenosine triphosphate (ATP)-binding cassette transporter localized to the lamellar bodies of AT-

2C. These rare disorders cause a sever RDS —like pictures, often in term infants, and are usually fatal without lung transplantation ***(Bhakta, 2008).***

7. **Familial predisposition:** In some families, several relatively mature babies have developed RDS. The reason for this is unknown, but it is presumably because of an inherited abnormality in surfactant synthesis ***(Greenough et al., 2004).***

8. **Perinatal asphyxia:** The association between asphyxia and RDS is also influenced by the fact that hypoxia and acidemia predispose to pulmonary hypertension and hypoperfusion, with a right to left shunt, a reduction in surfactant synthesis by inhibiting synthetic enzymes and muscle hypotonia, which reduces the baby's respiratory efforts, resulting in a diminished lung fluid removal and less surfactant secretion ***(Greenough et al., 2004).***

9. **Twin pregnancy:** Second-born twins: The second twin is much more likely to develop RDS since it has an increased chance to be asphyxiated ***(Pramanik, 2002).***

10. **Chorioamnionitis:** Recent data suggest that up to 60% of very immature preterm infants may have been exposed to chorioamnionitis, and a proportion of them may be born with inflamed lungs or signs of fetal inflammatory response ***(Lahra and Jeffery, 2004).***

Pathophysiology of RDS:

In premature infants, RDS develops because of impaired surfactant synthesis and secretion leading to atelectasis, ventilation-perfusion (V/Q) inequality, and hypoventilation with resultant hypoxemia and hypercarbnia. Blood gases show respiratory and metabolic acidosis that cause pulmonary vasoconstriction, resulting in impaired endothelial and epithelial integrity with leakage of proteinaceous exudate and formation of hyaline membranes (hence the name) ***(Serrano et al., 2006).***

The relative deficiency of surfactant decreases lung compliance and functional residual capacity, with increased dead space. The resulting large V/Q mismatch and right-to-left shunt may involve as much as 80% of the cardiac output ***(Serrano et al., 2006).***

Hypoxia, acidosis, hypothermia, and hypotension may impair surfactant production and/or secretion. In many neonates, oxygen toxicity with barotraumas and volutrauma in their structurally immature lungs causes an influx of inflammatory cell, which exacerbates the vascular injury, leading to BPD. Antioxidant deficiency and free-radical injury worsen the injury ***(Serrano et al., 2006).***

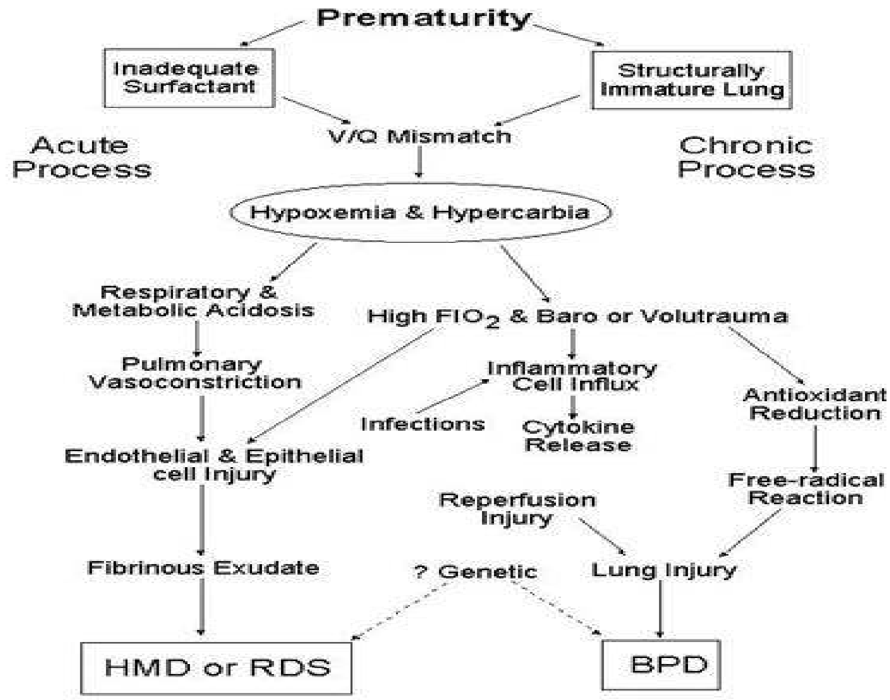

Fig. (1): Schematic outlines the pathology of RDS ***(Serrano et al., 2006).***

Diagnosis of RDS:

Diagnosis of RDS is based on a clinical picture of a premature infant with the onset of progressive respiratory failure shortly after birth, in conjunction with a characteristic chest radiograph ***(Wambach and Hamvas, 2015).***

Clinical presentations of RDS:

RDS is a condition of pulmonary insufficiency that in its natural course commences at or shortly after birth and increases in severity over the first 2 days of life. If left untreated, death