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Physiology of Fetal Lung Fluid Clearance and the Effect of Labor

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Respiratory morbidity in near term (≥34 and <37 weeks) infants delivered spontaneously or by elective cesarean section (ECS) has been well documented in the literature, and accounts for a significant number of admissions to intensive care units among these neonates. Given the high rates of near-term deliveries in the USA and worldwide, the public health and economic impact of morbidity in this subgroup is considerable. Causes of respiratory distress include transient tachypnea of the newborn (TTNB), surfactant deficiency, pneumonia, and pulmonary hypertension. There is considerable evidence that physiologic events in the last few weeks of pregnancy coupled with the onset of spontaneous labor are accompanied by changes in the hormonal milieu of the fetus and its mother, resulting in rapid maturation and preparation of the fetus for delivery and neonatal transition. A surge in endogenous steroids and catecholamines accompanies term gestation and spontaneous vaginal delivery, and is responsible for some of the maturational effects. Rapid clearance of fetal lung fluid clearance plays a key role in the transition to air breathing. The bulk of this fluid clearance is mediated by transepithelial sodium reabsorption through amiloride-sensitive sodium channels in the alveolar epithelial cells with only a limited contribution from mechanical factors and Starling forces. Disruption of this process can lead to retention of fluid in air spaces, setting the stage for alveolar hypoventilation. When infants are delivered near-term, especially by cesarean section (repeat or primary) before the onset of spontaneous labor, the fetus is often deprived of these hormonal changes, making the neonatal transition more difficult. This chapter discusses the physiologic mechanisms underlying fetal lung fluid absorption and explores potential strategies for facilitating neonatal transition.

KEYWORDS near-term infant, fetal lung fluid clearance, respiratory distress syndrome, transient tachypnea of the newborn, epithelial sodium channel

In North America, births at ≥34 and <37 weeks gestation (referred to herein as "near-term" births) account for a significant proportion of preterm births. Several studies have documented the high incidence of respiratory distress and NICU admissions in this population.[1-3] These infants have a higher incidence of transient tachypnea of the newborn, respiratory distress syndrome, pulmonary hypertension, and respiratory failure than term infants. Data about respiratory failure and outcomes in term and near-term infants are hard to obtain because of the lack of large databases, such as those available for preterm infants; however, it is estimated that 17,000 infants ≥34 weeks are admitted to neonatal intensive care units (NICUs) each year in the US alone, and these represent up to 33% of all NICU admissions.[4] Nearly 50% of infants born at 34 weeks gestation require intensive care; this number drops to 15% at 35 weeks and 8% at 36 weeks gestation. In addition to respiratory distress, these infants often have other neonatal complications, including hypoglycemia, hyperbilirubinemia, feeding difficulties, and difficulty in maintaining body temperature. Long-term morbidity information is even harder to gather; an estimated 9% infants with respiratory failure die in the neonatal period.[4] Factors associated with high morbidity and mortality include delivery by cesarean delivery, presence of maternal complications, male gender, and intrauterine growth retardation.

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Delayed Fetal Transition in Near-Term Infants: Role of Retained Fetal Lung Fluid

The fetus has an interesting challenge presented to it at birth. Often at short notice, sometimes with no notice at all, it is asked to rapidly clear its air spaces of the fluid that it has been secreting through much of the pregnancy. The ability of a neonate to self-resuscitate itself at birth after remaining "submerged" in fluid for much of its life is truly remarkable, considering victims of near-drowning faced with similar amounts of fluid in the lungs do so poorly.[5,6] The lung epithelium is a key player in this process, engineering the switch from placental to pulmonary gas exchange.[5,7-15] For effective gas exchange to occur, alveolar spaces must be cleared of excess fluid, and pulmonary blood flow increased to match *ventilation* with *perfusion*. Failure of either of these events can jeopardize neonatal transition and cause the infant to develop respiratory distress. We are still far from a complete understanding of the mechanisms by which fetal lungs are able to clear themselves of excessive fluid at birth. It is clear though that traditional explanations which relied on "Starling forces" and "vaginal squeeze" can only account for a fraction of the fluid absorbed.[5,16-20] Amiloride-sensitive sodium transport by lung epithelia through epithelial sodium channels (ENaC) has emerged as a key event in the transepithelial movement of alveolar fluid.[6-9,11,12,21-24] Disruption of this process has been implicated in several disease states, including transient tachypnea of the newborn[25] and hyaline membrane disease.[26] In later life, pulmonary edema can result either from excessive movement of water and solute across the alveolar capillary membrane, or from failure of reabsorption of lung fluid.[27,28]

A large fraction of what we know about fetal lung fluid dynamics is owed to the fetal lamb model. Orzaleski and coworkers[29] have shown that, in fetal lambs, lung water content remains fairly constant at 90% to 95% of total lung weight through much of the third trimester. Kitterman and coworkers[30] and others[31,32] found that, in fetal sheep, lung fluid production begins to decrease a few days before spontaneous vaginal delivery and alveolar fluid volume decreases from approximately 25 to 18 mL/kg. Bland and coworkers[10,13,14] showed that preterm delivery and operative delivery without prior labor results in excessive retention of lung fluid in preterm rabbits, and in fetal lambs. Sola and Gregory[33] showed that colloid oncotic pressure varies with mode of delivery and experience of labor, and may influence epithelial fluid absorption. More recently, Berger and coworkers[18] evaluated the effect of lung liquid volume on respiratory performance after cesarean section in lamb fetuses. Using chronically catheterized fetal lambs, the investigators found that lambs born with reduced lung liquid volume improved their arterial blood gas and acid base status quicker than those lambs born without a prenatal decrease in their lung liquid volume. This study also confirmed that the experience of vaginal delivery greatly enhances respiratory performance, and this effect is greater than that achieved by simple reduction of lung liquid volume to half in fetuses delivered without enduring labor. Removal of lung fluid thus started before birth continues postnatally with fluid being carried away by several possible pathways including pulmonary lymphatics,[14,34] blood vessels,[35] upper airway, mediastinum,[36] and pleural space.[36]

Role of Active Sodium Transport

It is now clear that active Na^+ transport across the pulmonary epithelium drives liquid from lung lumen to interstitium, with subsequent absorption into the vasculature. In the lung, Na^+ reabsorption is a two-step process. The first step is passive movement of Na^+ from lumen across the apical membrane into the cell through Na^+ permeable ion channels. The second step is active extrusion of Na^+ from the cell across the basolateral membrane into the serosal space. Several investigators have demonstrated that the initial entry step involves amiloride-sensitive Na^+ channels.

For example, O'Brodovich and coworkers,[7] using newborn guinea pigs, have shown that intraluminal instillation of amiloride delays lung fluid clearance. More recent studies using the patch-clamp technique have confirmed the role of AT-II cells in the vectorial transport of Na^+ from the apical surface.[24,37] Indeed, cDNAs which encode amiloride-sensitive Na^+ channels in other Na^+ transporting epithelia have also been cloned from airway epithelial cells.[37-39] The lung epithelium is believed to switch from a predominantly chloride-secreting membrane at birth to a predominantly Na^+-absorbing membrane after birth. These changes have also been correlated with an increased production of the mRNA for amiloride-sensitive epithelial Na^+ channels (ENaC) in the developing lung.[23] Much of this information has come from studies using AT-II cells. These cuboidal cells are responsible for the secretion of surfactant and for the vectorial transport of Na^+ from the alveolar space to the interstitium.[40-42] They also serve as the progenitor to the squamous type-I cells during normal lung development as well as in the repair process following epithelial injury.[43] Recent studies have shown that type-I pneumocytes also express sodium channels, although their precise role in net Na^+ transport is yet to be defined.[44]

Studies of Na^+ transport across AT-II cells have shown that Na^+ is reabsorbed via the same two-step absorptive process described above.[45] This allows diffusion of Na^+ across the apical membrane into AT-II cells, facilitated by a favorable electrochemical gradient maintained by the Na^+-K^+-ATPase located at the basolateral membrane.[46] Cation channels on the apical surface constitute the rate-limiting step in this process, offering more than 90% of the resistance to the transcellular Na^+ transport.[46,47] Several studies have shown that ENaC consists of three homologous but nonidentical subunits termed α, β, and γ.[39] The adult rat lung and fetal lung have been shown to express all three subunits of the ENaC.[23] The evidence includes immunocytochemical and Western blot studies consistent with the presence of proteins antigenically related to Na^+ channels, and Northern blotting studies