INTRODUCTION

Prematurity is defined as a birth that occurs before 37 completed weeks of gestation. It is associated with approximately one-third of all infant deaths. Complications of prematurity are the underlying reasons for the higher rate of infant mortality and morbidity in preterm infants compared to full term infants ***(Blencowe et al., 2012)***.

Respiratory distress syndrome (RDS), formerly known as hyaline membrane disease, is the most common respiratory disorder of premature newborns and its incidence is directly proportional to the degree of prematurity ***(Wambach and Hamvas, 2015).***

RDS is caused primarily by deficiency of pulmonary surfactant in an immature lung. It is a major cause of morbidity and mortality in preterm infants ***(Wambach and Hamvas, 2015).***

Despite recent advances in perinatal and neonatal care in RDS prevention and treatment, a considerable number of these neonates suffer from acute kidney injury (AKI) ***(Koralkar et al., 2011)***.

AKI is a complex disorder with clinical manifestations ranging from mild dysfunction to complex anuric kidney failure. It is an important contributing factor to the morbidity and mortality of critically ill neonates ***(Vieux et al., 2010)***. The

incidence of AKI range between 8 and 24 % of neonatal intensive care unit (NICU) admissions and it rises to 25 - 66% in neonates with RDS ***(Li et al., 2012)***.

The diagnosis of AKI is problematic, as current diagnoses rely on two functional abnormalities: functional changes in serum creatinine (s Cr) [marker of glomerular filtration rate (GFR)] and oliguria. Both these are late consequences of injury and not markers of the injury itself ***(Ottonello et al., 2014)***.

Although sCr is the most practical and often used method to monitor glomerular filtration rate, its use in the neonatal period is associated with some limitations. Serum Cr measurements are dependent of muscle mass, hydration status, sex and age ***(Libório et al., 2014)***.

During the first 48–72 h of life, neonatal sCr still reflects maternal levels and these values may decline at varying rates over days, depending on gestational age. Thereby, the levels of SCr during the first week after birth and its changes (or lack of change) may be difficult to interpret ***(Momtaz et al., 2014)***.

Moreover, s Cr concentrations may not change until 25–50% of the kidney function has already been lost and, at lower GFR, sCr will overestimate renal function due to tubular secretion of sCr ***(Ottonello et al., 2014)***.

CysC is a cysteine proteinase inhibitor with a molecular mass of 13 kDa that is expressed in all nucleated cells. CysC is produced at a constant rate and it is solely cleared by the kidneys **(*Angelidis et al., 2013***). Moreover, CysC is independent of body composition and size. It is believed that serum CysC (sCysC) does not cross the placenta and thus it truly reflects the renal `function of neonates in early postnatal life ***(Libório et al., 2014)***.

Early diagnosis of AKI helps in timely intervention to have favorable outcome ***(Peralta et al., 2011)***. Given the importance of the early diagnosis and treatment of AKI, there has been much recent focus on the discovery of novel biomarkers.

AIM OF THE WORK

To investigate the utility of serum cystatin C as a predictor of acute kidney injury in preterm neonates with respiratory distress syndrome.

PREMATURITY

Prematurity is a term for the broad category of neonates born at less than 37 weeks' gestation following onset of the last menstrual period. Different degrees of prematurity are defined by gestational age (GA) or birth weight (BW) ***(Blencowe et al., 2012)***.

Prematurity is associated with approximately one-third of all infant deaths. Complications of prematurity are the underlying cause of the higher rate of infant mortality and morbidity in preterm infants compared to full term infants ***(Blencowe et al., 2012)***.

The risk of complications increases with increasing immaturity. Thus, infants who are extremely premature, born at or before 25 weeks of gestation, have the highest mortality rate (about 50%) and if they survive, are at the greatest risk for severe impairment ***(Mathews and Mac Dorman, 2008)***.

Complications of the premature infant are divided into short-term complications (eg, respiratory and cardiovascular complications), which occur in the neonatal period, and long-term sequelae (eg, neurodevelopmental disabilities such as cerebral palsy) in patients who survive and are discharged from the NICU ***(Mandy, 2016)***.

Initial stabilization of a premature infant in the delivery room is important because proper management can reduce the

risk of short and long term complications. As an example, initiation of continuous positive airway pressure or the early administration of surfactant in very preterm infants can reduce the risk of RDS ***(Mandy, 2016)***.

Incidence:

Worldwide, the preterm birth rate is estimated to be about 11% (range 5 % in parts of Europe to 18 % in parts of Africa), and about 15 million children are born preterm each year (range 12 to 18 million). Of these preterm births, 84% occurred at 32 to 36 weeks GA, 10% occurred at 28 to <32 weeks GA, and 5 % occurred at <28 weeks GA ***(Blencowe et al., 2012)***.

Mortality:

Low BW and prematurity are major contributors to infant mortality ***(De Araújo et al., 2012)***, the shorter the term of pregnancy, the greater the risks of mortality and morbidity for the baby primarily due to the related prematurity. Preterm-premature babies have an increased risk of death in the first year of life (infant mortality), with most of that occurring in the first month of life (neonatal mortality).Worldwide, prematurity accounts for 10% of neonatal mortality, or around 500,000 deaths per year. In the U.S. where many infections and other causes of neonatal death have been markedly reduced, prematurity is the leading cause of neonatal mortality at 25% ***(Mathew and MacDorman, 2006)***.

Risk factors for preterm birth:

Risk factors associated with preterm labor and deliveries include the following sociodemographic 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.

Table (2): Problems of Prematurity ***(Stoll et al., 2010)***

Respiratory	Perinatal depression, RDS, aspiration, apnea, BPD
Temperature	Hypothermia or hyperthermia
GI – Nutritional	Poor sucking/swallowing reflexes, ↓intestinal motility, delayed gastric emptying, deficient lactase enzymes, ↓stores (Ca, PO4), NEC
Hepatic	↓Conjugation & excretion of bilirubin & ↓ vitamin Kdependent clotting factors
Renal	metabolic acidosis, ↓renal elimination of drugs, electrolyte imbalance (hypo/hypernatremia, hyperkalemia or renal glycosuria
Immunologic	↑Risk of infection
Neurological	Perinatal depression, IVH, PVL
Cardiovascular	Hypotension, PDA, CHF
Hematological	Anemia, ↑bilirubin, DIC, hemorrhagic disease
Metabolic	Hypocalcemia, hypo/hyperglycemia
Ophthalmologic	Retinopathy of prematurity

RDS: respiratory distress syndrome, BPD: bronchopulmonary dysplasia, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus, CHF: congestive heart failure, IVH: intraventricular hemorrhage, PVL: periventricular leukomalacia, DIC: disseminated intravascular coagulopathy.

Respiratory Distress Syndrome

RDS, formerly known as hyaline membrane disease, is the most common respiratory disorder of premature newborns and its incidence is directly proportional to the degree of prematurity. This disorder is caused primarily by deficiency of pulmonary surfactant in an immature lung (Figure 1). It is a major cause of morbidity and mortality in preterm infants ***(Saker, 2016)***.

Pathophysiology of RDS:

The primary cause of RDS is deficiency of pulmonary surfactant, which is developmentally regulated. The fetal lung is filled with fluid and provides no respiratory function until birth. In preparation for air breathing, surfactant is expressed in the lung during the third trimester of pregnancy. Surfactant reduces the alveolar surface tension, thereby facilitating alveolar expansion and reducing the likelihood of alveolar collapse atelectasis ***(Martin and Fanaroff, 2013)***.

Because of the developmental regulation of surfactant production, the most common cause of surfactant deficiency is preterm delivery. In addition, mutations in the genes encoding surfactant proteins SP-B and SP-C and the ATP-binding cassette (ABC) transporter A3 (ABCA3) may cause surfactant deficiency and/or dysfunction, and hereditary respiratory failure in infants born at term ***(Wert et al., 2009)***.

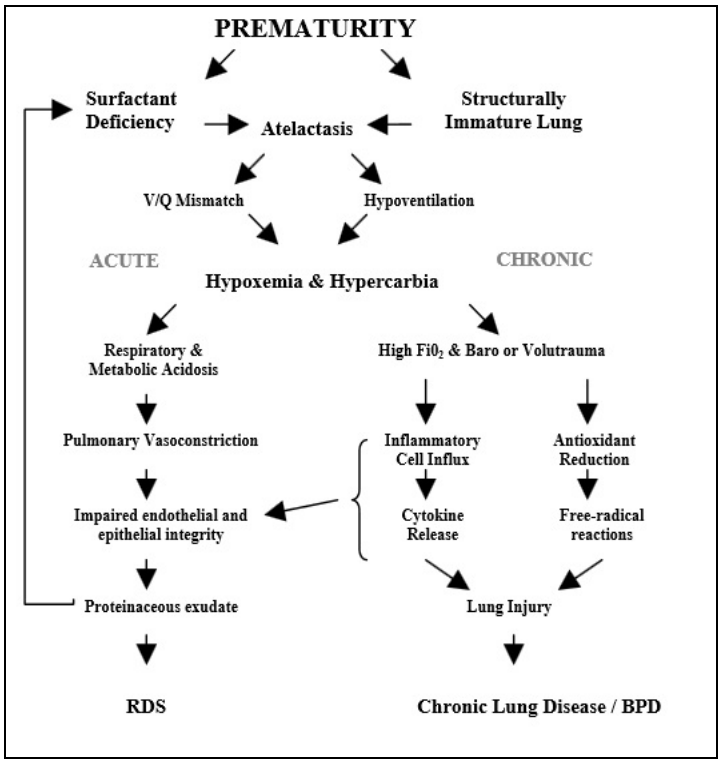

Figure (1): Pathogenesis of neonatal **RDS** ***(Ainsworth, 2005)***

Surfactant is synthesized within the alveolar type II cells starting with phospholipid synthesis in the endoplasmic reticulum, and then is processed through the Golgi apparatus to the lamellar bodies. Phospholipids combine with the surfactant proteins SP-B and SP-C to form the surfactant lipoprotein complex within the lamellar bodies. Lamellar bodies localize to the apical surface of the type II cell and are released into the alveoli by exocytosis. In the preterm infants, both quantitative and qualitative defects of surfactant contribute to decreased surfactant activity resulting in RDS ***(Akella and Deshpande, 2013)***.

In the premature lung with inadequate surfactant activity, the resultant higher surface tension leads to instability of the lung at end-expiration, low lung volume, and decreased compliance. These changes in lung function cause hypoxemia primarily due to a mismatch between ventilation and perfusion due to collapse of large portions of the lung (atelectasis), and additional contributions of ventilation/perfusion mismatch from intrapulmonary and extrapulmonary right-to-left shunts ***(Holme and Chetcuti, 2012)***.

Surfactant deficiency also leads to lung inflammation and respiratory epithelial injury, which may result in pulmonary edema and increased airway resistance. These factors further exacerbate lung injury and worsen lung function. At the same time, abnormal fluid absorption results in inefficient clearing of lung liquid in the injured, edematous lung that also impedes gas exchange ***(Holme and Chetcuti, 2012)***.

Infants with RDS typically have low urine output contributing to fluid retention in the first few days, which may exacerbate pulmonary edema, also hyponatremia caused by the increasing free water ***(Saker, 2016)***.

Incidence of RDS:

RDS is a common cause of neonatal death and disability, and almost 50 % of neonates with BW under 1,500 g are affected by RDS. The incidence of RDS increases with

decreasing gestational age. Although the incidence is lower, RDS still occurs in a significant number of late preterm infants (GA between 34 weeks, and 36 weeks) ***(Elmas et al., 2013a)***.

Clinical manifestations of RDS:

The clinical manifestations of RDS result primarily from abnormal pulmonary function and hypoxemia. Because RDS is primarily a developmental disorder of deficient surfactant production, it presents within the first minutes or hours after birth. If untreated, RDS progressively worsens over the first 48 hours of life. In some cases, infants may not appear ill immediately after delivery but develop respiratory distress and cyanosis within the first few hours of age. These infants may have a borderline amount of surfactant that is consumed or becomes inactivated ***(Martin and Fanaroff, 2013)***.

The affected infant is almost always premature and exhibits signs of respiratory distress that include tachypnea, nasal flaring, expiratory grunting, intercostal, subxiphoid, and subcostal retractions and cyanosis. On physical examination, auscultated breath sounds are decreased, and infants may be pale with diminished peripheral pulses. The urine output often is low in the first 24 to 48 hours and peripheral edema is common ***(Wambach and Hamvas, 2015).***

Clinical course:

Prior to surfactant use, uncomplicated RDS typically progressed for 48 to 72 hours. This was followed by an improvement in respiratory function associated with increased production of endogenous surfactant, and resolution of the respiratory disorder by one week of age ***(Wambach and Hamvas, 2015)***.

The natural history of RDS is greatly modified by treatment with exogenous surfactant, which dramatically improves pulmonary function, leading to the resolution of symptoms, and shortens the clinical course. In addition, the use of continuous positive airway pressure (CPAP) has also improved the clinical course of RDS, even in infants who do not receive surfactant therapy ***(Stoll et al., 2010)***.

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)***.

Radiographic grading of RDS:

The x-ray appearances depend on the severity of the disorder, with poorly inflated lung being the cardinal feature. In mild disease the lungs show fine homogenous ground glass

shadowing (Grade 1) but when more severe, widespread air bronchogram become visible (Grade 2) followed by the development of confluent alveolar shadowing (Grade 3) leading to a complete white lung fields with obscuring of the cardiac shadow in the most severe cases (Grade 4) (Figure 2) ***(Arthur, 2001)***.

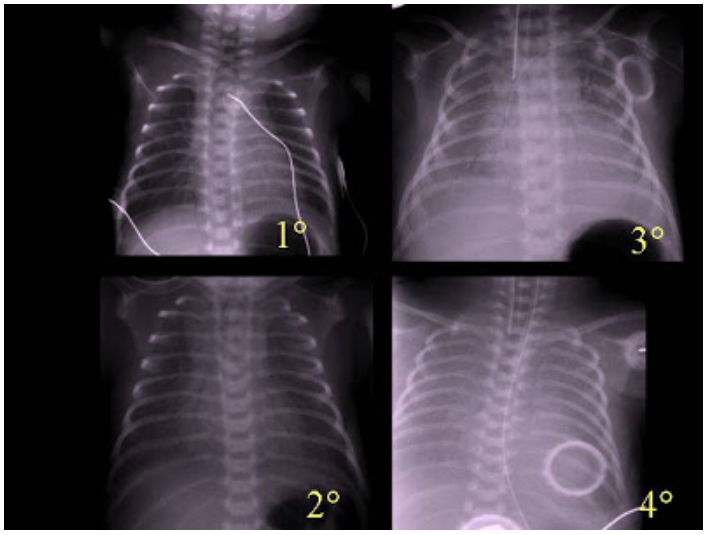

Figure (2): Chest x-ray findings in RDS (grade 1-4) ***(Arthur, 2001)***.

Laboratory findings:

Laboratory findings associated but not diagnostic for RDS include arterial blood gas measurements that typically show hypoxemia that responds to administration of supplemental oxygen. CBC and blood culture should also consider for each infant with a diagnosis of RDS because early onset sepsis can be indistinguishable from RDS on clinical ground alone. Echocardiography is a valuable diagnostic tool in the evaluation of an infant with RDS. It is used to confirm the

diagnosis of PDA as well as to document response to therapy, also to exclude congenital heart disease ***(Gomella, 2013)***.

Differential diagnosis:

The differential diagnosis for RDS includes other causes of respiratory distress, which are distinguished from RDS by their clinical features and course, as transient tachypnea of the newborn (TTN), bacterial pneumonia, air leak (eg, pneumothorax), congenital cyanotic heart disease (CCHD) and non-pulmonary systemic disorders such as hypothermia, hypoglycemia, anemia, polycythemia, and metabolic acidosis, may present with respiratory distress ***(Gomella, 2013)***.