Transient Tachypnea of the Newborn

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Introduction

The birth of a child is preceded by several changes to prepare for the transition from intrauterine to extrauterine life. The five major events that establish the lungs as the organ of gas exchange at birth include: clearance of fetal lung fluid, establishment of spontaneous breathing, decrease in pulmonary vascular resistance, release of surfactant, and cessation of the right-to-left shunting of venous blood returning to the heart. (1) During fetal life, fluid is secreted into the alveoli to maintain normal growth and function, (2) and fetal lung volume approximates the functional residual capacity that would be established once air breathing is initiated. (3) Clearance of lung fluid can be affected by several factors, and its impairment culminates in tachypnea and could necessitate transfer to an intensive care unit for monitoring and respiratory support.

Transient tachypnea of the newborn (TTN), which is believed to result from incomplete resorption of fluid from the lungs of the newborn, presents an important diagnostic and therapeutic dilemma in the newborn nursery. This review focuses on TTN, with emphasis on fetal lung fluid mechanics and possible mechanisms of fetal lung fluid resorption as well as its pathophysiology, clinical and diagnostic features, and management. Some neonatologists refer to TTN as retained fetal lung liquid syndrome.

Physiology of Fetal Lung Fluid

The lungs are filled with liquid in utero, which increases from 4 to 6 mL/kg body weight at mid-gestation to about 30 to 50 mL/kg near term in fetal lambs. (4) Jost and Policard (5) first demonstrated that fluid within the fetal lung arises from the lung and contributes to the volume of amniotic fluid. The rate of production ranges from 2 mL/kg per hour in the initial part of pregnancy to 5 mL/kg per hour at term, thereby contributing one third to one half of the daily turnover of amniotic fluid. The fluid gradually moves up the trachea and either is swallowed or goes into the amniotic fluid reservoir around the baby. The volume of fetal lung fluid is regulated by the larynx, which acts as a one-way valve, allowing only outflow of the lung fluid under normal circumstances (6) and creating a pressure gradient of approximately 1 cm of water between the airway lumen and amniotic cavity to keep the lungs distended. Such distention is essential for lung growth, and a decrease in fetal lung fluid (as reflected by oligohydramnios) can result in pulmonary hypoplasia. (7)

The pulmonary epithelium in the fetal lung (Fig. 1, left panel) secretes chloride into the alveolus. Chloride enters the lung epithelial cell across the basolateral membrane via a $Na^+/K^+/2\ Cl^-$ cotransporter, the target transporter for furosemide. The chloride ions are secreted into the alveolus by various chloride channels. The potassium ion extrudes through basolateral potassium channels. Sodium follows chloride through paracellular pathways, with water flowing between or through cells via aquaporins, thus helping to maintain adequate lung fluid. (8)

Although fetal sheep lung fluid remains fairly constant at 90% to 95% of total lung weight through much of the third trimester, the fluid begins to decrease a few days before spontaneous vaginal delivery from approximately 25 to 18 mL/kg. (9) With the onset of labor, the high circulating concentration of epinephrine activates the switch within the lungs from net secretion to net reabsorption. (6) Conventionally cited mechanisms related to vaginal squeeze of the thorax during birth and Starling forces also contribute to a very small proportion of lung fluid resorption. (10)

The currently accepted mechanism of transepithelial movement of lung fluid at the time

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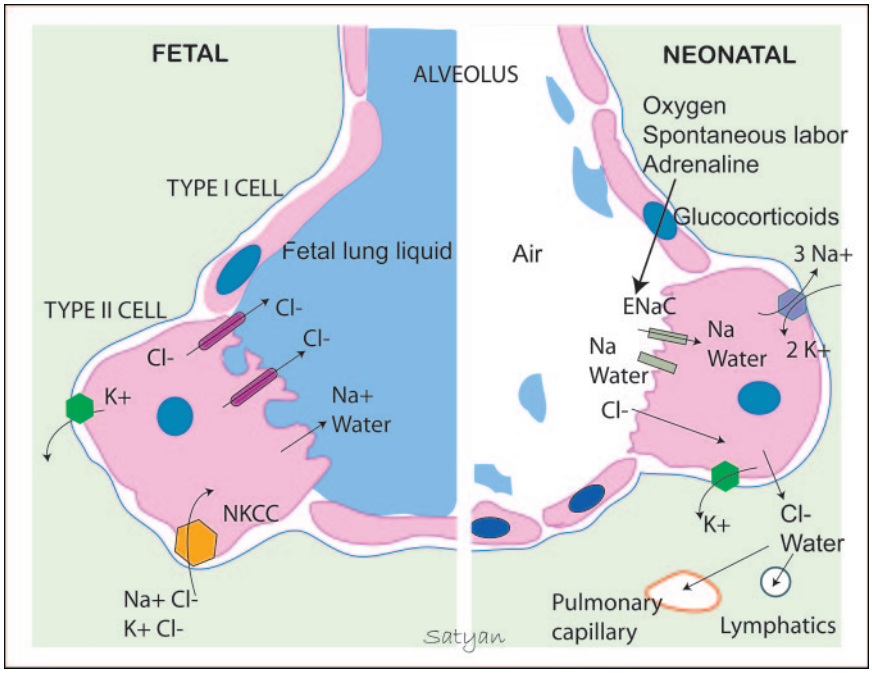


Figure 1. Mechanism of fetal and neonatal lung fluid transport. The left panel shows active secretion of chloride ions from alveolar cells into the alveolar space. Sodium (Na^+) and water accompany chloride (Cl^-). Around the time of birth (right panel), type II cell apical epithelial sodium channels (ENaC) become activated by adrenergic stimulation. Basolateral Na^+/K^+ ATPase helps move sodium into the interstitium, which brings chloride and water passively along with it through the paracellular and intracellular pathways. Most interstitial lung liquid moves into the pulmonary circulation; some drains via the lung lymphatics. K^+=potassium, NKCC=sodium, potassium, 2 chloride cotransporter

of birth is by passive movement of sodium through epithelial sodium channels (ENaC) (Fig. 1, right panel), which are believed to be closed during fetal life but become activated by adrenergic stimulation near birth. (11) The epinephrine stimulation of amiloride-sensitive ENaC channel-mediated alveolar fluid clearance is mediated by cyclic adenosine monophosphate (12) and Ca^{2+}, likely acting as an intracellular second messenger. (13) O'Brodovich and associates (14) showed that intraluminal instillation of amiloride in newborn guinea pigs delays lung fluid clearance and leads to hypoxemia and respiratory distress. Sodium then moves into the interstitium via ouabain-sensitive basolateral Na^+/K^+ ATPase, and inhibition of this channel reduces lung liquid clearance in animal models. Movement of sodium into the interstitium helps to move chloride and water passively along with it through the paracellular and intracellular pathways. Most interstitial lung liquid moves into the pulmonary circulation; some drains via the lung lymphatics.

Epidemiology

Epidemiologic data are scarce, but studies show that TTN occurs in 3.6 to 5.7 per 1,000 term infants. (15)(16) Retention of fetal lung fluid may be more common in preterm infants (up to 10 per 1,000 births), but there usually are coexisting problems such as respiratory distress syndrome (RDS) that may mask its presentation. (17) TTN is one of the most common causes of neonatal respiratory distress, (18)(19) and actually may be underdiagnosed. (20) Risk factors for TTN include birth by cesarean section with or without labor, male sex, family history of asthma (especially in mother), (21) lower gestational age, macrosomia, and maternal diabetes (Fig. 2). For babies born by elective cesarean section, the presence of labor and the timing of delivery significantly affect the presence of respiratory morbidity. The incidence of respiratory morbidity in babies delivered by cesarean section before the onset of labor is 35.5 per 1,000, compared with cesarean section with labor, in which the rate is 12.2 per 1,000. (22) With vaginal delivery, morbidity occurs in 5.3 per 1,000 births. Even late preterm delivery (between 34 and 37 weeks of gestation) increases the risk for TTN. (23) A significant reduction in respiratory morbidity can be achieved if elective cesarean section is performed after 39 weeks of gestation. (24)

Diagnosis and Clinical Features

The diagnosis of TTN is based on clinical and radiologic findings (Table 1). It frequently is a diagnosis of exclusion; other conditions such as RDS, pneumonia, and pneumothorax must be excluded. TTN usually presents within a few hours of birth with tachypnea, retractions, and grunting and occasionally with a requirement for supplemental oxygen. Respiratory rates are greater than 60 breaths/min, often in the range of 80 to 100 breaths/min, and sometimes higher. Because many babies experience tachypnea for a period of time after birth, shorter periods of tachypnea sometimes are referred to as "tran-

sitional delay." This may be part of the spectrum of retained fetal lung fluid syndromes, with TTN being more severe than typical transitional delay. Any chosen cutoff for the length of "normal" tachypnea after birth (ie, the minimum number of hours of tachypnea for a diagnosis of TTN) is arbitrary but could range from 2 to 12 hours. Six hours may be a practical choice for the cutoff between "transitional delay" and TTN because by this time, the baby may not be able to take feedings orally, requiring other arrangements.

Tachypnea due to TTN resolves by 72 hours in most cases but can persist longer. Ultimately, the tachypnea resolves, consistent with the "transient" in the name TTN. In a retrospective review of 95 newborns who had TTN, (25) clinical and laboratory findings were compared between two subsets: babies in whom tachypnea lasted fewer than 72 hours and those in whom it lasted more than 72 hours. The authors suggested that a peak respiratory rate of more than 90 breaths/min at 36 hours of age was highly predictive of prolonged tachypnea. Prolonged TTN was associated with lower white blood cell count and hematocrit values, longer hospitalization, and antibiotic treatment in this study.

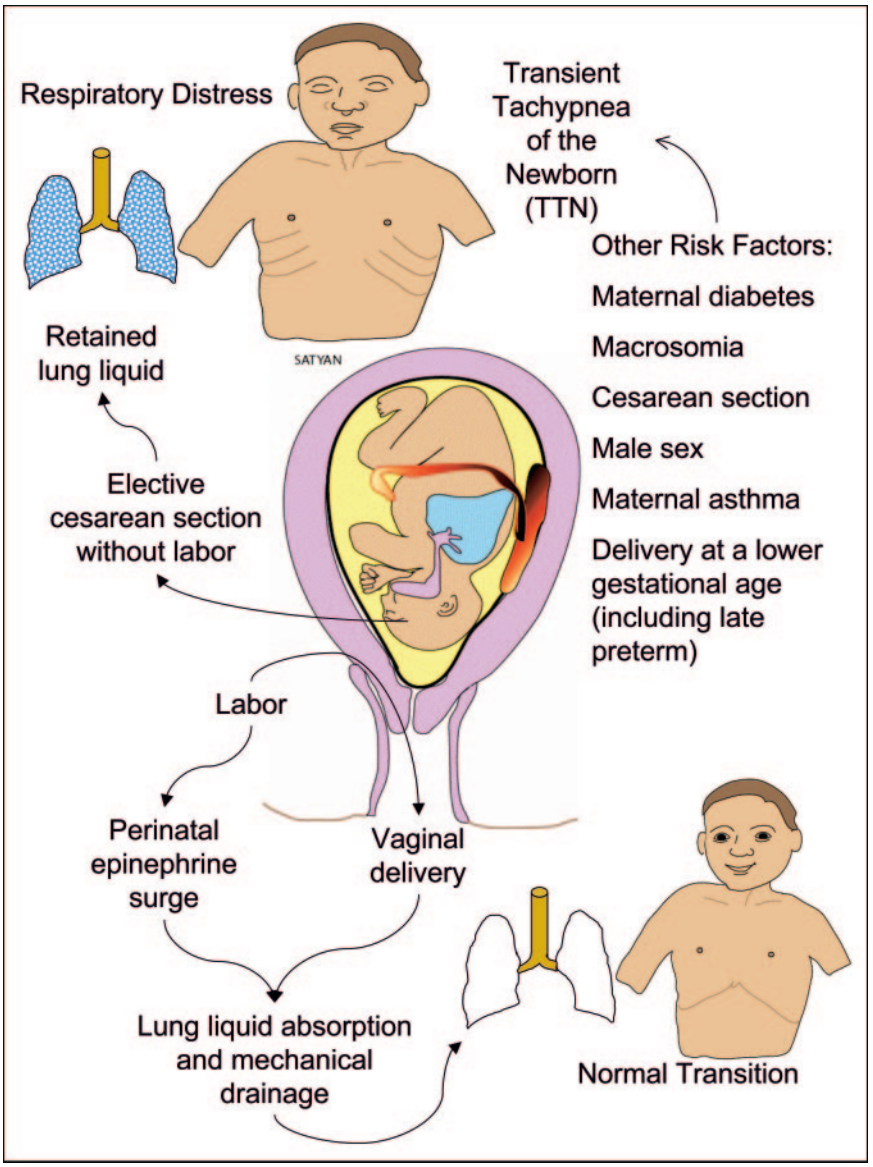


Figure 2. Risk factors associated with transient tachypnea of newborn. See text for details.

Grunting can be common immediately after birth and is considered part of transition. Among a cohort of 466 newborns, 17.4% had grunting respirations at birth, but the grunting subsided in most by 2 hours of age (68% stopped within 30 minutes, 85% by 1 hour, and 93% by 2 hours). (26) If grunting and other signs of distress persist, the baby may require further assessment and intervention. Another clinical sign of TTN is a barrel-shaped chest due to hyperinflation, which may push down the liver and spleen, making them palpable. Auscultation of the chest may reveal crackles, usually with associated tachycardia. Blood pressure remains unaffected, unless the newborn becomes severely symptomatic. (27)

Occasionally, some infants who have TTN develop severe hypoxemia and may require high concentrations of oxygen (>60%) to maintain their saturations. Such babies may need additional respiratory support (intubation and mechanical ventilation). Pulmonary hypertension with right-to-left shunting across the ductus or foramen ovale may be present because of possible elevation in the pulmonary vascular resistance associated with retained fetal lung fluid. Rarely, air leaks have been reported.

Table 1. Diagnosis of Transient Tachypnea of the Newborn

- Symptoms start within the first 6 hours after delivery
- Tachypnea and, in some cases, retractions, grunting, or nasal flaring; desaturation/cyanosis is uncommon; good response to oxygen supplementation (as verified clinically or by pulse oximetry); mechanical ventilation rarely required
- Chest radiograph consistent with retained fetal lung fluid, showing congestion, perihilar streaking, fluid in the interlobar fissure
- Symptoms and radiographic findings transient and self-limited, disappearing within the first postnatal week (usually within a few days)
- Other diagnoses excluded (eg, pneumonia, respiratory distress syndrome, pneumothorax)

Table 2. Causes of Tachypnea in a Newborn

Transient tachypnea of newborn
Respiratory infections (pneumonia)
Aspiration syndromes (meconium, blood, or amniotic fluid)
Congenital malformations (congenital diaphragmatic hernia, cystic adenomatoid malformations) and Central nervous system irritation (subarachnoid hemorrhage) or disease (hypoxic-ischemic encephalopathy)
Hyaline membrane disease (respiratory distress syndrome)
Edema, pulmonary (left-to-right shunts with failure, anomalous venous drainage)
Air leaks (pneumothorax) and Acidosis (metabolic)

Radiographic Features

Chest radiography (Fig. 3) typically shows prominent perihilar vascular markings due to engorged periarterial lymphatics, edema of the interlobar septae, and fluid in the fissures. There may be some degree of hyperinflation, and fluid may be seen at the costophrenic angles, with widening of intercostal spaces. Findings often become normal within 2 days, but complete disappearance of perihilar markings may require 3 to 7 days. (28) A retrospective review comparing the interpretation of the first chest radiograph obtained for 99 neonates admitted to the intensive care unit for mild-to-moderate respiratory distress, which was read by clinicians and radiologists independently, showed agreement only 48% of the time between the two for the diagnosis of TTN compared with 95% agreement for the diagnosis of RDS and 78% for pneumothoraces. (29)

Differential Diagnosis

The definitive diagnosis of TTN often is retrospective because by definition, the symptoms are "transient" and other conditions have been excluded. The common causes of tachypnea in a neonate can be remembered by using the mnemonic "TRACHEA" (Table 2). Besides RDS and pneumonia, another important disorder that should be considered, based on additional history, is tachypnea related to cerebral irritation from a subarachnoid hemorrhage or hypoxic brain injury (also called cerebral hyperventilation). Infants who have the latter diagnosis tend to have respiratory alkalosis, and chest

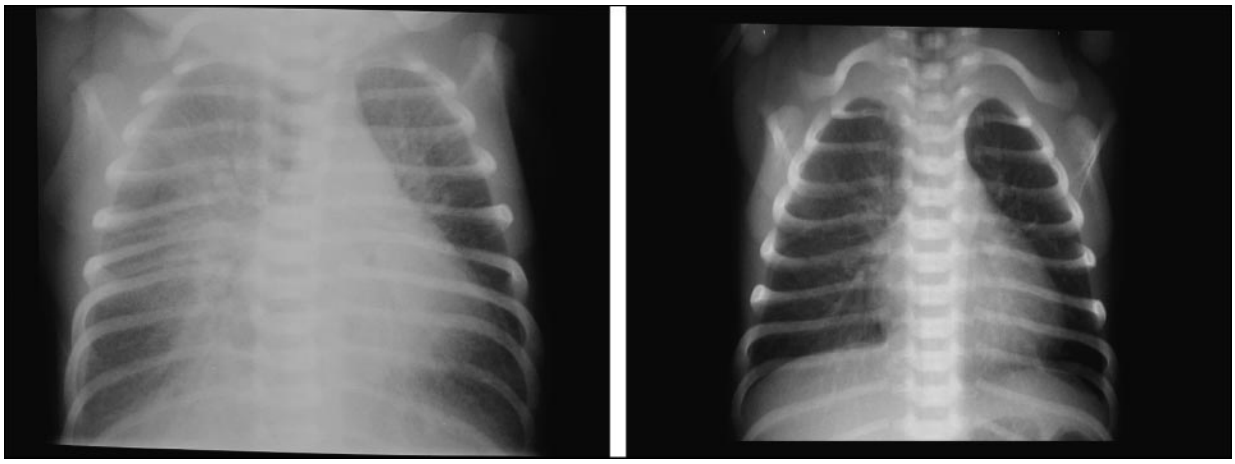


Figure 3. Radiographs of two babies who have transient tachypnea of the newborn of differing severity. Note the streaky lung opacities and fluid in the minor fissure on the right side.

radiography may show some cardiomegaly, with normal lung fields. Tachypnea due to metabolic acidosis should be considered and can be ruled out with measurement of a capillary or arterial blood gas. Because it is difficult to exclude pneumonia at presentation, many babies who have TTN are treated with antibiotics for the first 24 to 48 hours until the blood culture is negative; by that time, clinical symptoms and radiologic findings usually have resolved significantly, which is highly suggestive of TTN, obviating the need for continued treatment with antibiotics.

Lung Function in TTN

Lung function is difficult to measure immediately after birth, and data in newborns are limited. Lee and associates (30) measured the thoracic gas volume by using total body plethysmography and functional residual capacity by argon dilution at ages 4 to 6 hours and 24 hours in 10 babies delivered vaginally and 10 babies born by elective cesarean section. They noted lower mean thoracic gas volume at 4 to 6 hours in babies born by cesarean section compared with those born by vaginal delivery. They also showed a delay of up to 24 hours in the establishment of final lung volumes in babies born without exposure to labor or passage through the birth canal. They suggested that this finding may explain the increased respiratory morbidity associated with delivery by elective cesarean section. (30)

Faxelius and associates (31) looked at the correlation between the catecholamine surge associated with labor and lung function at 30 minutes and at 2 hours after birth by measuring cord pH and catecholamine and cortisol values in term babies born by different modes of delivery. They found lower tidal volume, minute ventilation, and dynamic compliance at 30 minutes and 2 hours after birth in infants delivered by cesarean section compared with those delivered vaginally. The catecholamine and cortisol concentrations at birth were higher in the vaginal group than in the cesarean section group, with significant correlation between the catecholamine concentrations and lung compliance at 2 hours in this group. Sandberg and colleagues (32) evaluated newborns who had tachypnea lasting more than 2 hours after birth and showed lower tidal volumes but normal-to-increased total ventilation due to increased respiratory rates and hyperinflation with reduced dynamic lung compliance.

Asthma and TTN

Literature about the link between asthma and TTN is increasing. Babies born to mothers who have asthma are at higher risk for the development of TTN. (33)(34) Conversely, babies experiencing TTN have an increase in physician-diagnosed preschool asthma. (35) Birnkrant and colleagues (36) examined a database of 18,379 term infants, from which 2,137 children who had asthma were compared with a similar number of birthday-matched controls, and showed that TTN was associated significantly with the diagnosis of childhood asthma. The association of TTN and asthma was statistically strongest among male infants, especially among males whose mothers lived at urban addresses, males of nonwhite race, and males whose mothers did not have asthma. The authors proposed that TTN may be a marker of deficient pulmonary function, reflecting inherited susceptibility to asthma. Asthma is a multifactorial disease, and the correlation with TTN remains to be elucidated clearly. Some factors may predispose to both diseases or TTN itself may be a risk factor for later development of asthma.

Management

An important question that arises in the community hospital setting is when to refer newborns to a level 2 or 3 neonatal intensive care unit for management of early-onset respiratory distress in newborns, especially babies suspected of having TTN. Hein and colleagues (37) have recommended the "rule of 2 hours," whereby the newborn is observed for 2 hours after the onset of respiratory distress. If there is no improvement in the degree of distress, a chest radiograph is obtained. Many newborn nurseries use pulse oximetry as an adjunct to clinical monitoring. If the baby exhibits desaturation in room air, a blood gas measurement may be useful. The baby then may be referred to a higher facility if the chest radiograph does not appear normal, the baby is worsening clinically, the baby requires more than 40% oxygen to maintain normal oxygen saturation, or there is no improvement after 2 hours of all feasible interventions.

If tachypnea is associated with increased work of breathing and is not resolving, the baby must be kept nil per os (NPO) and requires intravenous (IV) fluids (10% dextrose in water at 60 to 80 mL/kg per day). After the transition period (the first few hours after birth), increased work of breathing, as opposed to isolated tachypnea, should heighten concern that TTN may not be the correct diagnosis. Because these are term babies and it is easier to observe the respiratory status unbundled, they usually are observed in open radiant warmers. Typically, chest radiography is performed to support the diagnosis of TTN and rule out other conditions (eg, pneumothorax). A screening complete blood count with differential count and a blood gas analysis (especially in the presence

of increased work of breathing or oxygen requirement) should be considered.

Although the respiratory rate can be high for the baby who has typical TTN, other signs of increased work of breathing (grunting, flaring, retractions) resolve sooner than the tachypnea. As the TTN is resolving, and if the diagnosis is straightforward and the respiratory rate is less than 80 breaths/min, enteral feedings can be given. The feedings should be started on a gentle protocol by advancing volume in small increments (continuing to supplement total fluids with IV fluids) until the baby no longer exhibits tachypnea and has a respiratory rate of less than 60 breaths/min. For babies who continue to have tachypnea and are NPO or are receiving low-volume feedings for more than 1 day, electrolytes should be added to the IV fluids, and parenteral nutrition should be considered to provide optimal nutrition. Babies who have TTN need to be observed closely; in 74%, symptoms subside by 48 hours of age. (18)

If the pulse oximetry or blood oxygen value suggests that the baby needs oxygen, the preferred initial method of delivery is by oxygen hood. The concentration is adjusted to maintain a pulse oximetry reading in the low 90s. With nasal cannula delivery, the actual oxygen concentration delivered is more difficult to determine; this form of oxygen delivery may be used after the first 24 hours of age, when the diagnosis is more certain. In the uncommon event that a baby who has TTN needs intubation and higher oxygen concentration, the baby should remain NPO and an arterial line may be needed. Such infants are at risk for persistent pulmonary hypertension of the newborn, at times even requiring extracorporeal membrane oxygenator (ECMO) support. Although the total number of neonates requiring ECMO support for respiratory failure has declined from 1989 to 2006, the proportion delivered by elective cesarean section among them is rising. (38) Because there is a higher occurrence of respiratory morbidity in late preterm and term infants delivered by elective cesarean section, the relative numbers of infants who have TTN and require ECMO may signal a concerning trend.

Some infants finally diagnosed as having TTN can experience prolonged tachypnea. If tachypnea persists beyond 5 or 6 days, echocardiography should be considered to rule out congenital heart disease. In general, babies who have TTN cannot have a definitive diagnosis of TTN until the tachypnea resolves. Therefore, babies are not discharged until the tachypnea resolves (respiratory rates <60 breaths/min for at least 12 hours).

Both furosemide and racemic epinephrine have been studied for possible benefit in patients who have TTN. Treatment with furosemide was evaluated in a controlled, prospective, randomized trial in 50 infants having TTN. (39) The furosemide group was given 2 mg/kg orally at the time of diagnosis followed by 1 mg/kg 12 hours later if the symptoms persisted; the control babies received a placebo. No significant difference in the duration of tachypnea or in the length of hospitalization was observed with furosemide therapy.

A recent randomized, blinded, placebo-controlled pilot trial examined the safety and efficacy of racemic epinephrine for the treatment of TTN based on the hypothesis that infants who have TTN may have relatively low concentrations of epinephrine, which is known to mediate fetal lung fluid absorption. (40) Although no infant in either the treatment or control arm experienced an adverse event, including tachycardia or hypertension, there was no difference in the rates of resolution of tachypnea in the treatment and the control groups.

Prevention and Scope for Future Research

The ideal approach to preventing TTN is to reduce the incidence of cesarean section, which has been increasing and contributes significantly to respiratory morbidity in term newborns. The American College of Obstetrics and Gynecology (ACOG) recommends scheduling elective cesarean section at 39 weeks' gestation or later on the basis of menstrual dates or waiting for the onset of spontaneous labor. ACOG also provides criteria for establishing fetal maturity before elective cesarean section. However, the safety of this approach in mothers who previously have delivered by cesarean section has not been established in rigorous trials. A recent study demonstrated that antenatal betamethasone administered prior to an elective cesarean section reduced the incidence of respiratory morbidity in infants. (41) Although mortality is not a concern, TTN is very common and is a frustrating condition that sometimes requires transfer of the baby, separation from the mother if she cannot be transferred, multiple diagnostic studies, delay in discharge, prolonged hospitalization, and increased healthcare costs. Also, these babies may have an increased risk of asthma. Thus, additional research to elucidate mechanisms of lung fluid reabsorption that are dysfunctional in TTN and possible therapeutic interventions is warranted.

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