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An Overview on Relation between Lactate Dehydrogenase and Transient Tachypnea of The Newborn

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Abstract:

Background: Transient tachypnea of the newborn (TTN) is a self-limited respiratory condition commonly seen in term and late preterm neonates, typically occurring within the first few hours of life. It is characterized by rapid breathing due to delayed clearance of fetal lung fluid, leading to mild-to-moderate respiratory distress. TTN is usually benign but can be difficult to distinguish from more severe respiratory conditions in the early neonatal period. Lactate dehydrogenase (LDH) is a cytoplasmic enzyme found in most body tissues, including the lungs, and is released into the bloodstream in response to cellular damage or increased metabolic stress. Elevated serum LDH levels have been proposed as a potential biomarker of pulmonary inflammation or injury, which may be present even in non-severe neonatal respiratory conditions. Several studies have explored the relationship between LDH levels and neonatal respiratory diseases, including TTN. Some findings suggest that neonates with TTN may exhibit elevated LDH levels compared to healthy newborns, likely reflecting transient pulmonary stress or fluid retention in the alveoli. However, LDH levels in TTN are generally lower than those observed in more serious conditions like neonatal pneumonia or respiratory distress syndrome (RDS). Thus, LDH may help in differentiating TTN from other causes of neonatal respiratory distress, although its utility remains adjunctive and not diagnostic on its own. Understanding this relationship could assist clinicians in early risk stratification, reduce unnecessary antibiotic use, and guide further investigations when managing newborns presenting with tachypnea.

Keywords: Transient Tachypnea of the Newborn (TTN), Lactate Dehydrogenase (LDH), Neonatal respiratory distress, Pulmonary biomarkers, Fetal lung fluid, Neonatal lung injury, Early neonatal period, Respiratory morbidity in newborns, Diagnostic markers, Term and late preterm infants.

Introduction:

Transient tachypnea of the newborn (TTN) is one of the most common causes of respiratory distress in term and late preterm neonates. It typically presents within the first few hours after birth and is characterized by tachypnea, mild retractions, and increased oxygen requirement due to delayed absorption of fetal lung fluid **(1).** Although TTN is considered a benign, self-limited condition, its clinical presentation may mimic more severe pulmonary disorders such as neonatal pneumonia or respiratory distress syndrome (RDS), making early differentiation crucial for appropriate management.

Lactate dehydrogenase (LDH) is an intracellular enzyme involved in the conversion of pyruvate to lactate during anaerobic glycolysis. Elevated serum LDH levels are often associated with tissue injury or inflammation and have been studied as a potential biomarker in various neonatal and adult pulmonary conditions **(2).** In neonates, increased LDH levels may reflect pulmonary cellular stress or injury resulting from fluid retention, inflammation, or hypoxia.

Recent studies have explored the diagnostic role of LDH in neonatal respiratory distress, including TTN. While LDH levels are typically lower in TTN than in more severe conditions like RDS, they may still be elevated compared to healthy neonates, suggesting its potential as an adjunctive marker to support early differentiation of TTN from other respiratory illnesses **(3).** Early identification of TTN using biochemical markers like LDH could reduce unnecessary interventions and hospital stays.

Fetal lung fluid and TTN:

Fetal lung fluid is actively produced by the lungs rather than from amniotic fluid. The ionic composition of lung fluid is higher in chloride (Cl^-) and lower in sodium (Na^+) and bicarbonate concentration compared to amniotic fluid. Lung fluid arises from active Cl^- secretion (by type 2 pneumocytes) by the developing lung epithelium with concomitant passive flow of Na^+ and water into the fetal alveolar space **(4).**

Fetal lung fluid is critical for normal lung growth and function. Studies in fetal lambs have shown that the amount of fetal lung fluid is directly proportional to lung growth and development. Drainage of lung fluid in fetal lambs resulted in significant pulmonary hypoplasia while obstruction of outflow of lung fluid resulted in pulmonary hyperplasia and hyperexpansion **(5).**

Fetal lung fluid production increases from about 1.5 ml/kg/h in mid-gestation to 5 ml/kg/h near term to reach fetal lung volumes of 25–30 ml/kg, approximating the FRC of a term newborn. The distending pressure provided by the fetal lung fluid, which is 1 to 2 mmHg greater relative to the amniotic fluid, is essential for normal lung development **(6).**

This pressure differential also results in lung fluid to be passively expelled from the trachea into the oropharynx, where it is either swallowed or expelled, thus contributing to the amniotic fluid. From the onset of labor to the delivery of the newborn, ~100 ml of lung liquid needs to be cleared in a term newborn infant **(7).**

The primary mechanism responsible for airway liquid clearance at birth is believed to result from Na^+ uptake across the airway epithelium, which reverses the osmotic gradient leading to airway liquid reabsorption. Toward the end of gestation, there is a surge of fetal glucocorticoids and thyroid hormones that activates the Na^+ absorptive channels **(8).**

The stress of labor and birth results in the production of fetal epinephrine, which activates epithelial Na^+ channels (ENaC) and reverses the process of lung fluid secretion to fluid absorption. Aquaporin (AQ)4 and 5 (AQP4 and AQP5) water channels are expressed in type 1 alveolar pneumocytes and mediate the bulk of water transport across the apical membrane of alveolar epithelia **(9).**

AQP5 is the predominant water channel on type 1 alveolar cells. AQP1 is mainly located in pulmonary capillary endothelium. AQP5 expression has been found to be higher in TTN patients when compared to controls. It is unclear whether this upregulation of APQ5 is a contributing factor to the development of TTN or a compensatory mechanism to aid in clearing alveolar lung fluid **(4).**

The mechanical squeeze during vaginal delivery also contributes to the expulsion of the fetal lung fluid, but to a lesser extent. Most interstitial liquids move into the pulmonary circulation and some drains via the lung lymphatics. Following birth, the ongoing epinephrine surge and the abrupt rise in oxygen tension accelerate lung fluid absorption, and most of the lung liquid is cleared from the airways within 2–6 h **(8).**

Nitric oxide (NO) which is produced from l-Arginine via the enzyme NO synthase (NOS) plays a vital role in regulating pulmonary vasomotor tone and pulmonary blood flow. In fetal lambs, NO instillation into the fetal lung decreases lung liquid production. Asymmetrical dimethylarginine (ADMA) is an endogenous analog of l-arginine, which directly inhibits NOS **(10).**

ADMA levels were found to be elevated in patients with TTN compared to control newborns. While the exact mechanism is unknown, the role of ADMA in the pathogenesis of TTN may be due to a combination of increased synthesis of ADMA via protein arginine methyltransferases and reduced breakdown of ADMA via dimethyl arginine dimethylaminohydrolase(DDAH) **(6).**

TTN is thought to be influenced by the absence of the stress or hormonal influences of labor, which decreases Na+ reabsorption, resulting in fetal lung fluid retention. As air can only enter the lungs once the newborn's head is delivered and breathing starts, respiratory activity may play the final and possibly more significant role in airway liquid clearance **(5).**

Recent evidence suggests that the pathophysiology associated with TTN may not be exclusively due to lung fluid retention but also as a result from the presence of higher lung fluid volumes at the onset of respiration after birth. Greater volumes mean that more fluid must be contained within lung tissue following lung aeration, resulting in higher interstitial tissue pressures and a possibility of liquid pooling back into the airways when the lungs are at FRC **(7).**

Airway liquid clearance results from transepithelial pressure gradients generated during inspiration, which provides the pressure gradient for liquid to move across the epithelium into the surrounding lung tissue **(11).**

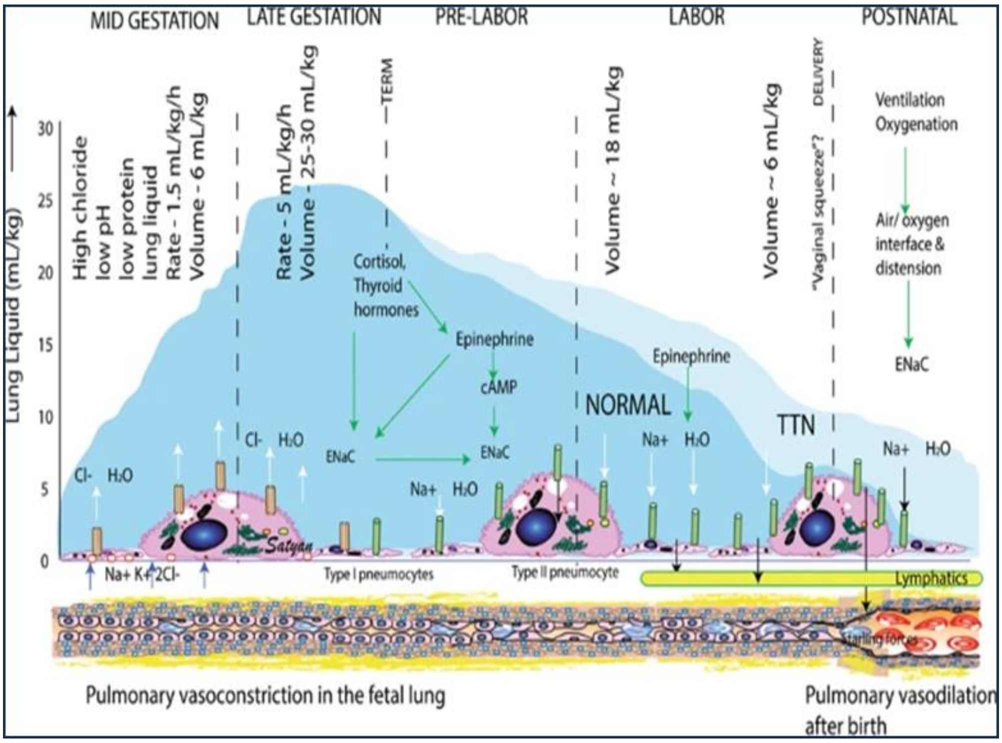

Figure (1): Illustration detailing mechanisms of lung fluid secretion and clearance during fetal gestation and after birth. During fetal gestation, type 2 alveolar pneumocytes actively secrete chloride (Cl−) into the alveolar space. Sodium (Na+) and water passively accompany Cl−. The fluid secretion peaks at 5 ml/kg/h at a maximum volume of 25–30 ml/kg in late gestation. During labor, epithelial sodium channels (ENaC) become activated by adrenergic stimulation. Basolateral Na+/K+ ATPase helps move Na+ into the interstitium along with Cl− and water. Most interstitial lung liquid moves into the pulmonary circulation; some drains via the lung lymphatics. The darker blue hue represents normal vaginal delivery, and the lighter hue represents delayed fluid resorption in TTN **(10).**

This has been shown in term newborn rabbits where pulmonary interstitial pressures increased initially from birth to 2 h and became sub-atmospheric at 5 h favoring movement of the interstitial fluid into the pulmonary capillaries. Premature rabbits also showed the same increase in interstitial pressures at 2 h, but their subsequent drop in interstitial pressures was significantly slowed in atelectatic regions, thereby promoting fluid movement from the circulation into interstitial space **(10).**

Additional studies in spontaneously breathing newborn rabbits using phase-contrast X-ray imaging have shown that lung aeration occurs almost entirely during inspiration with no liquid clearance occurring between breaths **(4).**

At birth, a term infant can generate mean inspiratory pressures of approximately −50 cm H2O (range −28 to −105 cm H2O) to achieve an inspired volume of around 40 ml. The first breaths generate even higher expiratory pressures (mean 71 cm H2O; range 18–115 cm H2O) to facilitate air distribution within the lung and promote lung fluid clearance **(9).**

Furthermore, the newborn's first breaths are characterized by short deep inspirations followed by prolonged expiratory phases through a partially closed larynx, known as expiratory braking, often observed during crying immediately after birth. Accordingly, newborns who have decreased respiratory effort at birth are at increased risk to develop TTN **(7).**

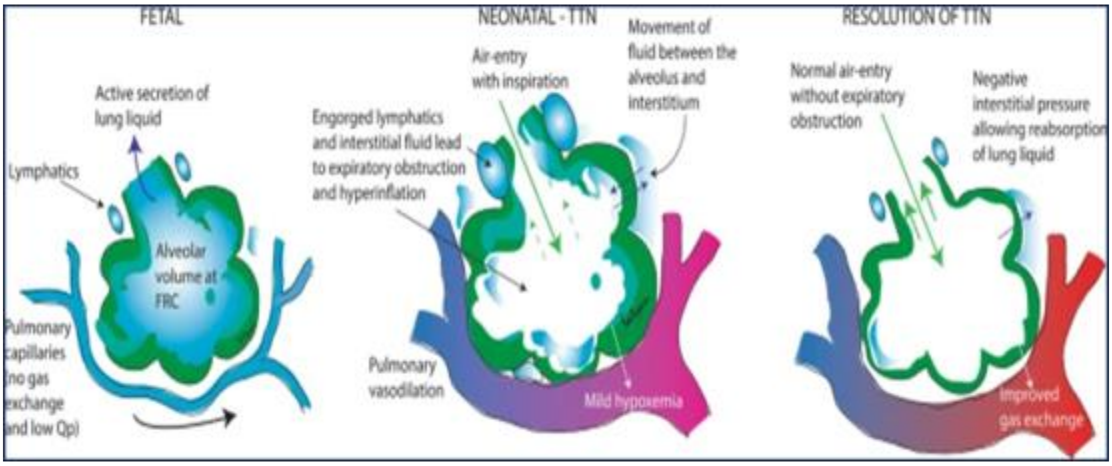

Figure (2): Airway liquid retention and role of respiration. The fetal fluid-filled lungs do not participate in gas exchange, but the lung volume approximates the functional residual capacity (FRC) of the air-filled lung after birth. Following delivery of the head and air breathing, the pressure from inspiration creates a pressure differential that promotes airway liquid to move into the lung tissue, which can raise interstitial pressure. A high interstitial pressure at end-expiration may shift fluid back into the alveoli **(10).**

LDH and TTN hypoxemia:

Lactate dehydrogenase (LDH) is an intracellular enzyme found in the cytoplasm of nearly all human tissues. Injured cells with loss of cell membrane integrity leak their LDH into the surrounding extracellular spaces. Cellular injury in newborns may be a result of different conditions, not only pre- and peri-partum, but also ongoing injury post-partum **(12).**

Measurement of plasma LDH is routinely available in most hospitals. LDH has been extensively studied in neonates and has been used as a marker of the severity of various conditions. The suggested neonatal LDH cut-off values to identify "general illness" and the need for NICU support are 600 and 800 IU/L for different sensitivities and specificities **(4).**

In asphyxiated newborns, initial LDH levels may be useful in predicting the severity of their illness and the subsequent duration of mechanical ventilation **(13).**

It is well known that enzymes leak out of cells after damage induced by ischemic hypoxemia. Lactate and LDH are considered good predictors of asphyxia. LDH is an enzyme that mediates the conversion of lactate to pyruvate as well as the reverse reaction. It is found in several organs and tissues such as the liver, heart, lungs, lymphatic tissues, and blood cells **(6).**

When cells are damaged, LDH is released out of cells into the bloodstream which elevates its level in plasma. There are several types of LDH known as isoenzymes, which are distinguished from each other by slight differences in structure and by the organs where they exist. LDH level increases in the case of hypoxia and its highest level are within 72 hours after birth. It returns to normal within the first 10 days of life **(12).**

Depending upon the type of tissue injury, the enzyme can remain elevated for up to 7 days in the bloodstream. The elevated LDH in serum as a result of organ destruction occurs due to significant cell death that results in loss of cytoplasm. Causes of tissue damage can be diseases such as acute myocardial infarction, anemia, pulmonary embolism, hepatitis, acute renal failure, etc. **(8).**

Elevated levels of more than one isoenzyme may be indicative of more than one cause of tissue damage, e.g., in conditions where pneumonia may also be associated with heart attack. Very levels of LDH appear to correlate with severe disease or multiple organ failure **(4).**

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