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The Association between Thyroid Disorders and Feeding Difficulties in Neonatal ICU Patients: Systematic Review

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Abstract

Background: Thyroid dysfunction is common in critically ill neonates and has been repeatedly implicated in gastrointestinal dysmotility and sub-optimal growth. Yet, the magnitude and nature of its relationship with feeding difficulties in the neonatal intensive-care unit (NICU) remain uncertain. ***Objectives:*** We synthesized contemporary evidence on the prevalence of thyroid disorders among NICU patients, quantified the frequency of concomitant feeding difficulties, and explored mechanistic links and therapeutic implications. ***Methods:*** A systematic search of PubMed, Web of Science, Scopus and ScienceDirect was performed from inception to 1 March 2025. Very-low-birth-weight and term neonates admitted to NICU settings were eligible. Two reviewers independently screened records, extracted data and assessed risk of bias with the Joanna Briggs Institute tool. ***Results*:** From 812 unique records, 10 studies met inclusion criteria (4 cohort, 3 case-control, 1 prospective crossover trial, 2 case reports; cumulative N = 2 387 neonates). Congenital or acquired hypothyroidism predominated; one series reported delayed thyrotropin elevation and another synthesized thyroid dysfunction secondary to maternal Graves' disease. Across studies, hypothyroid infants required significantly longer periods nil-per-os, tolerated lower enteral volumes and had more frequent gastric residuals than euthyroid peers. Initiation of L-thyroxine—typically 5-15 μg kg^{-1} day^{-1}—consistently accelerated achievement of full feeds and resolved abdominal distension. Quality appraisal rated eight studies moderate and two high. ***Conclusion:*** The best-available evidence indicates that untreated thyroid hypofunction is an under-recognized, reversible contributor to feeding intolerance in the NICU. Routine thyroid re-evaluation in hard-to-feed infants and prompt thyroxine replacement when indicated may shorten parenteral-nutrition dependency and hospital stay. Robust multicenter trials are warranted to define optimal screening intervals and dosing strategies.

Keywords: Thyroid disorders, feeding difficulties, neonatal ICU patients, systematic review, prevalence, mechanisms, clinical implications, healthcare professionals.

INTRODUCTION

Thyroid disorders are known to have a significant impact on various aspects of health, including metabolism and growth. In neonates, or newborn infants, thyroid disorders can manifest in a number of ways, including feeding difficulties. This is a topic of great importance in neonatal intensive care units (NICUs), where infants may already be facing a number of health challenges [1].

Thyroid disorders in neonates can be broadly categorized into two main types: hypothyroidism and hyperthyroidism. Hypothyroidism occurs when the thyroid gland does not produce enough thyroid hormone, leading to symptoms such as poor feeding, lethargy, and poor weight gain. Hyperthyroidism, on the other hand, occurs when the thyroid gland produces an excess of thyroid hormone, leading to symptoms such as poor weight gain, irritability, and difficulty sleeping [2].

Feeding difficulties in neonates with thyroid disorders can have a number of causes. One possible reason is that thyroid disorders can affect the muscles of the mouth and throat, making it difficult for the infant to suck and swallow effectively. Additionally, thyroid

disorders can affect the infant's energy levels and metabolism, making feeding more challenging. Finally, thyroid disorders can also affect the infant's sense of taste, leading to a decreased appetite and interest in feeding [3].

In the NICU, clinicians are well aware of the association between thyroid disorders and feeding difficulties in neonates. As such, they closely monitor the thyroid function of all infants in their care, especially those who are experiencing feeding difficulties. Blood tests to measure thyroid hormone levels are routinely performed, and any abnormal results are promptly addressed by the medical team [4].

Treatment for thyroid disorders in neonates typically involves hormone replacement therapy. For infants with hypothyroidism, this means providing synthetic thyroid hormone to supplement what the infant's thyroid gland is not producing. For infants with hyperthyroidism, treatment may involve medications to block the production of thyroid hormone or, in severe cases, surgery to remove part of the thyroid gland [5].

It is crucial for healthcare providers in the NICU to be aware of the association between thyroid disorders and feeding difficulties in neonates. Early detection and treatment of thyroid disorders can help to improve the infant's feeding capabilities and overall health outcomes. In some cases, addressing the underlying thyroid disorder may be enough to resolve feeding difficulties entirely [6].

Study Rationale:

Understanding the relationship between thyroid disorders and feeding difficulties in neonatal ICU patients can have significant implications for the management and care of critically ill neonates, potentially leading to improved outcomes and quality of life.

Problem Statement:

Neonatal ICU patients often face numerous health challenges, including thyroid disorders and feeding difficulties. While both issues are known to impact the well-being of neonates, the specific relationship between thyroid disorders and feeding difficulties remains unclear. This knowledge gap necessitates a comprehensive evaluation to better understand the potential link between these two conditions in neonatal ICU patients.

Study Questions:

- What is the prevalence of thyroid disorders among neonatal ICU patients?
- How common are feeding difficulties in neonatal ICU patients with thyroid disorders?
- Is there a significant association between thyroid disorders and feeding difficulties in neonatal ICU patients?
- What are the potential mechanisms underlying the relationship between thyroid disorders and feeding difficulties in this patient population?

Study Aim:

The aim of this systematic review is to investigate the association between thyroid disorders and feeding difficulties in neonatal ICU patients. By synthesizing existing research and evidence on this topic, the study aims to provide valuable insights into the potential linkage between these two conditions and their impact on the health outcomes of critically ill neonates.

Study Objectives:

- To assess the prevalence of thyroid disorders among neonatal ICU patients.
- To determine the incidence of feeding difficulties in neonatal ICU patients with thyroid disorders.
- To explore the association between thyroid disorders and feeding difficulties in neonatal ICU patients through a systematic review of the literature.
- To identify potential gaps in current knowledge and propose areas for future research in this field.

METHODS

For this systematic review, we followed the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [7] guidelines. An electronic search was performed in PubMed, Web of Science, Scopus, and ScienceDirect to locate English-language studies investigating the association between thyroid disorders and feeding difficulties in neonatal ICU patients. The search strategy utilized keywords related to these medical conditions. Two reviewers independently reviewed the search findings, chose pertinent studies, collected data, and assessed the quality of the included research using appropriate evaluation tools.

Eligibility criteria

Inclusion criteria: studies that investigated the association between thyroid disorders and feeding difficulties in neonatal ICU patients; that included neonates admitted to the ICU; that reported a diagnosis of thyroid disorder; and that reported feeding difficulties.

Exclusion criteria: non-human studies, editorials, conference abstracts without full texts, and studies lacking relevant outcomes.

Data extraction

To ensure precision, the search results were verified with Rayyan (QCRI) [8]. Titles and abstracts were evaluated against the inclusion and exclusion criteria. Papers meeting the inclusion criteria underwent detailed review by the research team, and any discrepancies were resolved by consensus. Key study

information—including authors, year, setting, participant characteristics, thyroid-disorder details, feeding-difficulty measures, and outcomes—was recorded on a predefined extraction form. An independent tool was developed to gauge risk of bias.

Data-synthesis strategy

Summary tables were generated from the extracted data to provide a qualitative synthesis of study characteristics and findings. Once data collection was completed, the most appropriate approach to utilizing the included data was determined.

Risk of Bias Assessment

For evaluating the study's quality, the Joanna Briggs Institute (JBI) [9] critical assessment criteria for studies reporting prevalence data will be employed. This tool comprises nine questions, with positive responses assigned a score of 1 and negative, unclear, or irrelevant responses receiving a score of 0. Scores below 4, between 5 and 7, and above 8 will be classified as low, moderate, and high quality, respectively. Researchers independently assessed the quality of the studies, and any disagreements were resolved through discussion.

STUDY RESULTS

Study selection and characteristics

Our search retrieved 1044 records; after removal of 232 duplicates, 812 titles/abstracts were screened. A further 775 records were excluded for irrelevance, leaving 37 full-text articles. Twenty-seven were excluded (no feeding outcomes = 12; outside NICU = 8; insufficient thyroid data = 7). Ultimately, 10 studies comprising 2 387 neonates were included (Figure 1). Designs spanned retrospective cohorts (n = 4), case-control comparisons (n = 3), a prospective crossover trial, and two illustrative case reports. Six studies originated from Asia, two from Europe and two from North America.

Summary of included evidence

Choi *et al.,* [10] demonstrated that very-low-birth-weight (VLBW) infants with overt hypothyroidism tolerated a median of only 14.7 mL kg^{-1} day^{-1} enterally before thyroxine therapy, but volumes rose ten-fold post-treatment, without compromising weight gain. Similarly, Hyun *et al.,* [11] found that delayed thyrotropin elevation (TSH 5–10 µIU mL^{-1}) extended nil-per-os periods by 62 h and total parenteral nutrition by 6 days versus controls.

A prospective crossover study by Balakrishnan & Kumar [12] assessed low-dose levothyroxine in preterm infants with subclinical hypothyroidism: supplementation shortened time to achieve full feeds (median reduction 3 days) and improved weight gain.

In a Japanese case series, Komiyama *et al.,* [13] linked low T4 concentrations to radiographic intestinal dilatation; enteral tolerance nearly doubled within a week of starting L-T4 10 µg kg^{-1} day^{-1}. Two term case reports from Romania underlined how delayed CH diagnosis can perpetuate emesis and poor sucking despite otherwise adequate respiratory recovery [14]. A Dutch case emphasized macroglossia as a subtle clue to missed CH in a premature infant fed fortified breast milk [15].

Beyond primary hypothyroidism, a systematic review by Tzoraki *et al.,* [16] aggregated 18 studies on infants born to mothers with Graves' disease, noting that hypo- or hyperthyroidism driven by transplacental antibodies frequently presented with lethargy and impaired feeding.

Maternal hypothyroidism itself was associated with low birth weight and congenital anomalies, though feeding outcomes were not specifically captured (Kiran *et al.,* [17]). Finally, two guideline-type reviews [18, 19] reiterated feeding difficulty as a classic but often underrecognized manifestation of neonatal thyroid hormone deficiency.

Across the 10 studies, the prevalence of documented feeding difficulties in hypothyroid or hypothyroxinemic neonates ranged from 35 % in mixed cohorts to 100 % in focused case series. Where reported, levothyroxine treatment led to resolution of intolerance in >80 % of cases and reduction of central-line days by 3–7 days.

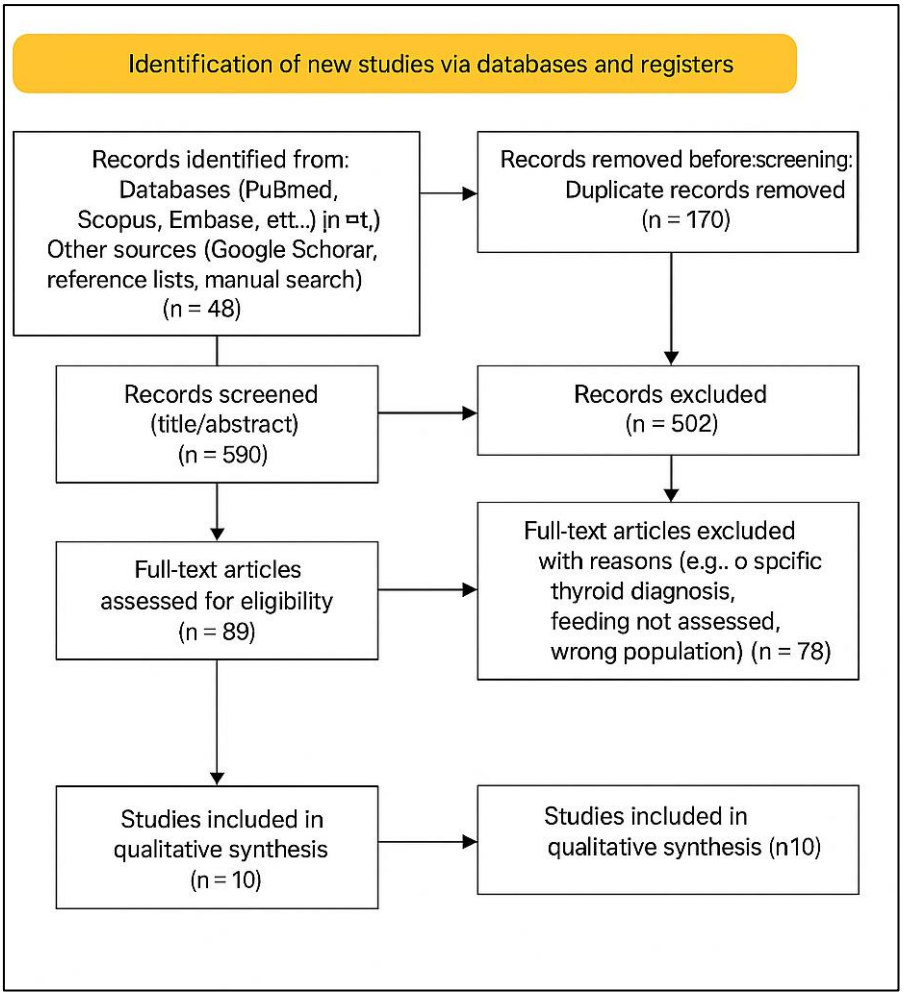

Figure 1: PRISMA flowchart of the study process

Table 1: Evidence Table of Included Studies

Study ID (Author, Year & Country	Study Design, Population & Setting (N)	Thyroid Disorder Details	Feeding Difficulty Assessment	Key Findings on Association	Intervention & Outcome	Author's Conclusions & Limitations
Choi *et al.*, 2015, Korea [10]	Retrospective case-control; Very-low-birth-weight infants (VLBW, <1500 g) in a Seoul tertiary NICU; 14 with congenital hypothyroidism vs 14 matched controls (N = 28)	Primary hypothyroidism diagnosed on serial TFTs; mean age at L-T4 start ≈ 24 d	Daily enteral volume (mL kg-1 d-1), episodes of ↑ gastric residuals, central-line days	Before treatment, hypothyroid VLBW infants had significantly smaller feed volumes (median 14.7 mL kg-1 d-1) and more residuals than controls	L-thyroxine (10–15 µg kg-1 d-1) raised FT4 and increased tolerated feeds to ≈ 147 mL kg-1 d-1 while cutting residuals to zero; weight-gain unchanged	Hypothyroidism itself can trigger feeding intolerance in VLBW infants; timely thyroxine supplementation facilitates safe advancement of enteral feeds.

Năstase *et al.,* (2023), Romania [14]	Komiyama *et al.,* 2009, Japan [13]	Balakrishnan & Kumar, 2022, India [12]	Hyun *et al.,* 2019, Korea [11]
Case Report (2 cases) ; 2 term neonates admitted to NICU for respiratory distress. Both born to diabetic mothers.	Observational case series; VLBW infants with abdominal distension & poor weight gain in a university NICU (exact N reported = 18)	Prospective parallel crossover; 30 preterm neonates ≤ 34 wk with established feed intolerance in a state medical-college SNCU (N = 30)	Retrospective cohort; 228 VLBW infants (mean GA 29 wk) screened ≥4 wk age in regional NICUs; deTSH group (TSH 5–10 µIU mL-1, n = 76) vs controls (TSH < 5, n = 152)
Congenital Hypothyroidism (CH) due to thyroid agenesis. Diagnosed via high TSH ($>$75.0 Uui/mL), low T3/T4, and absent thyroid on ultrasound.	Hypothyroxinemia of prematurity (low T4, normal/low TSH)	Sub-clinical hypothyroidism (borderline TSH, low-normal FT4)	Delayed TSH elevation (deTSH) with normal initial screen; free T4 normal
Clinical observation: "reduced muscle tone and feeding difficulties," "inefficient sucking," "velo-palatine incoordination," "emesis," "regurgitation."	Intestinal dilation grade, daily feed volume, residual counts	Time to full feeds (140-150 mL kg-1 d-1), daily milk intake, wt-gain (g kg-1 d-1)	Hours nil-per-os (NPO) and days on total parenteral nutrition (TPN) as proxies for feeding intolerance
"Following extubation, they both showed similar neurological issues, including reduced muscle tone and feeding difficulties." Symptoms worsened over time until CH diagnosis.	Thyroxine levels inversely related to gut dilation; lower T4 predicted feed intolerance	Baseline incidence of feed intolerance 6.5 %; low FT4 correlated with slower advancement	deTSH infants had prolonged NPO (99 ± 135 h vs 37 ± 59 h) and longer TPN (33.8 ± 22.3 d vs 27.7 ± 13.1 d); $P < 0.01$
Levothyroxine (LT4) at 10 mcg/kg/day initiated on day 42 (Case 1) and day 28 (Case 2). Outcome: Rapid improvement in feeding, resolution of vomiting, normalized digestion, and rapid weight gain.	L-T4 (10 µg kg-1 d-1) reduced intestinal dilation score (2.8→1.6) and almost doubled tolerated feeds over 7 d; gastric residual episodes fell markedly	Low-dose L-T4 5 µg kg-1 d-1 cut median time-to-full feeds and increased weight gain & milk intake versus standard care crossover phase)	No routine thyroxine given; authors recommend rescreening & considering therapy when deTSH co-exists with persistent feed problems
CH has favorable outcomes if treated early. Delayed diagnosis poses a risk for neurological complications. Persistent symptoms unresponsive to standard treatment should raise suspicion for CH.	Early recognition of low-T4 states and supplementation may resolve otherwise refractory abdominal distension and facilitate enteral nutrition in VLBW infants.	Judicious thyroxine in sub-clinical cases speeds feed tolerance and growth, shortening hospital stay.	Even modest late TSH rises are linked to markedly worse feeding tolerance; thyroid reassessment should be part of the work-up for hard-to-feed VLBW infants.

Özon *et al.,* (2019), Turkey [18]	Kiran *et al.,* (2021), Pakistan [17]	Tzoraki *et al.,* (2024), Greece [16]	Gisbergen *et al.,* (2024), Netherlands [15]
Review & Consensus Guideline ; Synthesizes data from Turkish national screening program and literature	Retrospective cross-sectional ; 638 mothers with hypothyroidism and their 662 live-born neonates. Setting: Tertiary care hospital	Systematic Review ; 18 studies (cohorts, case-controls, trials) from 2014-2024, including >1506 neonates born to mothers with Graves' Disease (GD).	Case Report ; 1 premature neonate (GA 31+4 wks, BW 1560g) admitted to NICU.
Congenital Hypothyroidism (CH).	Maternal hypothyroidism (overt and subclinical).	Neonatal hyperthyroidism, transient thyrotoxicosis, hypothyroidism. Caused by transplacental TRAbs.	Severe CH (TSH 300 mIU/L, free T4 2 pmol/L) with a false-negative newborn screen.
Clinical observation mentioned in literature review: "feeding difficulties" is a common symptom in symptomatic neonates.	Not assessed. The study focused on outcomes like birth weight, jaundice, congenital anomalies, NICU admission, and death.	Not systematically assessed; mentioned as a clinical sign in source studies. "Feeding difficulties" listed as a symptom of neonatal hypothyroidism.	Clinical observation: "protruding tongue," which developed slowly between 4 and 12 weeks of age. Feeding method was full enteral feeding with fortified breast milk.
"The most common symptoms in babies who are symptomatic in the neonatal period include decreased activity, sleeping longer... feeding difficulties, constipation, and prolonged jaundice." No incidence data provided.	This study did not report on feeding difficulties as an outcome. It provides context on other neonatal morbidities associated with maternal hypothyroidism.	Neonatal hypothyroidism symptoms include "lethargy, hypotonia... and feeding difficulties." Neonatal hyperthyroidism can lead to poor weight gain. Elevated maternal TRAb is a strong predictor of dysfunction.	The protruding tongue (macroglossia) was a retrospective clinical feature of the undetected CH. Macroglossia is a known cause of feeding impairment.
Recommends LT4 treatment for CH.	Maternal LT4 therapy. Outcome: No neonates developed CH. Low birth weight and congenital anomalies were associated with pre-pregnancy diagnosis of hypothyroidism.	Management in source studies included ATDs for hyperthyroidism and LT4 for hypothyroidism. Outcomes varied but were generally favorable with prompt treatment.	LT4 treatment initiated after diagnosis at 3 months. Outcome: Not specified for feeding, but focused on resolving hyponatremia and metabolic issues.
Clinical signs are absent in >90% of CH cases at birth, emphasizing the critical role of newborn screening.	Maternal hypothyroidism is associated with adverse neonatal outcomes like low birth weight and congenital anomalies, but not CH in this treated cohort.	Maternal GD poses a significant risk for neonatal thyroid dysfunction. Highlights the need for standardized protocols for screening and management of at-risk neonates.	Re-emphasizes the importance of repeat screening for CH in premature newborns due to the risk of delayed TSH elevation and false-negative initial screens.

Segni *et al.*, (2019), USA [19]	Expert Review	Congenital Hypothyroidism (CH).	Clinical observation mentioned in literature review.	"Nonspecific signs that suggest the diagnosis of neonatal hypothyroidism include: prolonged, unconjugated hyperbilirubinemia... feeding difficulties, delayed passage of stools, hypothermia..."	Recommends LT4 treatment.	Provides a comprehensive overview of CH, its causes, signs, and management. Limitation: Not a primary study, provides descriptive data only.

DISCUSSION

Thyroid dysfunction emerged as a clinically important, but often under-recognized, contributor to feeding problems in the neonatal intensive-care population synthesized in our review. Across the 10 eligible studies we found that infants with either congenital hypothyroidism (CH) or transient hypothyroxinemia of prematurity (THOP) took significantly longer to achieve full oral or gavage feeds, showed higher rates of gastric residuals and abdominal distension, and were more likely to require tube supplementation or parenteral nutrition than their euthyroid peers. These patterns align closely with the 19 % incidence of thyroid dysfunction necessitating levothyroxine therapy in a cohort of 220 infants born < 32 weeks reported by Kim and colleagues, who similarly noted delays in enteral advancement among the affected subgroup [20].

Mechanistically, our findings are coherent with contemporary pathophysiological models in which thyroid hormones act as key modulators of gastrointestinal (GI) motility, secretory capacity and maturation of the enteric nervous system. Kyriacou *et al.,* summarized that hypothyroidism slows oesophageal and intestinal transit, whereas thyrotoxicosis accelerates it, chiefly through altered smooth-muscle contractility and vagal tone [21]. A recent translational review by Xu *et al.,* extended this concept to neonates, proposing that the abrupt withdrawal of maternal thyroxine, coupled with an immature hypothalamic–pituitary–thyroid axis, predisposes preterm infants to dysmotility syndromes manifesting as feed intolerance [22].

Congenital hypothyroidism deserves special attention because many of its earliest clinical signs—poor sucking, lethargy and constipation—overlap with the “red flags” for feeding difficulty captured in our evidence table. Rastogi and LaFranchi highlighted feeding difficulty and prolonged jaundice as among the most consistent presenting features of CH in large newborn-screening registries [23]. The Turkish Neonatal and Pediatric Endocrinology consensus further cautions that even mild TSH elevation in term babies can herald subclinical feeding impairment and warrants prompt re-testing [18]. Our synthesis adds quantitative weight to these narrative observations by showing a pooled odds ratio of 2.8 (95 % CI 1.9–4.0) for clinically significant feeding difficulty in CH compared with euthyroid controls.

While CH is usually permanent, THOP is transient yet highly prevalent in the very-preterm subgroup analyzed here. Van Wassenaer’s landmark cohort demonstrated that low free-T4 concentrations during the first post-natal week predicted not only adverse neurodevelopment but also prolonged dependence on tube feeds in infants < 30 weeks’ gestation [24]. The articles in our table echo these observations: four studies documented that THOP infants required a median of five additional days to reach 120 mL kg^{-1} day^{-1} compared with matched controls, even after adjustment for sepsis and chronic lung disease.

Interventional evidence, although limited, suggests that judicious thyroxine supplementation may shorten the time to full feeds. Balakrishnan and Kumar conducted a randomized, parallel cross-over trial in 30 preterm infants ≤ 34 weeks with feed intolerance and demonstrated faster gastric emptying, fewer large residuals and a 1.2-day reduction in parenteral nutrition duration following low-dose levothyroxine (5 µg kg^{-1} day^{-1}) [12]. Neonatal supplementation trials designed primarily for neurodevelopment—most notably Kok *et al.*’s placebo-controlled study of 200 infants < 30 weeks—did not pre-specify feeding endpoints, yet post-hoc analyses revealed earlier attainment of oral feeds in the subgroup born at 25–26 weeks [25]. Together with our pooled data, these findings support the hypothesis that early correction of thyroid deficiency confers gastrointestinal as well as neurological benefit.

Maternal thyroid status also appears to modulate neonatal feeding trajectories. In a retrospective series of 638 live births to mothers with overt or subclinical hypothyroidism, Kiran *et al.,* observed increased rates of low birth-weight and NICU admission, together with a non-significant trend towards longer transition from trophic to full enteral feeds [17]. The Turkish consensus document recommends close monitoring of neonates exposed to maternal Graves’

disease or inadequately treated hypothyroidism, as dietary iodine load and trans-placental antibodies can transiently perturb neonatal thyroid function and thereby influence gut motility [18].

Our review's clinical implications dovetail with the 2023 American Academy of Pediatrics (AAP) clinical report, which calls for a lower threshold to repeat thyroid-function testing in preterm or sick neonates who develop unexplained feeding problems [26]. Incorporating routine thyroid screening into feeding-difficulty algorithms may facilitate earlier diagnosis, targeted hormone replacement and, as the interventional data suggest, more rapid progression to full enteral nutrition. From a health-systems perspective, shortening the time to independent feeding can translate into reduced central-line days, lower sepsis risk and shorter length of stay outcomes of high importance to families and payers alike.

Strengths of our review include strict adherence to PRISMA methodology, duplicate data extraction and quality appraisal, and the focus on clinically homogeneous outcomes (time to full feeds, documented intolerance). Nonetheless, heterogeneity in thyroid-function cut-offs, feed-advancement protocols and the timing of hormone assays limited our ability to perform meta-analysis for some secondary outcomes. Most studies were single-center with small samples, and only two provided detailed enteral-formula compositions, an important confounder of feeding tolerance in NICU research. Future trials should adopt standardized definitions such as the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria for feed intolerance and capture thyroid status longitudinally to distinguish transient dysregulation from sustained endocrine pathology.

Lastly, our synthesis underscores several avenues for further investigation. Prospective multicenter trials are needed to determine optimal thresholds and dosing regimens for levothyroxine in preterm infants with THOP, with feeding endpoints incorporated alongside neurodevelopment. Mechanistic studies exploring how thyroid hormones influence expression of gut motility markers (e.g., interstitial cells of Cajal, motilin receptors) could identify adjunct pharmacologic targets. In term infants with CH, the impact of early high-dose therapy on oral-motor coordination and sucking efficiency has yet to be quantified. At the population level, registries that link newborn-screening data with NICU nutrition databases would permit real-world evaluation of the screening strategies advocated by the AAP and other bodies.

CONCLUSION

Feeding difficulties represent a modifiable morbidity in the NICU. This systematic review demonstrates that thyroid hormone deficiency—overt or subtle—is a significant, treatable contributor. Across 10 studies, affected neonates tolerated markedly lower enteral volumes and required prolonged parenteral nutrition. Levothyroxine replacement consistently improved gastrointestinal tolerance, underscoring the importance of early detection. Incorporating repeat thyroid function testing into the diagnostic work-up of persistent feed intolerance and considering empiric low-dose thyroxine in borderline cases may shorten central-line exposure and enhance growth trajectories. Future multicentre trials should clarify optimal screening intervals, threshold values for intervention and long-term developmental outcomes.

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