TTN
Transient Tachypnea of the Newborn

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TTN
"Wet Lung" Disease

Fetal and Neonatal Lung Fluid Physiology

Objectives

- Review fetal → neonatal lung fluid physiology
- Review the:
  - Clinical presentation,
  - Pathophysiology,
  - Differential diagnosis,
  - Management … of TTN

Formation and removal of fluid from fetal and neonatal lung

- Secretion of fetal lung fluid
  - Composition and dynamics of fetal lung fluid
  - Decrease of lung fluid before birth: effect of labor
  - Hormonal effects on production and absorption of fetal lung fluid
  - Mechanism of lung liquid clearance at birth: Increased epithelial cell Na transport
  - Postnatal clearance of fetal lung fluid
  - Pathways for removal of fetal lung liquid
  - Summary of postnatal clearance of fetal lung liquid

Fetal lung fluid

- Fetal lung, not the amniotic sac, is the source of fluid that fills the lung during development
  - Fetal lung is physiologically (breathing movements) and metabolically active (surfactant, **secrete** liquid into potential air spaces)
  - Intrauterine lung growth depends on balance between adequate production and controlled drainage of luminal fluid
  - Switch from placental to pulmonary gas exchange at birth requires rapid removal of fluid from the lung lumen

Fetal lung fluid

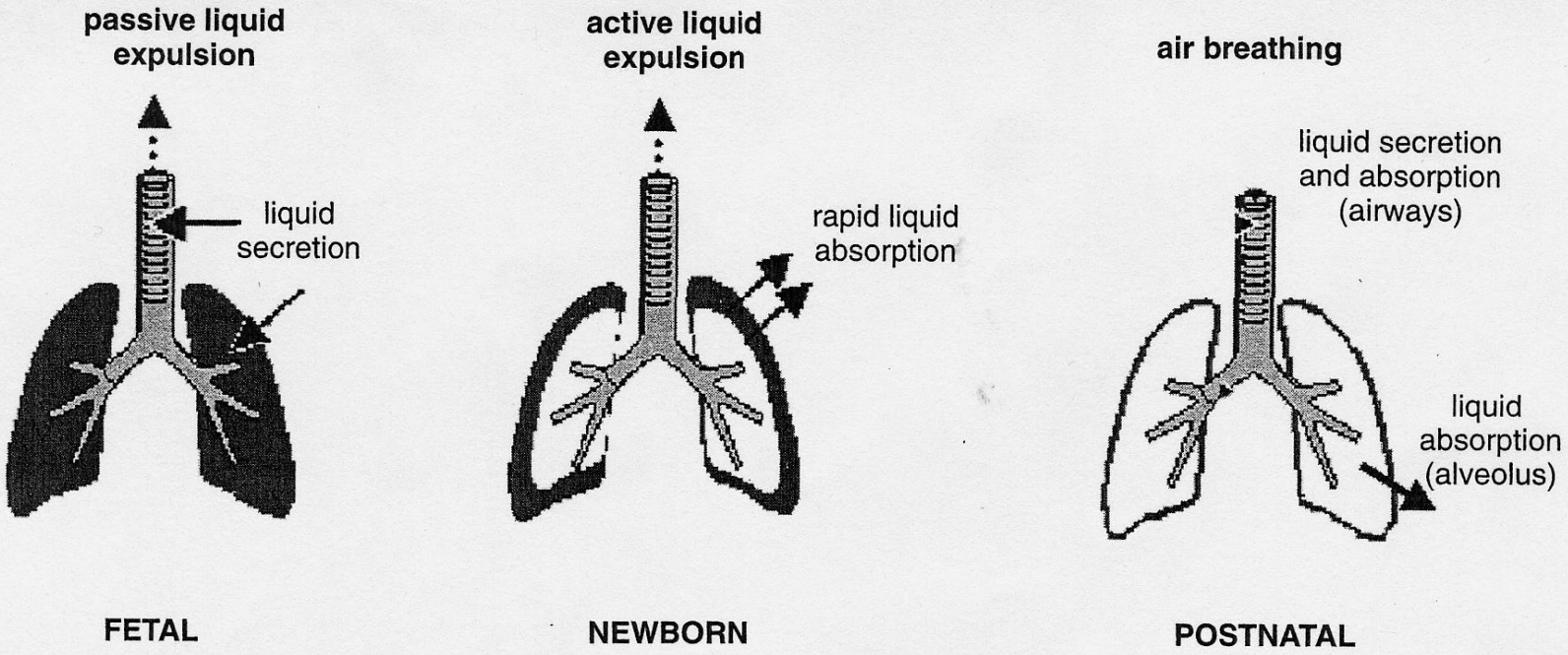


Figure 80–1. Fetal, neonatal, and postnatal phases of liquid flow across lung epithelia.

Fetal lung fluid

- Concept of " vaginal squeeze" or the mechanical compression of chest during vaginal delivery squeezing out most lung fluid through trachea into mouth is simplistic
- Recent reports show that transition from liquid (intrauterine) to air inflation (post delivery) is significantly more complex

Fetal lung fluid

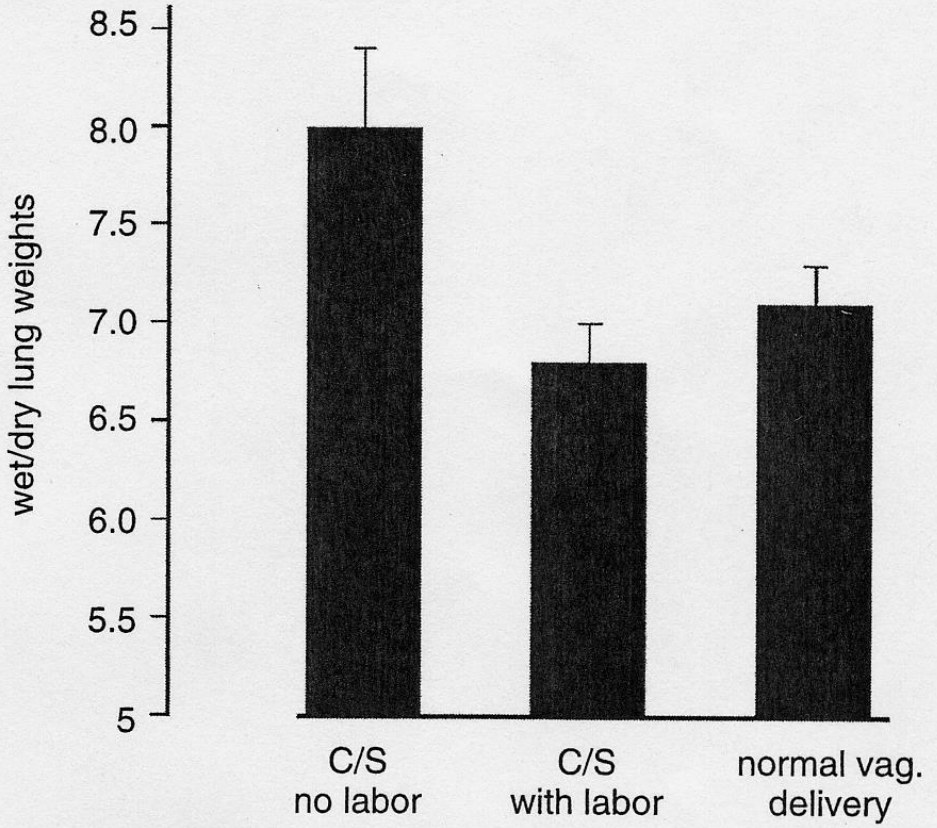


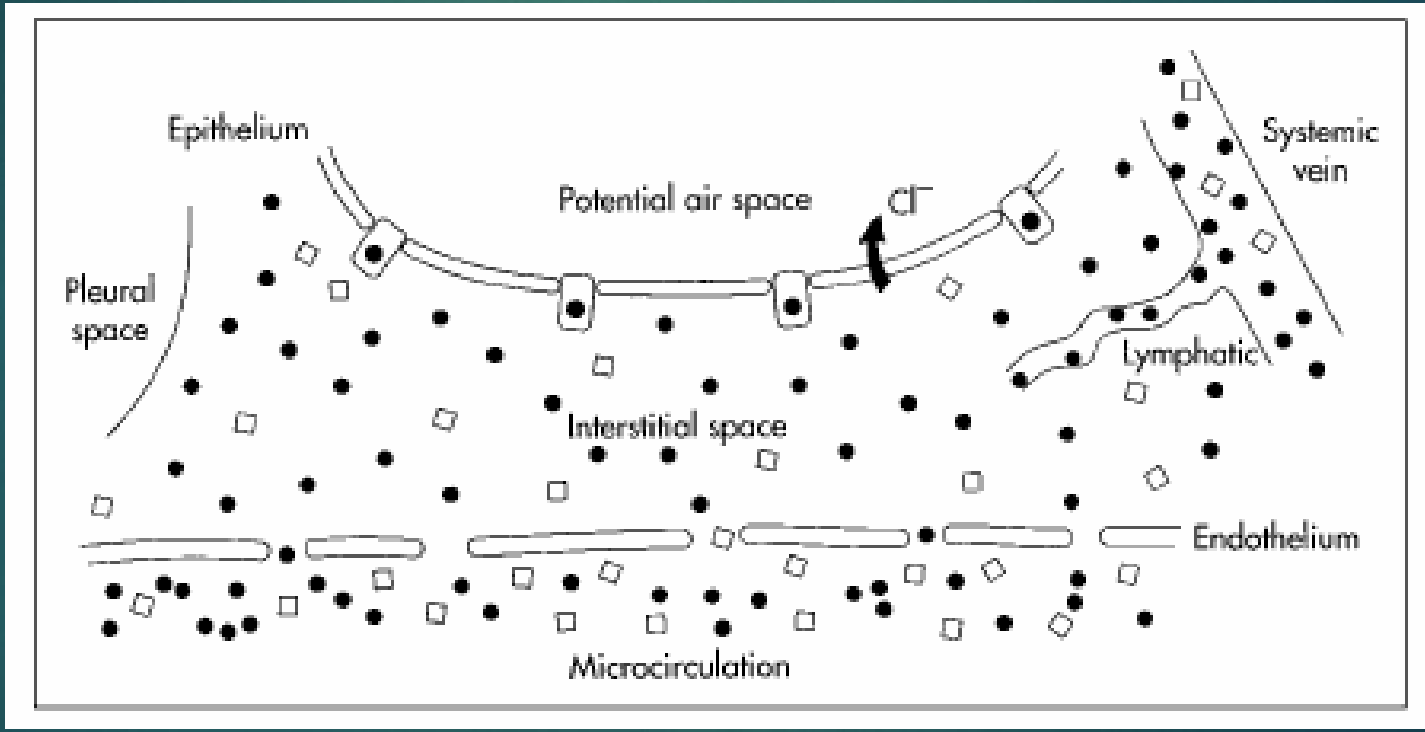
Figure 80–2. Effect of labor on lung water content (wet/dry weight) of newborn rabbit pups born after normal vaginal (vag.) delivery or by cesarean section (C/S). (Data from Bland RD, et al: Am J Obstet Gynecol *135*:364–37, 1979.)

Secretion of fetal lung fluid & lung growth

- Adequate volume of secreted lung fluid is important for normal lung growth and development (before birth)
  - Conditions with **decreased** lung fluid production (pulmonary artery occlusion, diaphragmatic hernia, oligohydramnios) inhibit fetal lung growth

Secretion of fetal lung fluid

- Schematic diagram of the fluid compartments in the fetal lung



Secretion of fetal lung fluid

- Potential air space fluid is rich in **chloride** (Cl) and has almost no protein
  - Lung epithelium have tight intercellular junctions while vascular endothelium have wider openings
  - Liquid in interstitial space has protein concentration 100 times > than in lung lumen
  - Despite large transepithelial protein osmotic pressure difference, liquid moves from pulmonary microcirculation through interstitium into potential air space
  - This is due to electro-chemical gradient across lung epithelium of about –5mV due to active chloride ion secretion

Composition and dynamics of fetal lung fluid

Table. Composition of Lung Luminal Liquid, Lymph, Plasma, and Amniotic Liquid of Fetal Lambs Late in Gestation*

	Sodium (mEq/L) [mmol/L]	Potassium (mEq/L) [mmol/L]	Chloride (mEq/L) [mmol/L]	Bicarbonate (mEg/L) [mmol/L]	pH	Total protein (g/dL) [g/L]
Luminal liquid	150±1	6.3±0.7	157±4	2.8±0.3	6.27±0.01	0.03±0.002 [0.3±0.02]
Lung lymph	147±1	4.8±0.5	107±1	25±1	7.31±0.02	3.27±0.41 [32.7±4.1]
Plasma	150±1	4.8±0.2	107±1	24±1	7.34±0.04	4.09±0.26 [40.9±2.6]
Amniotic liquid	113±7	7.6±0.8	87±5	19±3	7.02±0.09	0.10±0.01 [1.0±0.1]

*Values are mean ± SEM and are taken from the work of Adamson et al (21) and Humphreys et al (88).

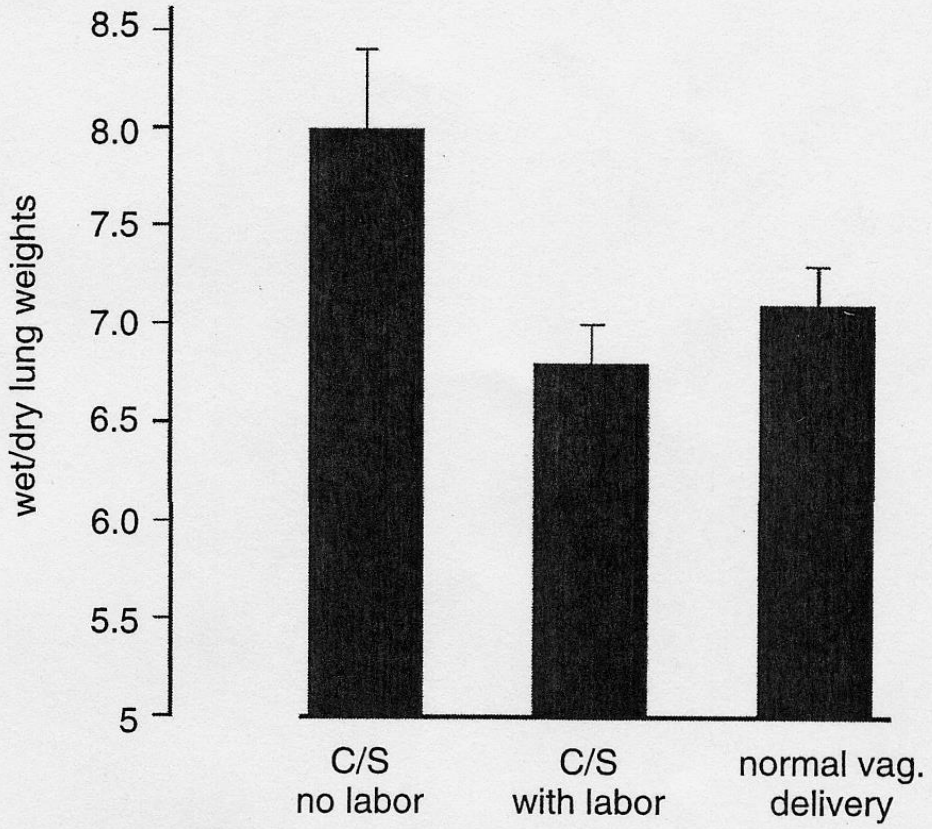
Composition and dynamics of fetal lung fluid

- Concentration of Cl^- in fetal lung lumen 50% > plasma, but Na^+ concentration identical
  - pH of lung lumen liquid 6.3
  - Hypothesis that lung epithelium in sheep may transport bicarbonate actively out of lumen
  - In fetal rat lung epithelial cells, acid pH might activate Cl^- channels, contributing to lung fluid

Decrease of lung fluid before birth: effect of labor

- Rate of lung fluid production and volume of fetal lung lumen decreases before birth, most notably during labor
  - Lung water is 25% greater after preterm birth than at term
  - Lung fluid after C/S without labor is significantly greater than when delivered vaginally or C/S after onset of labor

Decrease of lung fluid before birth



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Decrease of lung fluid before birth

Table 96–2. Data from Studies of Lung Water Content in Fetal and Newborn Lambs

Lambs	Gestation (days)	Body Weight (kg)	Plasma Protein Concentration (g/dl)	Dry Lung Weight (g)	Extravascular Lung Water / Dry Lung Tissue (g/g)
Fetuses without labor (n = 10)	138 ± 2	3.3 ± .4	3.9 ± .1	9.8 ± 1.2	12.3 ± .8
Fetuses in labor (n = 9)	139 ± 2	3.3 ± .3	4.3† ± .1	8.6 ± .9	6.8† ± .4
Newborns 6 hr after birth (n = 5)	139 ± 3	2.7 ± .1	4.7† ± .2	8.8 ± 1.3	4.3† ± .2

Values are mean ± SEM and are taken from the work of Bland, et al.[66]
†Significantly different from values for fetuses that did not have labor, $p < .05$.

Mechanism of lung fluid clearance at birth: Increased epithelial cell Na transport

- Both type I and type II cells are important for clearing fluid from lung lumen during and after birth
  - Na,K-ATPase in distal lung epithelial cells increases around birth
  - In rabbit lung epithelium, Na pump activity increases at birth and the number of Na pumps per cell increase postnatally
  - Glucocortcoids may upregulate expression of Na,K- ATPase, Na channels and aquaporins in the developing rat lung

Mechanism of lung fluid clearance at birth: Increased epithelial cell Na transport

- One potential candidate is the 7-fold increase in the ambient oxygen concentration that the respiratory epithelium "sees" at birth
  - Increased oxygen concentration around birth may have an important role in signaling the switch from Cl^- secretion to Na absorption in lung epithelium near birth

Postnatal clearance of fetal lung fluid

- 2 components of luminal fluid absorption during and after birth: Transepithelial flow of fluid from lumen into interstitium followed by flow of fluid into bloodstream by either flow directly into pulmonary circulation or via lymphatics into systemic venous circulation
  - First process is rapid to allow development of effective gas exchange and lung volume immediately after birth
  - Subsequent uptake of fluid from interstitium into vasculature or lymphatics is slower

Postnatal clearance of fetal lung fluid

- Animal data (rabbits):
  - Continues for several hours
  - Pulmonary blood volume increases with start of air breathing but lung water does not begin to decrease until 30-60 min after birth
  - Air inflation shifts residual liquid from lung lumen into distensible perivascular spaces around large pulmonary blood vessel and airways

Postnatal clearance of fetal lung fluid

- Animal data (rabbits):
  - Puddling of fluid in these connective tissue spaces, allows time for small pulmonary blood vessels and lymphatics to expel the remaining fluid with little or no impairment of lung function
  - In delivered term rabbits, perivascular fluid cuffs are of maximum size 30 min after birth and vanish by 6 hours after birth

Pathways for removal of fetal lung fluid

- Potential routes for lung fluid drainage at birth include: lung lymphatics, pulmonary circulation, pleural space, mediastinum and the upper airway
  - Lung lymphatic drainage: no more than 15%
  - Pulmonary circulation: most drainage after birth
  - Mediastinum or pleural space: minor
  - Upper airway: no more than minor role in clearing lung fluid during normal labor; may allow more fluid to escape at birth with C/S without labor

Persistent postnatal pulmonary edema

- Term newborns: TTN

- Preterm (associated conditions that may contribute to delayed fetal lung fluid removal):
  - impaired Na-pump activity in epithelial cells
  - high filtration pressure in pulmonary circulation
  - reduced microvascular surface area
  - low plasma protein osmotic pressure

Summary of postnatal clearance of fetal lung fluid

- Fluid in potential air spaces contains almost no protein
  - Pulmonary interstitial fluid has protein conc. 30mg/ml
  - Transepithelial osmotic pressure difference of >10 cm H_2O draws water from lung lumen into interstitium, as Cl^- secretion decreases and eventually stops

Summary of postnatal clearance of fetal lung fluid

- Increased activity of epithelial Na pumps/Na, K-ATPase during labor provides main driving force for lung fluid absorption
  - Transpulmonary pressure associated with lung inflation drives bulk flow of fluid from lung lumen into the interstitium
  - Together, these increase protein osmotic pressure difference between plasma and interstitial fluid

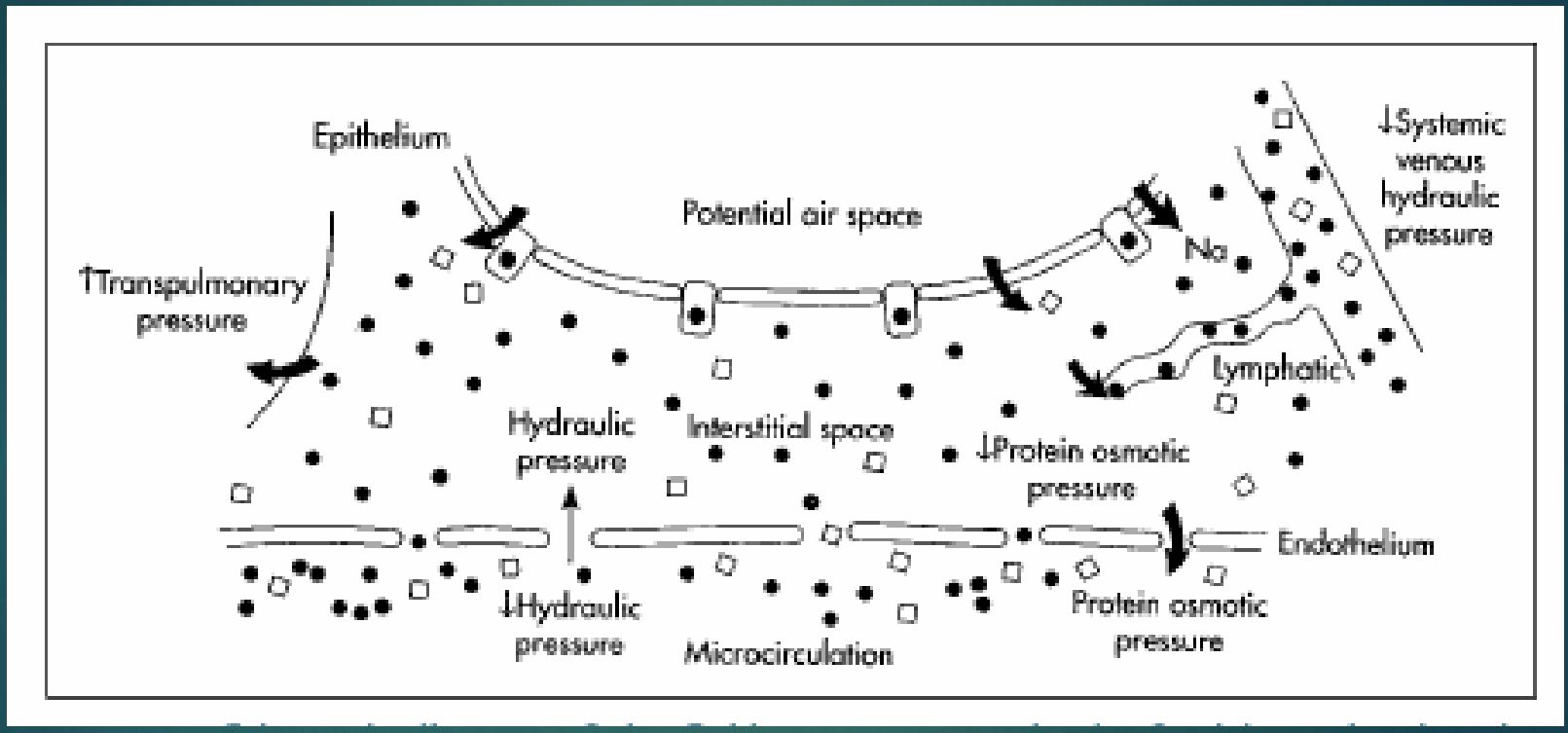
Summary of postnatal clearance of fetal lung fluid

- Air entry into lungs not only displaces liquid, it also decreases hydraulic pressure in pulm. circulation, and increases pulmonary blood flow, which in turn, increases lung blood volume and effective vascular surface area for fluid uptake
  - These circulatory adjustments facilitate absorption of liquid into pulmonary vascular bed
  - About 10-15% of luminal liquid exits lungs through lymphatics into the systemic venous system

Summary of postnatal clearance of fetal lung fluid

- With spontaneous breathing, postnatal reduction in intrathoracic pressure decreases systemic venous pressure, which may augment lymphatic drainage, but most of displaced liquid from lung lumen enters the pulmonary microcirculation

Summary of postnatal clearance of fetal lung liquid



TTN – Clinical presentation

- Clinical characteristics:
  - Mild, self-limiting disease
  - Late Preterm or Term infants
  - Tachypnea (within the first 6 h after birth); mild retractions or mild cyanosis; ± grunting
  - Good air entry with crackles/rales
  - ABG may show mild hypoxemia
  - Supplemental O2 less than 40%
  - Respiratory failure is rare
  - Usually resolve in 12-24 hours, but can last up to 48-72 hours

TTN - Pathophysiology

- Pathophysiological mechanism: delayed fetal lung fluid absorption
  - Fluid accumulates in bronchovascular spaces and peribronchial lymphatics
  - Air trapping and hyperinflation due to compression and bronchiolar collapse
  - Decreased lung compliance leading to respiratory distress and increased work of breathing (tachypnea, retractions, etc)

TTN - Risk factors

- Premature delivery, precipitous birth
- C/S delivery without labor
  - Impaired lung fluid clearance after C/S when chest is not subjected to the same pressures as in "vaginal squeeze" during vaginal birth

TTN - Risk factors (cont.)

- Effects of delivery by C/S on lung mechanics and lung volume *(Milner et al, Arch. Dis. Child 1978)*
  - SVD vs C/S: Thoracic gas volume (ml/kg) 32.7 vs 19.7
  - Chest circumference same in both groups
  - Conclusion: C/S infants have high volumes of interstitial and alveolar fluid with decreased thoracic gas volume

- Establishment of FRC in infants delivered vaginally vs elective C/S. *(Hagevik, Early Hum Dev 1991)*
  - Conclusion: Failed to show higher FRC in vaginally delivered infants

TTN - Risk factors (cont.)

- Delayed cord clamping
- Male gender, macrosomia, multiple gestations
- Birth to an asthmatic mother: may be related to an altered sensitivity to catecholamines which may delay lung fluid clearance

- Less consistent associations:
  - excessive sedation
  - prolonged labor
  - large volume of IV fluids administered to mother

TTN - Differential diagnoses

- Pneumonia/sepsis
- RDS
- Cyanotic congenital heart disease
- Central hyperventilation
- Others: MAS, PPHN and polycythemia

- Differentiation from pneumonia or MAS may be difficult if postnatal history includes risk factors for these

TTN – Evaluation and Management

- NPO; IVF
- Work up and diagnosis
  - Labs:
    - CBC with differential
    - ABG
    - Blood culture (± antibiotics?)
  - Chest X ray

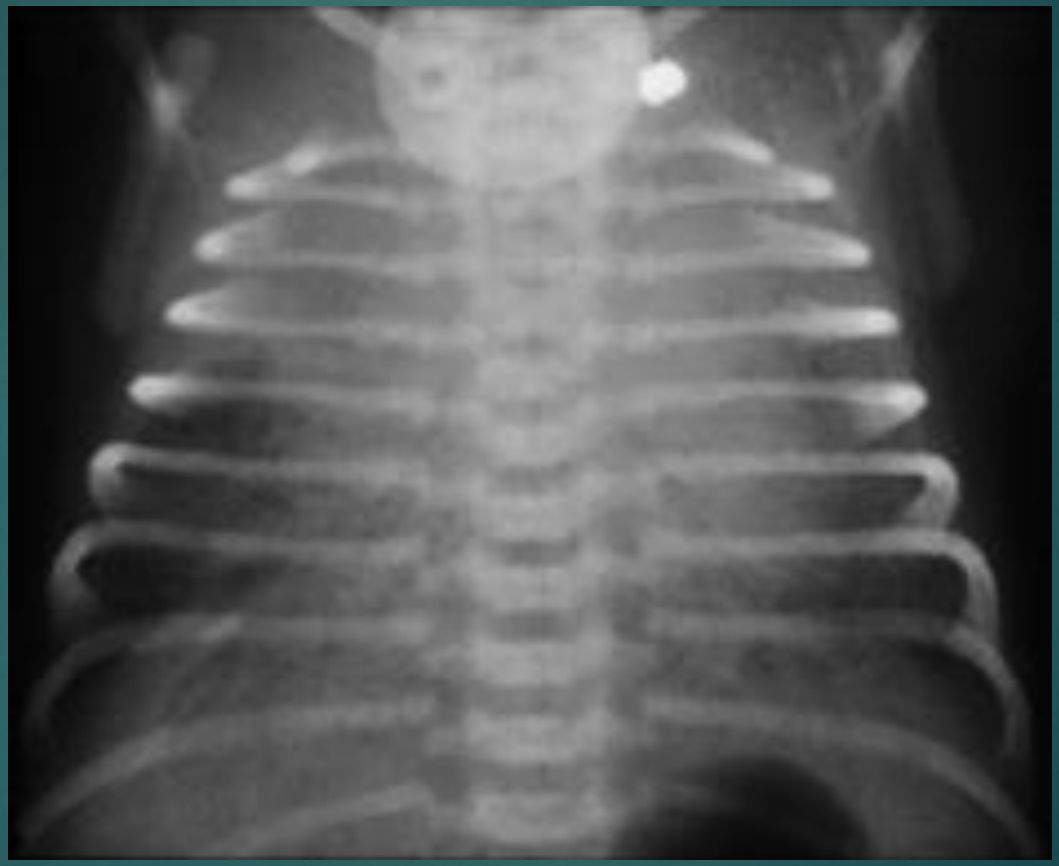
CXR: MAS mimics TTN

TTN

- X ray: characteristic findings
  - Prominent perihilar streaking which may represent engorgement of peri-arterial lymphatics and bronchovascular spaces
  - Mild-moderate cardiomegaly
  - Coarse, fluffy densities due to liquid filled alveoli
  - Fluid in the minor fissure and/ or the pleural space
  - Hyperinflation

- Xray findings clearance within 48 hours and sooner (depending on respiratory support)

TTN



TTN

TTN – Management (cont.)

- Evaluation, monitoring and basic supportive care must include consideration of the differential diagnoses
- Respiratory support may need to be escalated: O2 support via NC, CPAP or NIMV, etc
- Antibiotic coverage may need to be started (independent of maternal infectious considerations – e.g. PPRM, fever, GBS status, etc) and stopped at 36-48 hours of negative cultures.

TTN – Management (cont.)

- • RCTs investigating the effect of Furosemide (Lasix) on TTN
  - Orally *(Pediatrics, 1985)*
  - IV *(J Paediatr Child Health, 2006)*

- No effect on clinical course of TTN

TTN - Prognosis

- Self-limiting disease with no risk for recurrence or residual pulmonary dysfunction

Association of TTN and childhood asthma *(Birnkrant et al. Pediatr Pulmonol. 2006)*

- Sampling of 18,379 term infants (1996-2000)
  - Case control study
  - Cohort of all term NB who subsequently developed asthma (n=2137)
  - Similar number of birthday matched controls

Association of TTN and childhood asthma *(Birnkrant et al. Pediatr Pulmonol. 2006)*

- Potentially confounding factors were adjusted for
  - TTN significantly associated diagnosis of childhood asthma (*adjusted* OR=1.50, 95% CI: 1.13-1.99; *p*=0.005)
  - Other significant associations: male infants, males with urban maternal address, males of non-white race, males whose mother did not have asthma

- *Conclusion*: TTN a marker of deficient pulmonary function reflecting inherited susceptibility to asthma?

Thank you!