INTRODUCTION

Preterm births continue to increase despite of major advances in prenatal care, especially in developed countries. Prematurity and low birth weight (LBW < 2500g) accounted for 11.3% and 8.5% of all infant deaths in 2013 ***(Murphy et al., 2015).***

Premature infants with surfactant deficiency are frequently managed with tracheal intubation and mechanical ventilation. They are at increased risk for gastroesophageal reflux (GER) and microaspiration especially because the used endotracheal tubes are not cuffed ***(Aly et al., 2015).***

Aspiration due to GER in premature neonates on ventilatory support carries the risk of causing ventilation associated pneumonia or lung injury and plausibly may predispose to chronic lung diseases ***(Farhath et al., 2008).***

The diagnosis of GER is difficult since clinical signs and symptoms are nonspecific. Diagnosis can also be difficult due to technical limitations. None of the currently available agents has been proven to prevent regurgitation. The efficacy and safety of GERD therapy have not been studied systematically in preterm infants ***(Winter et al., 2012).***

Detection of pepsin in tracheal aspirate samples has been proposed as a reliable marker of gastric contents and microaspiration. The role of pepsin as a marker of GER related pulmonary aspiration is emerging in neonates ***(Elabia and Zhang, 2011).***

Aim of the Work

This work aimed at evaluating the effect of positioning on tracheal aspirate pepsin levels as a marker of aspiration of gastric content in ventilated 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% ***(Hannah 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 birth rate 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:

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

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) ***(Hannah 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) Apnea of prematurity:

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 et al., 2013).***

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

d) Patent ductus arteriosus (PDA):

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 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 severe neurologic sequelae due to central nervous system infection, as well as from secondary hypoxemia resulting from septic shock, persistent pulmonary hypertension, and severe parenchymal lung disease ***(Puopol, 2008).***

RESPIRATORY DISTRESS SYNDROME

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 increases 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 35–36 weeks and is almost 0% by 39 weeks gestation. Accordingly, it is estimated that the incidence rate of RDS is at 80% for infants weighing <750 g at birth and 55% for infants weighing 750–1000 g. RDS accounted for 6.8% of cases of RDS in term or near-term infants ***(Jing et al., 2010).***

Prematurity is defined as an underdeveloped newborn child with a low birth weight that is born before 37 weeks of gestation. Other terms used to describe prematurity are: "preterm" and "preemie." Infants having a gestational age of 34 and 37 weeks are termed 'moderately premature,' those born between 29 and 33 weeks of gestation are termed 'very premature', and those born at 28 weeks of gestation or less are termed 'extremely premature ***(Swammy et al., 2008).***

Infants can also be categorized by birth weight. A low birth weight infant weighs less than 2500g, a very low birth weight infant weighs less than 1500g and an extremely low

birth weight infant weighs less than 1000g which helps in determining their true gestational age. Accurate gestational age is critical because the variation of 1 week in the determined age of an extremely premature infant (25 weeks instead of 24 weeks, for example) produces a far different set of prognostic implications. The initial complete examination at birth is the best way to assess gestational age accurately ***(Swammy et al., 2008)***.

Surfactant composition:

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. Dipalmitoylphosphatidylcholine (DPPC), or lecithin, is functionally the principle phospholipid. Phosphatidylglycerol makes up 4-15% of the phospholipids; although it is a marker for lung maturity, it is not necessary for normal lung function ***(Sun et al., 2015).***

Surfactant protein A, B, C and D (SP-A, -B, -C and -D) are the four key proteins. Despite forming a small proportion of the surfactant molecule, these proteins are vital to the stabilisation and functioning of surfactant. Without surfactant protein, DPPC is at increased risk of forming semi-crystalline domains during expiration ***(Gerber et al., 2007).***

SP-A and -D are large hydrophilic lectin proteins involved in pulmonary host defence activates phagocytic clearance by alveolar macrophages along with formation of reactive oxygen species and nitrogen intermediates , Release of neutrophil chemotactic factors by alveolar type II pneumocytes is also regulated by SP-A ***(Kresch et al., 2010).***

SP-B and -C, on the other hand, play an intricate role in sustaining alveolar ventilation. Because of their small hydrophobic properties, SP-B and -C interact with polar head groups of DPPC to form a surface-active film, which lowers surface tension and allows alveoli to maintain patency. SP-B, in particular, is crucial in the maturation of surfactant. The high level of hydrophobicity allows numerous bonds to be formed between other molecules ***(Antharam et al., 2008).***

Risk factors for RDS:

RDS frequently occurs in the following individuals (Qiu et al., 2008):

- White male infants.
- Infants born to mothers with diabetes.
- Infants born by means of cesarean delivery.
- Second-born twins.
- Infants with a family history of respiratory distress syndrome.

In contrast, the incidence of RDS decreases with the following:

- Use of antenatal steroids.
- Pregnancy-induced or chronic maternal hypertension.
- Prolonged rupture of membranes.
- Maternal narcotic addiction.

Secondary surfactant deficiency may occur in infants with the following (Qiu et al., 2008):

- Intrapartum asphyxia.
- Pulmonary infections (e.g, *group B beta-hemolytic streptococcal pneumonia*).
- Pulmonary hemorrhage.
- Meconium aspiration syndrome.
- Oxygen toxicity along with barotrauma or volutrauma to the lungs.
- Congenital diaphragmatic hernia and pulmonary hypoplasia.

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 hypercarbia. 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) ***(Holme and Chetcuti, 2012)***.

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 ***(Holme and Chetcuti, 2012)***.

Hypoxia, acidosis, hypothermia, and hypotension may impair surfactant production and/or secretion. In many neonates, oxygen toxicity with barotrauma and volutrauma in their structurally immature lungs causes an influx of inflammatory cell, which exacerbates the vascular injury, leading to bronchopulmonary dysplasia (BPD). Antioxidant deficiency and free-radical injury worsen the injury ***(Holme and Chetcuti, 2012).***

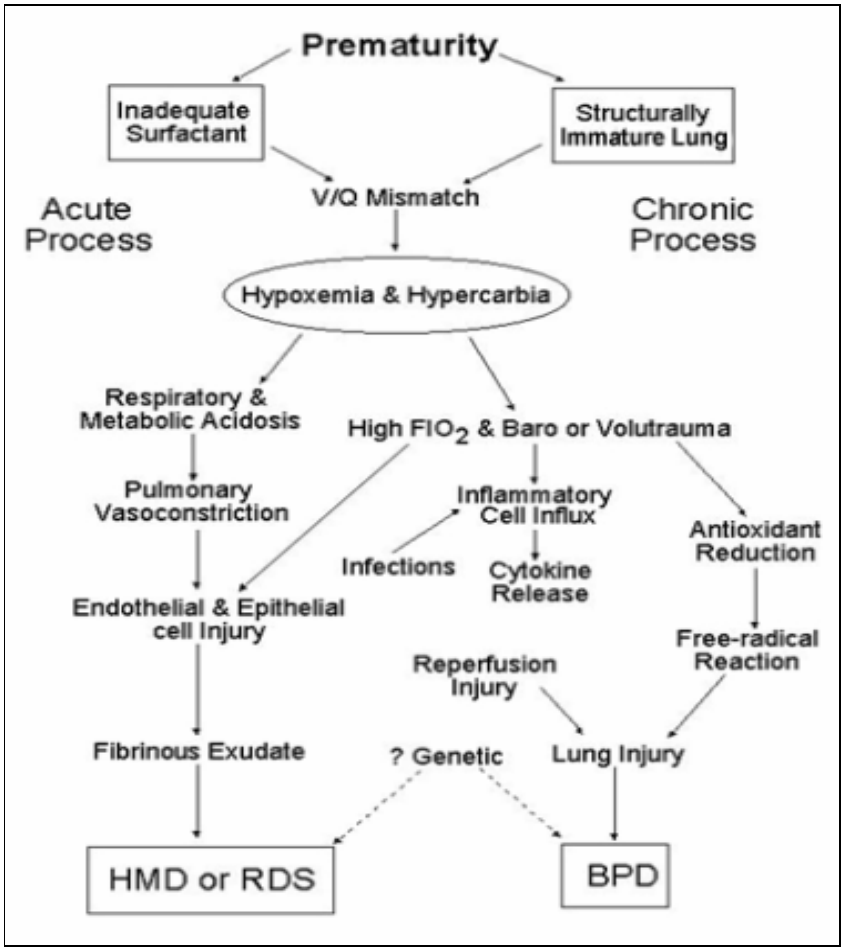

Fig. (1): Schematic outlines the pathology of RDS
(Holme and Chetcuti, 2012).

Diagnosis of RDS:

The diagnosis is made on the basis of clinical features combination including (Dushianthan et al., 2014):

- Grunting respiration.
- Intercostal recession.

- Nasal flaring.
- Cyanosis.
- Increased oxygen requirement.
- Radiological features (diffuse reticulogranular pattern with air bronchograms).

The natural history is for the clinical signs to develop within 6 hours of life, with progressive worsening over the first 48 to 72 hours of life followed by recovery according to the clinical condition.

Different scoring systems for RDS:

1- Downes score:

An index designed to objectively assess the clinical severity of hyaline membrane disease. The scores have therapeutic and prognostic significance but are not as reliable as blood gas measurements. They are to be used as an adjunct to (not as a substitute for) blood gas determinations ***(Wood et al., 1972).***

Allow the infant to stabilize for at least 5 minutes at a constant FIO2 before scoring.

Table (2): Downes Scoring-System ***(David et al., 1972).***

RDS Score	0	1	2
Cyanosis	None	Cyanotic in air	Cyanotic in 40% O_2
Retractions	None	Mild	Severe
Grunting	None	Audible with stethoscope	Audible without stethoscope
Air entry-make baby cry and listen to breath sounds while baby cries	Clear	Delayed or decreased	Barely audible
Respiratory rate	60	60 to 80	80 or apneic episodes

An RD score of 4 or more for at least 2 hours during the first 8 hours of life denotes clinical RD and requires assessment of the infant by a physician.

An RD score of 6 or more is an indication for ventilator assistance.