



Evaluating Clinical Outcomes and Physiological Perspectives in Studies Investigating Respiratory Support for Babies Born at Term With or at Risk of Transient Tachypnea: A Narrative Review

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Respiratory distress in the first few hours of life is a growing disease burden in otherwise healthy babies born at term (>37 weeks gestation). Babies born by cesarean section without labor (i.e., elective cesarean section) are at greater risk of developing respiratory distress due to elevated airway liquid volumes at birth. These babies are commonly diagnosed with transient tachypnea of the newborn (TTN) and historically treatments have mostly focused on enhancing airway liquid clearance pharmacologically or restricting fluid intake with limited success. Alternatively, a number of clinical studies have investigated the potential benefits of respiratory support in newborns with or at risk of TTN, but there is considerable heterogeneity in study designs and outcome measures. A literature search identified eight clinical studies investigating use of respiratory support on outcomes related to TTN in babies born at term. Study demographics including gestational age, mode of birth, antenatal corticosteroid exposure, TTN diagnosis, timing of intervention (prophylactic/interventional), respiratory support (type/interface/device/pressure), and study outcomes were compared. This narrative review provides an overview of factors within and between studies assessing respiratory support for preventing and/or treating TTN. In addition, we discuss the physiological understanding of how respiratory support aids lung function in newborns with elevated airway liquid volumes at birth. However, many questions remain regarding the timing of onset, pressure delivered, device/interface used and duration, and weaning of support. Future studies are required to address these gaps in knowledge to provide evidenced based recommendations for management of newborns with or at risk of TTN.

Keywords: transient tachypnea of the newborn, respiratory distress, respiratory support, end-expiratory pressure, airway liquid

INTRODUCTION

Respiratory distress is most commonly associated with preterm newborns, due to lung immaturity, poor respiratory effort, and surfactant deficiency (1, 2). However, a growing number of otherwise healthy babies born at term (>37 weeks' gestation) are presenting with respiratory distress symptoms within the first few hours of life, requiring admission to intensive care for treatment (3). These babies are commonly diagnosed with transient tachypnea of the newborn (TTN), which is characterized by tachypnea, expiratory braking, grunting and poor oxygenation (4, 5). TTN is often diagnosed retrospectively and historically has been considered a benign and self-limiting condition in most newborns. However, some can develop more severe respiratory distress and suffer serious morbidity including persistent pulmonary hypertension of the newborn (5).

The incidence of TTN is greatest in babies born at term by cesarean section (CS) without labor and is increasing in parallel with the growing rates of elective CS worldwide (3, 6, 7). Historically, treatment of TTN has largely focused on targeting molecular airway liquid clearance mechanisms, which includes the pharmacological stimulation of sodium reabsorption with beta-receptor agonists and restricting newborn fluid intake (**Figure 1**). As determined by systematic review and meta-analysis, these methods have produced low-quality evidence over the years with limited impact on widespread management of the condition (8). These findings can be explained by recent evidence indicating that elevated airway liquid volumes, rather than delayed airway liquid clearance in the first few hours of life, cause the respiratory symptoms that characterize TTN after birth (9, 10). More liquid simply means that higher volumes of liquid need to be accommodated in lung tissue after birth (9, 10). This explains why newborns at greatest risk of TTN are those born at term by CS without labor. Newborns delivered by this method do not lose airway liquid via their nose and mouth during uterine contractions associated with labor, which is the only clearance mechanism that avoids liquid from entering lung tissue during lung aeration.

Recent studies have documented the pathophysiology associated with elevated airway liquid volumes at birth. These include:

1. The chest wall expands further and the diaphragm flattens (9), which reduces the newborn's ability to inspire and increases the work of breathing.
2. Reduced end-expiratory lung volumes between breaths (functional residual capacity, FRC) (9, 11). As the reduction in FRC can be localized to lung regions with elevated liquid, this clearly demonstrates that the local clearance of liquid into lung tissue is the primary cause for the reduction in FRC (12).
3. Large reduction in lung compliance (9), which contributes to the reduced FRC and also limits inspiration.
4. Reduced respiratory gas exchange capacity, which increases the need for supplemental oxygen to maintain adequate oxygenation (13).

5. Reduced pulmonary blood flow (13) and increased pulmonary vascular resistance, potentially leading to persistent pulmonary hypertension of the newborn.
6. Induces tachypnea, grunting and expiratory braking in spontaneously breathing newborns, which are common physical symptoms observed in newborns with TTN (9, 11).

In recent years, clinical studies investigating the management of TTN have focused on providing respiratory support and the role of oxygen supplementation to support lung function (see **Figure 1**). However, while non-invasive respiratory support, particularly continuous positive airway pressure (CPAP), is currently the mainstay for managing TTN clinically, many questions remain and there is considerable heterogeneity in the approaches used. Importantly, use of respiratory support in term newborns with respiratory distress has been extrapolated from knowledge regarding respiratory support for preterm newborns. However, lung maturity and the pathophysiology underlying the respiratory distress are very different between preterm and term newborns. This narrative review synthesizes the current clinical evidence on the use of non-invasive respiratory support for term babies with or at risk of TTN. We have compared and contrasted study design, birth factors (gestational age, mode of delivery, and exposure to antenatal corticosteroids), application of respiratory support (timing, type, interface, device, and pressure) and clinical outcomes between studies. In addition, we provide insights into the current understanding of physiological mechanisms and impact of respiratory support in term newborns with TTN.

SYNTHESIS OF CURRENT EVIDENCE

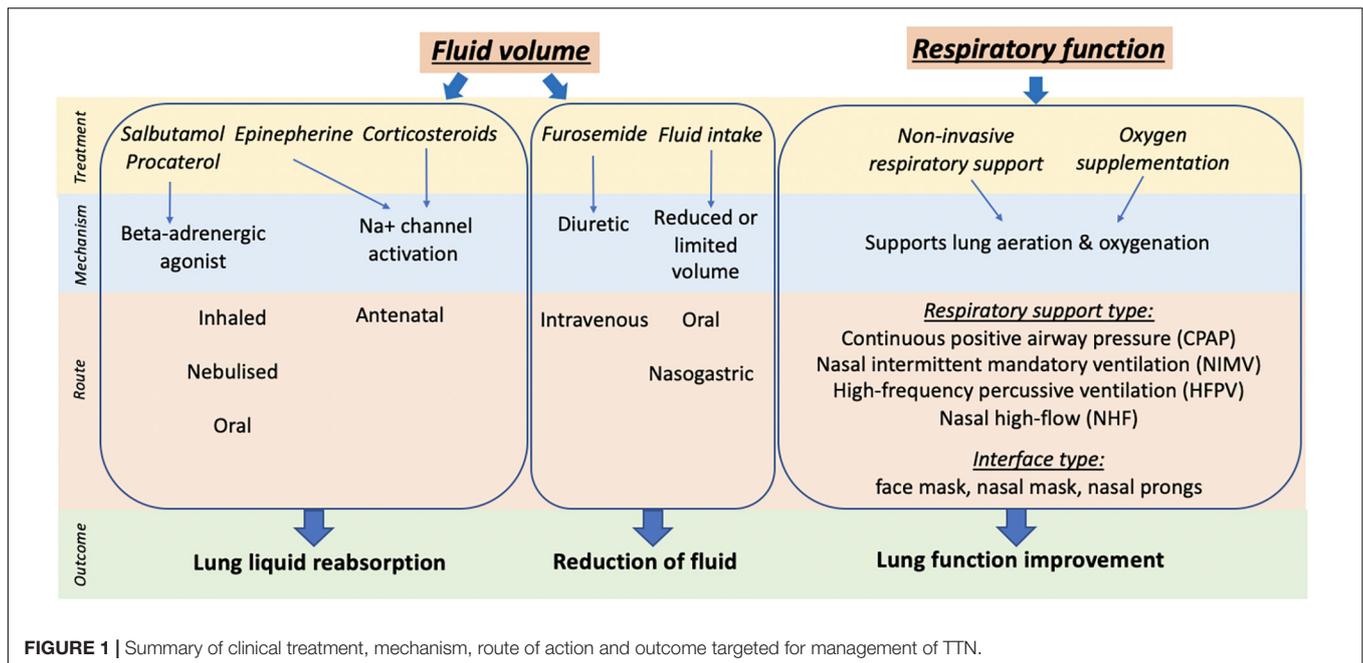
Search Strategy

A literature search identified studies investigating the use of respiratory support in term newborns with or at high risk of TTN. Clinical studies published in English prior to January 2022 were evaluated and review articles were also examined to identify any relevant articles not captured by the electronic search.

A diagnosis of TTN represents a specific type of morbidity along the spectrum of respiratory distress severity. However, within a population of newborns with TTN there is significant heterogeneity in onset, severity and duration of symptoms. Thus, limiting this review to studies using respiratory support in the context of TTN, rather than any diagnosis of respiratory distress, enabled the heterogeneity in study characteristics and outcomes to be directly compared and contrasted. This allows a better understanding of the reported findings from studies investigating the respiratory management of newborns with or at risk of TTN.

Tabulation of Study Factors

Study demographics (author, year, country, study type, and sample size), birth factors (gestational age, CS rate, and exposure to antenatal corticosteroids), characteristics for TTN diagnosis (physical characteristics, timing of tachypnea, imaging, and other parameters), timing of intervention (prophylactic



or interventional), demographics of control and intervention groups (type of support, interface/device, and pressure), study aim, primary outcome, and overall study findings between groups were tabulated (Table 1). Studies are listed in chronological order to provide insights into approaches over time (Table 1).

Study Demographics

Many studies have investigated treatments targeting sodium reabsorption and liquid volume on TTN management (Figure 1) (8, 14–17), with only eight studies investigating the use of non-invasive respiratory support (see Table 1), which were published between 2011 and 2021. The average gestational age at enrollment was early-term newborns (>37–38 + 6 weeks' gestation), however, some studies did report newborns enrolled in groups which included some late preterm newborns (overall range 35–42 weeks' gestation; see Table 1). The studies were conducted in hospitals in Egypt, France (two studies), Italy, Turkey (four studies) and the United States. Study types included six prospective studies (all were randomized) and two retrospective cohort studies (i.e., study design is not randomized). One was a multicenter cohort study while the remainder were single-center clinical studies. Studies compared outcomes between two different modes of respiratory support [continuous positive airway pressure (CPAP), nasal intermittent mandatory ventilation (NIMV), high frequency percussive ventilation (HFPV)], high-flow or supplemental oxygen exposure alone. One study was a comparative crossover investigating the influence of CPAP delivering device in the same newborns.

The studies varied in sample sizes from 40 to 259 newborns (average was 50). Three studies included babies born exclusively by CS, who are at greatest risk of developing TTN (gestational age range of newborns ~36.5–38.5 weeks; see Table 1). The remaining studies investigated outcomes from babies with TTN

born vaginally or by CS (CS rate ranged from 6 to 91% of those enrolled in individual studies; gestational age range of newborns ~34.6–41 weeks). Antenatal corticosteroids were not used in two studies (gestational age range of newborns 36.5–39 weeks), whereas exposure ranged from 6.5 to 57.1% of newborns in other studies (gestational age range of enrolled newborns ~32–42 weeks). Exposure to antenatal corticosteroids was not reported in two studies (gestational age range of newborns ~35.5–39 weeks).

All studies reported outcomes in newborns displaying physical TTN symptoms and three used the Silverman or modified Silverman score (most commonly ≥ 5), which assesses respiratory distress severity in newborns without respiratory support. Six studies used tachypnea onset within 6 h and three studies used tachypnea lasting for at least 12 h to classify TTN. Six studies also relied on chest radiograph to confirm TTN, with varying numbers of pathological observations required for diagnosis.

Non-invasive Respiratory Support Intervention Characteristics

Non-invasive respiratory support was given either prophylactically at birth (one study) or as an intervention following the development TTN after birth (seven studies). The largest study compared standard care (no respiratory support; $n = 125$) with prophylactic CPAP for 20 min initiated within 5–10 min of birth ($n = 134$) (18). The remaining studies provided non-invasive respiratory support to newborns with TTN at 20 min after birth (one study), on NICU admission (five studies; onset time unknown) or were randomized at 6 h after birth (one study). Two studies compared supplemental oxygen therapy with CPAP and five studies compared two different types of respiratory support for TTN (type/device/pressure). One study

was a comparative crossover in newborns receiving respiratory support with two different devices (nasal mask vs. bi-nasal short prongs). Two studies provided CPAP for 20 min, using it as both a prophylactic and “early rescue” interventional therapy. In the remaining studies, the period of respiratory support was not set, but determined by the presence or absence of symptoms and ranged from 3 to 50 h (see Table 1).

Method of Delivering Non-invasive Respiratory Support

Non-invasive respiratory support was provided by CPAP (eight studies), HFPV (one study), NIMV (one study), or high-flow

(one study). CPAP was provided via nasal probe (one study), nasal prongs (five studies), face mask (three studies), or nasal mask (one study). In addition to standard CPAP (three studies), the type of CPAP used included bubble (one study), variable flow (two studies), and bi-level CPAP (one study). In the study that compared supplemental oxygen therapy with CPAP, oxygen was directly administered into an incubator equipped with an oxygenation sensor.

The CPAP level ranged between 5 and 8 cmH₂O, while 4 cmH₂O PEEP was administered during NIMV and 5 cmH₂O administered during NHFPV. In one study, variable flow CPAP commenced with 4 cmH₂O which was increased to a maximum of 6 cmH₂O as needed and supplemental oxygen was provided

TABLE 1 | Clinical studies investigating the use of non-invasive respiratory support prophylactically in newborns at risk of TTN or interventional use in newborns diagnosed with TTN.

Study characteristics				TTN diagnosis							Timing of intervention		Control group			Intervention group			Study aim	Primary outcome	Intervention vs. Control outcome				
Study	Country	Study type	Sample size (n)	Gestational age (weeks)	Cesarean birth (%)	Antenatal steroids (%)	Chest movement/retractions	Expiratory grunting	Tachypnea	Silverman score ≥5	Tachypnea within 6 hours after birth	Tachypnea lasting at least 12 hrs	Chest radiograph	Exclusion of other respiratory disorders	Prophylactic	Interventional	Type of support	Interface/Device				Pressure	Type of support	Interface/Device	Pressure
Dumas et al., 2011 (41)	France	Prospective unblinded randomized controlled trial	20 CPAP 20 HFPV	38 ± 0.5 37 ± 0.4	100 100	0 0									Within 20 mins after birth		CPAP	Nasal probe	5 cmH ₂ O	HFPV	Nasal probe	5 cmH ₂ O	To determine if nasal HFPV decreases duration of tachypnea compared to nasal CPAP	Duration of respiratory distress	↓ duration TTN symptoms (105 ± 20 vs. 377 ± 150 min; p<0.001) ↓ duration oxygen therapy (6.3 ± 3.3 vs. 19.1 ± 8.1 min; p<0.001) ↓ level of oxygen administered during treatment (O ₂ supplementation index = 0.29 ± 0.16 vs. 0.46 ± 0.50 % min ⁻¹ ; p<0.001)
Demirel et al., 2013 (42)	Turkey	Prospective, unblinded, randomized single centre clinical trial	20 nasal CPAP 20 NIMV	38.1 ± 1.0 37.6 ± 0.8	6 7	0 0											nCPAP	Nasal prongs	6 cmH ₂ O	NIMV – non synchronized mode, 30bpm	Nasal prongs	PEEP 4 cmH ₂ O PIP 16 cmH ₂ O	To compare effect of NIMV to nasal CPAP for management of TTN	Duration of TTN	↔ duration TTN (67.6 ± 36.5 vs. 63.6 ± 39.1 h; p=0.480) ↔ duration of respiratory support (28 ± 19.2 vs. 32.3 ± 23.3 h; p=0.0231) ↔ initial level of oxygen administration (44 ± 5.7 vs. 45.9 ± 14.7%; p=0.501) ↔ O ₂ therapy duration (31.2 ± 15.6 vs. 29.9 ± 19.3 h; p=0.187) ↔ hospitalization (6.2 ± 2.6 vs. 5.4 ± 2.0 d; p=0.330)
Gizzi et al., 2015 (30)	Italy and France	Retrospective multicenter cohort study	40 oxygen therapy 42 CPAP	39.7 ± 1.5 39.3 ± 1.2	52.5 57.1	52.5 57.1									On NICU admission		Supplemental oxygen therapy	Directly into incubator	N/A	CPAP (variable flow)	Nasal prongs	Started at 4 cmH ₂ O and increased to 6 cmH ₂ O as needed. Given oxygen at 6 cmH ₂ O it was not enough to maintain adequate oxygenation	To compare if CPAP is more effective compared to oxygen supplementation alone on management of TTN	NICU length of stay, maximal FiO ₂ , incidence of air leaks during treatment	↓ NICU stay (2.5 ± 2 vs. 4.4 ± 2.6 d; p<0.001) ↓ maximal O ₂ administration (25.7 ± 5.1 vs. 30.5 ± 7.9 %; p=0.002) ↔ air leaks (16.7 vs. 30 %; p=0.16)
Celebi et al., 2016 (23)	Turkey	Prospective randomized study	125 standard care 134 prophylactic	37.7 ± 0.8 37.6 ± 0.7	100 100	0 0									For 20 minutes for 5-10mins of birth		Standard care (no CPAP)	N/A	N/A	CPAP	Face mask	5 cmH ₂ O	To evaluate the effect of prophylactic CPAP in the delivery room after elective CS on TTN/NICU admission	Incidence of TTN and NICU admission due to respiratory distress	↔ TTN incidence (0.7 vs. 4.8 %; p=0.059) ↓ NICU admission (3 vs. 8.8 %; p=0.045)

(Continued)

newborns was greater in the bi-level CPAP group, even though the duration of respiratory support and hospital stay were not different. Interventional use of CPAP (start at 4 cmH₂O and increase to 6 cmH₂O if required) was more effective than supplemental oxygen in newborns with TTN, reducing NICU stay and overall oxygen need. The crossover study reported that two nasal interfaces (mask vs. bi-nasal short prongs) had similar effects on transpulmonary pressure in newborns with TTN (19).

DISCUSSION

Our review has provided insights into the clinical evidence for using non-invasive respiratory support to manage term newborns with or at risk of TTN (Table 1). Our analysis builds upon a previous systematic review (20) which included three studies reporting outcomes using non-invasive respiratory support for TTN. They concluded that the evidence was limited and low-quality due to heterogeneity in study design and an inability to pool data. While this heterogeneity in study design remains a problem, we have included more recent publications to further explore the potential benefit of non-invasive respiratory support. While the outcomes appear to favor the use of non-invasive respiratory support for the treatment of TTN, the significant heterogeneity between studies currently is a limitation that makes direct comparisons between them difficult and precludes a rigorous assessment of the respiratory support approaches that can be used to treat or mitigate the risk of TTN. Furthermore, it is important to note that no studies were conducted in low- or middle-income countries and, as a result, these perspectives do not include an understanding of how TTN is or could be managed in these countries.

Diagnosis and Severity of Transient Tachypnea of the Newborn

While all studies reported inclusion and exclusion criteria for TTN diagnosis, some relied on symptoms alone while others required further radiographic evidence or a scoring system (Silverman score) for diagnosis confirmation and severity assessment. One study reported the degree of respiratory distress as mild or severe, but did not stratify outcomes based on this clinical observation (18). It is possible that some selection bias may have occurred when enrolling newborns, as TTN is a diagnosis largely made retrospectively after the respiratory distress has resolved. As such, newborns with more severe or longer lasting respiratory distress symptoms are often excluded. These factors may explain the relatively short length of therapies and duration of hospital stay reported in the majority of studies, and color the perception that respiratory distress in term newborns is usually mild and self-resolving. However, these interventions remain a burden for families and health care systems. Indeed, this influence on diagnosis and inclusion criteria that may be partially based on outcomes could result in selection bias, particularly in retrospective cohort studies (2/8 studies included in this review; Table 1). Indeed, in these studies a TTN diagnosis will only be made if the newborn does not progress to more severe respiratory distress, whereas other

newborns may have the same disease, but a more severe form that manifests into additional problems, including lung injury. This observation highlights the clinical problem faced when managing newborns born late preterm (>34 weeks gestation), early term (>37 weeks gestation), or full term (>39 weeks gestation) and who develop respiratory distress, as there is undoubtedly a spectrum of symptom severity. While the problem of diagnosis accuracy is not easy to counter, it is important to recognize this as a limitation. Future trials should take into consideration the reporting of factors such as severity of TTN based on symptoms (i.e., Silverman score), diagnostic tools (conventional X-ray or lung ultrasound) and degree of treatment provided to newborns. This will provide useful information for enabling comparison within and between studies. Large randomized trials which evaluate the spectrum of TTN severity and include outcomes in newborns that start with TTN but then develop more severe disease are also required to overcome the selection bias.

Study Characteristics

Gestational Age

As most studies had small sample sizes (average 50 total newborns included), they had limited ability to stratify outcomes by subgroups, including that of gestational age, which could provide valuable insights into the respiratory support outcomes in subpopulations of newborns (21, 22). However, one study was large enough (259 newborns) to stratify into late preterm (34–36 + 6 weeks; 35 newborns) and early term (37–39 + 6 weeks; 224 newborns) comparing CPAP with standard care. They showed a significant difference in NICU admission across the entire cohort, which was driven largely by a difference in late preterm newborns (23). However, with regard to TTN incidence, while no significant difference between prophylactic CPAP and standard care was seen across the whole cohort ($p = 0.059$), a subgroup analysis revealed that the TTN incidence was greater in early-term ($p = 0.057$) compared late preterm newborns ($p = 0.565$) (23). Thus, future studies should avoid including newborns of a broad gestational age, without the capacity to stratify based on gestational age. Indeed, as the underlying cause and optimal treatments for the respiratory distress symptoms will likely differ in these two population subgroups, mixing these subgroups will greatly reduce the effect size.

Mode of Birth

It is well established that delivery by CS in the absence of labor is a major risk factor for TTN (6), but despite this knowledge there was significant heterogeneity between studies for the inclusion of babies born by CS (range from 6 to 100%) and if the CS was planned or unplanned (usually in labor). Nevertheless, prophylactic CPAP (5 cmH₂O) administration for 20 min within 5–10 min of birth in newborns born exclusively by CS (those at greatest risk of TTN) (23), was found to significantly reduce NICU admission, but had no statistically significant effect on TTN incidence ($p = 0.059$) (23). There was significant variability in the outcomes: the number needed to treat with non-invasive respiratory support to benefit newborns with TTN was 25 (OR

6.711; 95% CI: 0.795–55.55). Although the sample size in this study was one of the larger studies captured in this review (295 total newborns; 135 receiving CPAP), it is unclear how many of these newborns would be expected to have suffered from TTN. With a rate of ~1 in 10 term babies born by CS expected to develop respiratory distress, the small but not significant difference in TTN or NICU admission is unsurprising. Nevertheless, it raises an important point about the efficacy of supporting newborns to clear airway liquid in the delivery room in order to mitigate the TTN symptoms that may develop and avoid the need to admit newborns into intensive care in the hours after birth. While the prophylactic CPAP study provides an important perspective into early intervention to reduce the risk of TTN, this study was undertaken in a teaching and research hospital in a high-income country. The logistical issues of applying prophylactic CPAP after CS birth in resource-limited settings and the large number of newborns needed to treat to show benefits, would likely preclude its use in less resourced hospitals and in low- and middle-income countries.

The physiological benefits of being exposed to labor and uterine contractions (i.e., CS with labor vs. elective CS) can reduce the risk of respiratory distress after a CS delivery, but still carries a greater risk compared to vaginal birth (6). As delivery by elective CS is the greatest risk factor for TTN, avoiding planned CS without medical indication would appear logical and is consistent with the World Health Organization recommendations (24). However, there is considerable heterogeneity between countries and hospitals as to the timing of planned CS deliveries, which can occur before 39 weeks, despite a higher risk of respiratory distress after birth. Furthermore, the increase in CS deliveries has led to an increase in the number of otherwise healthy babies, born at term, experiencing TTN. This is a growing concern, particularly as it is projected that by 2030, 28.5% of women worldwide will give birth by CS, equating to 38 million CSs annually, of which 33.5 million will be in low-middle income countries (7).

As it will always be necessary to deliver some newborns by CS, there is considerable merit in finding mechanisms to help prevent TTN from arising in the most at-risk newborns. As it is not feasible to adopt a wide-spread prophylactic approach (e.g., CPAP) for all CS births, a better understanding of the mechanisms causing respiratory distress in these newborns is required (**Figure 2**). In addition, identifying the specific risk conferred by CS birth, may allow identification of the sub-groups at greatest risk so that prophylactic treatment can be targeted to these newborns. Alternatively, rather than applying respiratory support to aid lung function before or after symptom onset, it may be possible to reduce the risk of TTN from developing by reducing airway liquid volumes at CS birth. This is the focus of a current clinical trial which aims to replicate the dorso-ventral spinal flexion usually achieved during uterine contractions following membrane rupture and amniotic fluid loss during CS delivery (Clinical Trial Number L74285.058.20). The resulting loss of liquid decreases the volume of liquid in the airways at birth, reduces the volume liquid that must be absorbed into lung tissue and thereby reduces the risk of TTN. While further large studies are required, proposed approaches should

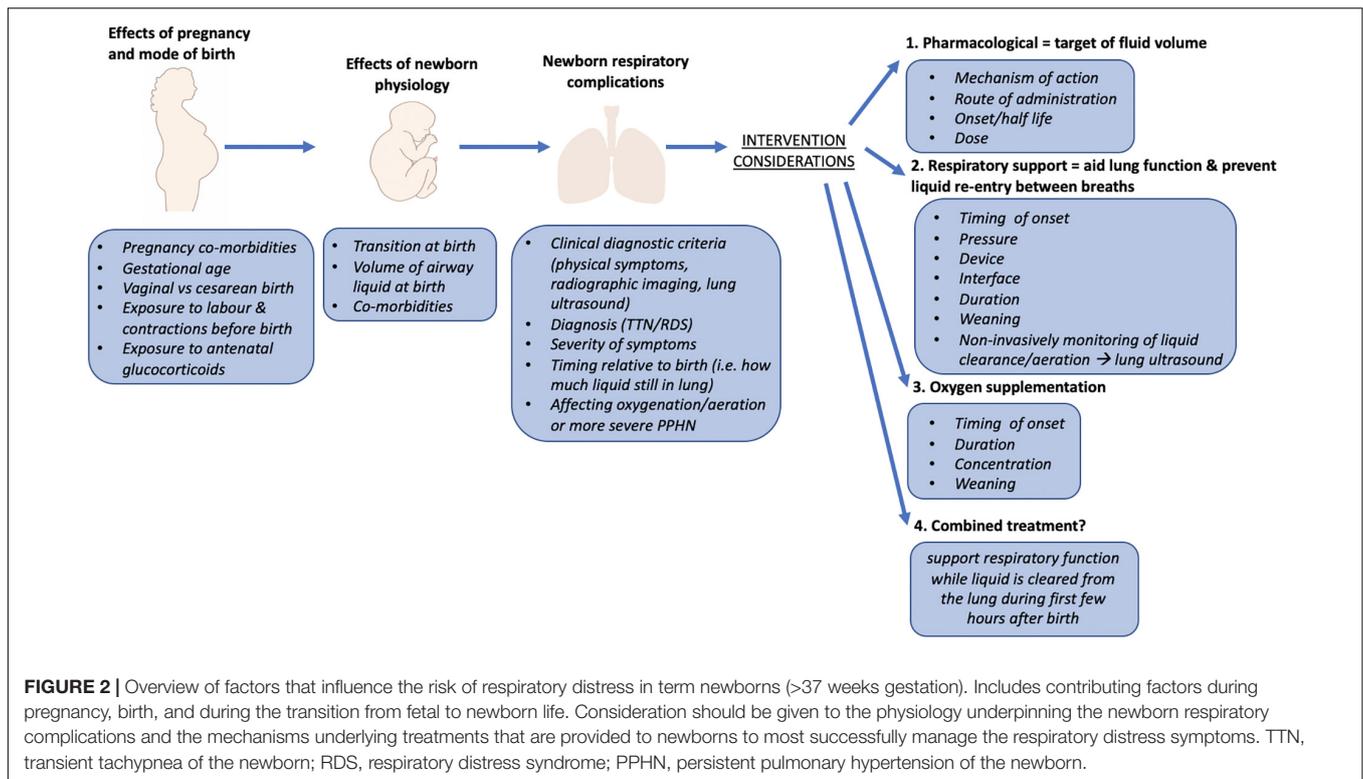
also take into consideration applicability to both low-middle income settings as well as high-income countries.

Antenatal Corticosteroid Exposure

Some studies investigating respiratory morbidity after early term (37–39 weeks' gestation) CS birth, specifically excluded newborns exposed to antenatal corticosteroids (22). In other studies, exposure to antenatal corticosteroids in newborns enrolled in individual studies ranged from 6 to 100%, which is consistent with the large variability in gestational age (32–42 weeks' gestation) of enrolled newborns. While corticosteroids have been investigated for preventing respiratory morbidity in babies born by CS at term (25, 26), their use has been questioned (27) and systematically reviewed with a meta-analysis (28). Nevertheless, the underlying rationale for using antenatal corticosteroids and the precise mechanisms underlying its mode of action in TTN is unclear. It is assumed that they improve TTN outcome by accelerating lung maturity, enhancing liquid reabsorption, and reducing lung tissue density. However, there is some scientific evidence to indicate that reducing lung tissue density may increase the risk and severity of disease (11). It is possible that the large variability observed in both antenatal corticosteroid use and gestational age range of enrolled newborns within and between studies has compounded the heterogeneity in TTN incidence and outcomes between studies. Combining late preterm and term age groups into one cohort is problematic as it assumes that the underlying cause of the respiratory distress is similar and that the proposed treatment will be equally efficacious. Indeed, the evidence for administering corticosteroids to women undergoing CS up to 39 weeks (28) is conflicting, with some obstetricians doubting the evidence at 37–39 weeks. Thus, we suggest that all future studies should report antenatal corticosteroid exposure in their cohort demographics and that the gestational age range be minimized so that findings can be more reliably interpreted.

Respiratory Support Interventions for Babies With or at Risk of Transient Tachypnea of the Newborn

The majority of studies (7/8) captured in this review used respiratory support as an intervention in newborns diagnosed with TTN. However, the timing of onset markedly varied from 20 min after birth, at NICU admission or at 6 h after birth. As airway liquid clearance after birth increases lung interstitial tissue pressures (29), recent scientific evidence indicates that these elevated pressures play a key role in respiratory distress symptoms displayed by term or near-term newborns (9, 12). As a result, it is difficult to compare outcomes between studies when the lung is at different stages of transition, with respect to clearing this liquid from the airways and tissue (10). As such, reporting information about the timing of respiratory support onset and severity of disease is needed to better understand the underlying physiology of the newborns at the time of intervention and provide better context for the reported findings.



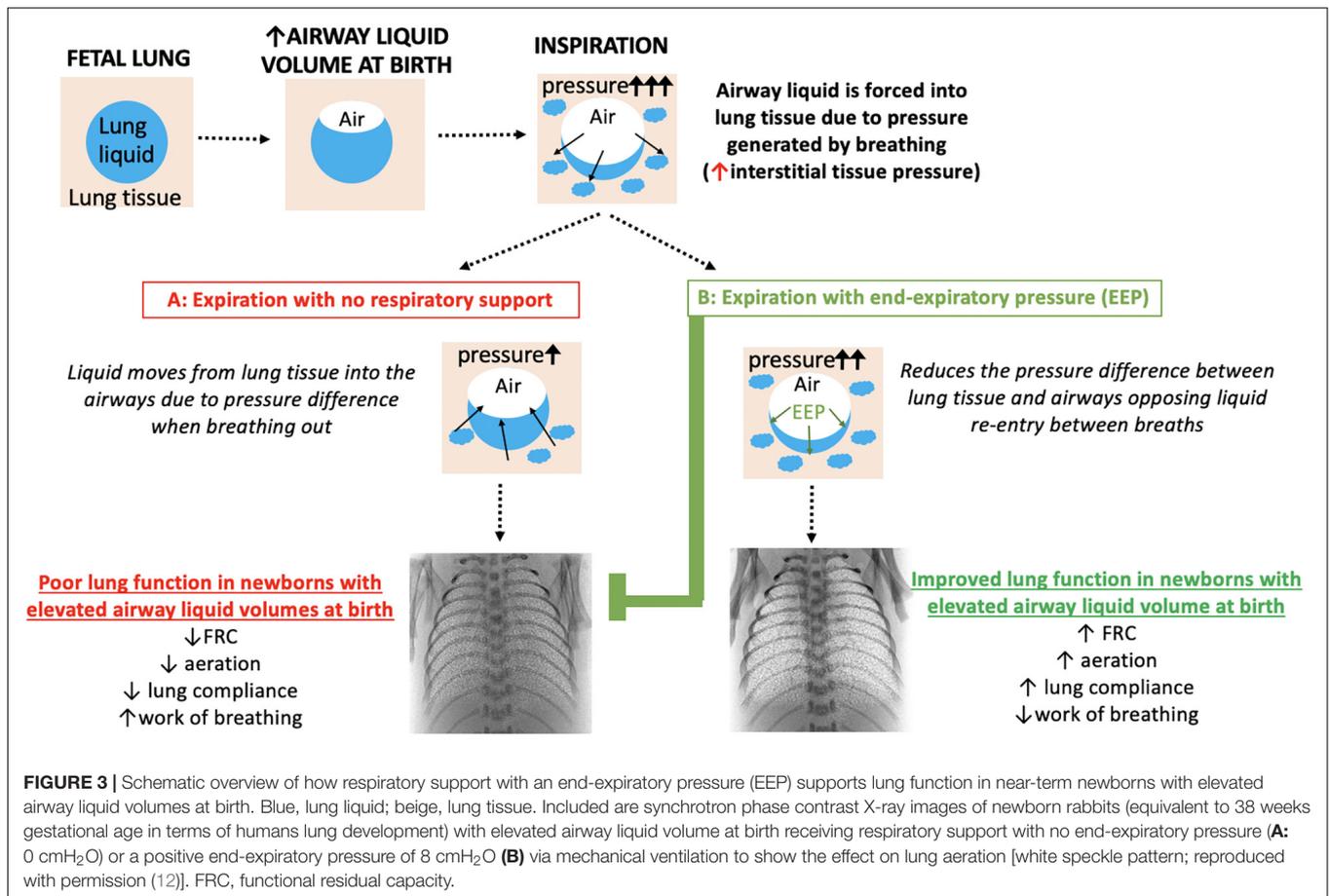
While all studies (**Table 1**) focused on newborns with or at risk of TTN, the large variation in study design makes it difficult to directly compare outcomes. Differences include (1) prophylactic CPAP vs. no intervention, (2) supplemental oxygen vs. CPAP, (3) different types and interfaces for applying the respiratory support, (4) different pressure levels, and (5) different timings for treatment onset and TTN diagnosis. Two studies (one randomized double blind clinical trial and one retrospective cohort study) indicate that CPAP may reduce tachypnea duration, NICU stay and maximal FiO_2 exposure compared with oxygen alone (18, 30). However, it is difficult to draw conclusions with regard to the “early rescue” use of CPAP as the timing of application was not reported, particularly in regard to disease progression. As such, it remains unclear when CPAP should be applied. Importantly, these studies indicate that oxygenation in itself is not the main driver of TTN symptoms and that an end-expiratory pressure can mitigate disease progression. The findings are also consistent with the concept that CPAP helps to improve lung function when high volumes of liquid must be cleared over the first 4–6 h of life. While the initial oxygen levels provided and the amount of supplemental oxygen provided after CPAP levels were increased varied between studies, the FiO_2 level was likely titrated against arterial oxygen saturations. Nevertheless, variability in these factors makes it difficult to tease apart the relative contribution of respiratory support and oxygenation for improving clinical outcomes in newborns with TTN.

Different respiratory support devices for TTN have been discussed previously (31) and different types of respiratory

support have also been compared (five studies). All newborns in these studies received respiratory support by either nasal prongs or nasal mask (see **Table 1**), but variability in methods between studies precludes a rigorous comparison and not all studies were randomized. Unfortunately, no clinical studies have yet investigated the effect of different pressures with the same device to specifically examine the effect of pressure.

In the studies examined, the duration of respiratory support ranged from a few hours to a few days (3–50 h), which suggests that disease severity differed between studies, with some studies including those with more severe respiratory distress, as TTN is thought to resolve within the first day or so after birth. This heterogenous requirement for respiratory support may also reflect the intersection between gestational age dependent effects on lung immaturity and surfactant maturity and/or function on lung aeration. Thus, differences in disease severity, the timing of treatment onset relative to symptom onset and the rationale for providing treatment also reduces the capacity to compare outcomes between studies. However, as the findings indicate small but significant benefits of prophylactic or early CPAP use, larger studies with better defined inclusion criteria and treatment regimens are required. Indeed, while there was considerable heterogeneity in approaches, all studies reported that non-invasive respiratory support was well tolerated by newborns and was not associated with an increased risk of air leaks.

As for preterm newborns, it is important to identify the best methods for supporting term newborns with TTN and how the respiratory support provided facilitates or impedes the transitional changes in newborn physiology (**Figure 2**). This review has highlighted the need for future studies to identify



interfaces, devices and pressures that most effectively support newborns with TTN, which may or may not be similar to what is used in premature newborns. However, while higher CPAP levels may reduce the need for supplemental oxygen (32), it is important to ensure that it does not impair cardiovascular function (2).

Physiological Perspectives and Considerations for Treating the Underlying Cause of Transient Tachypnea of the Newborn

In contrast to premature newborns, little is known about the benefits of end-expiratory pressures to support lung function in term newborns with respiratory distress shortly after birth. Recent scientific studies indicate that greater airway liquid volumes at birth underpin the respiratory symptoms suffered by newborns with TTN, including tachypnea and expiratory grunting with rapid and labored breathing (9, 11). They have also shown that an end-expiratory pressure of 8 cmH₂O (vs. 5 cmH₂O) improves FRC and lung mechanics in mechanically ventilated newborn rabbits with airway liquid volumes similar to that expected following elective CS birth (~37 ml/kg) (12). The higher end-expiratory pressures prevented liquid from re-flooding the airways between inflations, resulting in higher FRCs

(Figure 3) and improved gas exchange (10) by increasing the lung's surface area available for gas exchange throughout the respiratory cycle. However, the optimal end-expiratory pressures are still unknown and are likely to differ depending on disease severity and the volume of airway liquid present at birth.

Gestational age and exposure to antenatal corticosteroids are likely to be major complicating factors because the density of lung tissue relative to airspace volume is greatly reduced in a mature lung. As such, a larger volume of airway liquid must be accommodated by a relatively smaller volume of lung tissue, which likely explains the higher prevalence of TTN in mature term newborns. In contrast, when the lung is less mature a relatively smaller volume of airway liquid can be absorbed into a relatively greater tissue volume, which greatly reduces the impact on lung function (11). Thus, respiratory distress in preterm newborns (e.g., 32 weeks), which is sometimes classified as TTN because it is relatively mild, is likely to have a lung immaturity component to it. While it can also be treated with CPAP, the underlying cause is substantially different.

In addition to CPAP level, many other factors should be considered when assessing potential treatments for TTN. These include the timing of treatment onset after birth, the duration of treatment and the goals that can be used to indicate when support can be weaned (Figure 2). As a “one-size-fits-all” approach is unlikely to be sufficient (Figures 2, 3), there is a need to

develop methods that provide greater clarity of treatment success and the ability to monitor progress over time. A recent study has investigated the use of non-invasive forced oscillometry to quantify respiratory mechanics in term newborns with TTN and may have some utility in assessing respiratory mechanics. However, as it was conducted in newborns on postnatal days 1 and 3, it is unclear how effective it is during the first day after birth (33). Furthermore, as lung ultrasound can monitor lung aeration in newborns (34) and assess the relative levels of airway liquid, it can identify pathological changes in lung function characteristic of TTN (35, 36). As lung ultrasound is non-invasive, does not involve radiation and can be conducted at the bedside with common ultrasound machines, it has much clinical utility. Lung ultrasound can detect TTN (37), monitor changes in lung function associated with repositioning newborns (38), monitoring clinical progression of TTN (39) and can potentially predict those newborns likely to require intensive care admission for TTN (40). As such, future studies aimed at investigating respiratory support approaches for newborns with TTN may benefit from utilizing lung ultrasound to more accurately assess the effectiveness of treatments.

CONCLUSION

While the studies reviewed have shown that respiratory support interventions can improve outcomes for newborns with TTN, numerous questions remain unanswered. For instance, the timing of respiratory support onset (prophylactic/interventional), the method of support (device/interface), the pressure of support delivered and the approaches for weaning this support are currently unknown (Figure 2). When considering the best approach for supporting newborns with TTN, the mode of birth (elective CS vs. CS with labor vs. vaginal) and the time after birth of TTN symptom onset must also be considered as they will influence the success of treatment (Figure 2).

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It is clear that further understanding of the continuum of respiratory distress severity and the mechanisms causing respiratory distress and TTN in term newborns is needed. While the most effective way to reduce the incidence of TTN is to avoid non-medically indicated elective CS deliveries, there is still a pressing need to find ways to best support newborns who develop TTN. Further large clinical trials are needed to identify approaches that reduce the risk of TTN in at-risk newborns or by better supporting respiratory function in newborns who develop TTN to minimize its severity.

Overall, this narrative literature review provides insights and considerations for future studies aimed at characterizing the effects of supporting term newborns with or at risk of TTN. This is an important step toward generating the highest quality evidence for guiding and informing recommendations for the most effective management strategies to improve outcomes for the growing burden of TTN in this group of otherwise healthy term babies.

AUTHOR CONTRIBUTIONS

EM, AP, and SH were responsible for the conception and design of the project and drafted the manuscript. EM conducted the data acquisition and synthesis. EM, AP, TA, JK, MT, and SH were involved in analysis and interpretation of the data. All authors contributed to the final version.

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