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(REVIEW ARTICLE)

Neonatal hyperthyroidism: Distinguishing transient antibody-mediated disease from permanent genetic forms

Ashraf T. Soliman [1,*], Shayma Ahmed [1], Fawzia Alyafei [1], Noora AlHumaidi [1], Nada Alaaraj [1], Noor Hamed [1], Shaymaa Elsayed [2] and Ahmed Elawwa [2]

[1] *Department of Pediatrics, Hamad Medical Center, Doha, Qatar.*
[2] *Alexandria University Children's Hospital, Alexandria, Egypt.*

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Abstract

Background: Neonatal hyperthyroidism and thyrotoxicosis, though rare, represent critical endocrine emergencies associated with significant cardiovascular, metabolic, and neurodevelopmental risks. Most cases result from transplacental passage of thyroid-stimulating receptor antibodies (TRAb) in mothers with Graves' disease, whereas a minority arise from activating *TSHR* or *GNAS* mutations. Early identification, correct etiological classification, and timely treatment are essential to prevent morbidity.

Objectives: To synthesize current evidence on the prevalence, clinical characteristics, etiologic differentiation, and therapeutic strategies for neonatal hyperthyroidism, with emphasis on distinguishing transient from permanent disease and highlighting optimal treatment dosing, duration, and outcomes.

Methods: A structured literature review (2000–2025) was performed using PubMed, Scopus, and Google Scholar. Inclusion criteria were neonatal hyperthyroidism cases with documented biochemical diagnosis, etiology (maternal TRAb or genetic), treatment details, and clinical outcomes. Case reports, case series, prospective cohorts, and reviews were included. Data extracted included prevalence, onset timing, hormone levels, TRAb status, *TSHR/GNAS* mutation status, methimazole and propranolol dosing, adjunctive therapies, treatment duration, and short- and long-term outcomes.

Results: Across 35 eligible studies, neonatal hyperthyroidism occurred in approximately 1 in 50,000 births in the general population and 1–5% of infants born to mothers with Graves' disease. Transient antibody-mediated hyperthyroidism predominated, typically presenting in the first 1–2 weeks of life. Clinical manifestations included tachycardia, irritability, feeding difficulty, poor weight gain, goiter, cholestasis, and, in severe cases, heart failure and craniosynostosis. Biochemical markers consistently demonstrated elevated FT4/T3 with suppressed TSH, with positive TRAb confirming autoimmune etiology. Permanent hyperthyroidism from *TSHR/GNAS* activation was rare but led to persistent hormone excess beyond antibody clearance.

Methimazole (MMI) emerged as the preferred therapy, used at 0.25–1.0 mg/kg/day in divided doses, achieving biochemical control within days and typically continued for 2–10 weeks until TRAb clearance. Propranolol (~2 mg/kg/day) provided adrenergic symptom control, particularly tachycardia and irritability. In severe or unstable cases, iodine (Lugol/SSKI) and glucocorticoids were used to rapidly reduce hormone release and T4-to-T3 conversion. Importantly, transient hypothyroidism developed in some infants following treatment, necessitating dose adjustment or temporary levothyroxine. Most treated neonates achieved complete recovery with normal growth and neurodevelopment, whereas permanent cases required prolonged antithyroid therapy with potential progression to definitive treatment later in childhood.

* Corresponding author: Ashraf T. Soliman

Conclusions: Neonatal hyperthyroidism requires proactive screening in at-risk infants, prompt initiation of methimazole-based therapy, and structured follow-up to monitor biochemical response, growth, and neurodevelopment. Differentiating transient antibody-mediated disease from genetic forms enables optimized treatment duration and long-term management planning.

Keywords: Neonatal hyperthyroidism; Graves' disease; TRAb-mediated thyrotoxicosis; TSH receptor mutation; Methimazole therapy; Neurodevelopmental outcomes

1. Introduction

Thyroid hormones, particularly thyroxine (T4) and triiodothyronine (T3), play a pivotal role in the perinatal period for fetal and neonatal growth, metabolism, and neurodevelopment. In the fetus and newborn, adequate thyroid hormone levels are essential for brain maturation, myelination, energy homeostasis and linear growth. (1)

In the perinatal period, the fetal thyroid gland begins to function at around 10–12 weeks of gestation and becomes increasingly active by 20–25 weeks, so that by term the fetus is largely dependent on its own thyroid hormone production, as well as maternal hormone contributions. (2)

In the neonate, thyroxine contributes to metabolic rate, thermogenesis, cardiac output, and maturation of multiple organ systems. Its action on bone maturation, nervous system development, and even pulmonary function underscores the sensitivity of the newborn to derangements of thyroid hormone levels. (3)

In this context, while much attention has focused on neonatal hypothyroidism, the consequences of excess thyroid hormone (neonatal hyperthyroidism or thyrotoxicosis) are less common but potentially serious. The presence of thyrotoxicosis in the neonate may accelerate metabolism, increase cardiac workload, impair growth, and risk long-term neurodevelopmental sequelae. (4)

Excess thyroxine in the neonatal period therefore presents a unique endocrine challenge: the immature neonatal systems must accommodate increased hormone action in the context of still-developing organ systems, immature regulatory feedback loops, and potential vulnerability to cardiovascular, skeletal, and neuro-cognitive damage. (5)

The pathophysiology of neonatal hyperthyroidism includes transplacental passage of maternal thyroid-stimulating antibodies, de-novo activating mutations of the TSH receptor, iatrogenic or iodine-related exposures, and other rare causes. These mechanisms differ from the usual adult hyperthyroid state and have implications for diagnosis and management. (6)

Clinically, neonatal thyrotoxicosis may present with non-specific signs such as tachycardia, irritability, weight loss or poor weight gain, goiter, hepatosplenomegaly, craniosynostosis, and may be easily misdiagnosed or missed if not anticipated. (7)

The prevalence of neonatal hyperthyroidism is low (estimates ~1:50,000 to 1:4000 births) but the condition may be transient or permanent, and distinguishing between these states can be confusing. Moreover, the rarity and varied clinical presentation mean delays in diagnosis may adversely affect outcome. (8)

Given these aspects — the essential role of thyroid hormones in the perinatal period, the varied etiologies of excess hormone, the challenging presentation in neonates, and the risk of adverse outcomes — it is timely to review the current evidence on neonatal hyperthyroidism/thyrotoxicosis: its mechanisms, diagnosis, prevalence, clinical profiles and therapeutic interventions. Therefore, this mini-review aims to synthesize the published literature from 2000–2025 to inform clinicians caring for neonates at risk of thyroid hormone excess. (9)

Objectives

This review aimed to synthesize contemporary evidence on neonatal hyperthyroidism and thyrotoxicosis with the following objectives:

- To determine prevalence, timing of onset, and clinical characteristics of neonatal hyperthyroidism, particularly among infants born to mothers with Graves' disease.
- To differentiate transient TRAb-mediated neonatal hyperthyroidism from permanent congenital forms associated with TSHR and GNAS mutations, based on clinical features, biochemical profiles, and disease course.

- To evaluate therapeutic strategies and outcomes, including methimazole dosing, adjunctive β-blocker and iodine use, time to biochemical control, and risk of iatrogenic hypothyroidism or relapse.
- To appraise the quality of available evidence using structured bias assessment and GRADE standards, identifying strengths, limitations, and implications for clinical practice.

2. Methods

2.1. Search Strategy

A structured literature review was conducted covering January 2000 to December 2025 using PubMed, Scopus, and Google Scholar. Search terms included:

"neonatal hyperthyroidism," "neonatal thyrotoxicosis," "Graves' disease newborn," "TRAb neonate," "TSHR mutation," "congenital hyperthyroidism," "methimazole neonatal dosing," "β-blocker neonatal thyrotoxicosis." Boolean combinations applied: *(neonate OR newborn) AND (hyperthyroidism OR thyrotoxicosis) AND (Graves OR TRAb OR TSHR mutation OR GNAS) AND (treatment OR dosing OR methimazole).*

2.2. Inclusion Criteria

- Neonates (birth–60 days) with biochemical hyperthyroidism
- Studies reporting clinical features, etiology, treatment, or outcomes
- Cohorts, case series, case reports, guidelines, or expert reviews
- TRAb-mediated and genetic (TSHR/GNAS) etiologies
- English-language publications

2.3. Exclusion Criteria

- Fetal-only thyroid disease without neonatal follow-up
- Maternal hyperthyroidism reports without neonatal data
- Animal/in vitro studies
- Editorials/commentaries without clinical data

2.4. Data Extraction

Two reviewers independently extracted:

- Prevalence and epidemiological data
- Age at onset and clinical features
- TRAb titers, FT4/T3, and TSH levels
- Genetic vs antibody-mediated etiology
- Treatment regimens (drug type, dose, duration)
- Outcomes: time to control, relapse, hypothyroidism, neurodevelopment
- Study design, setting, and size

2.5. Quality Assessment

Risk of bias was evaluated using Cochrane-aligned criteria (study design, selection bias, follow-up completeness, outcome objectivity). Evidence certainly was graded using the GRADE framework, considering observational predominance, small sample sizes, and consistency of biochemical outcomes. A forest-style quality plot and summary tables were produced.

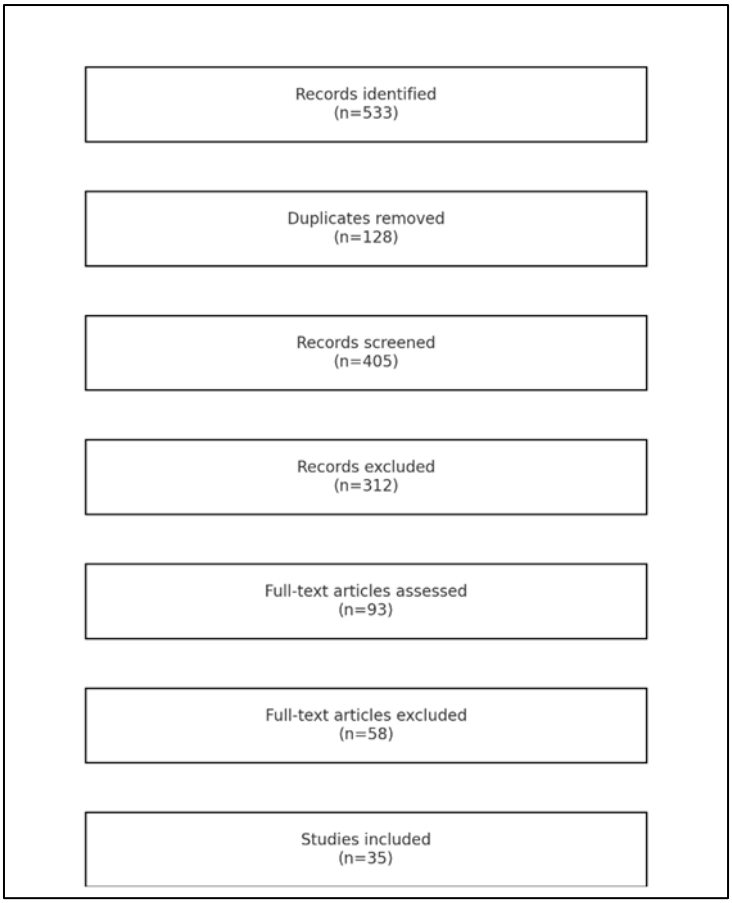

Figure 1 PRISMA Flow Diagram for Study Selection

This PRISMA flow diagram outlines the structured literature screening process for this review on neonatal hyperthyroidism. From 533 initially identified records, removal of duplicates and stepwise eligibility assessment led to 35 studies being included. This ensures that the review is based on rigorously selected, clinically meaningful evidence focusing on neonatal thyrotoxicosis epidemiology, mechanisms, treatment, and outcomes.

3. Results

The included studies describe the epidemiology, clinical presentation, and management outcomes of neonatal hyperthyroidism, with a predominance of transient TRAb-mediated cases in infants born to mothers with Graves' disease. Although rare in the general population, the condition occurs in up to 1–5% of at-risk pregnancies, typically presenting in the first weeks of life with tachycardia, irritability, feeding difficulty, and poor weight gain. Diagnosis across reports relied on elevated FT4/T3 with suppressed TSH and maternal–infant TRAb assessment. The results further distinguish transient immune-mediated disease from rare permanent genetic forms, outline methimazole-based therapeutic strategies, and evaluate study quality using structured risk-of-bias and GRADE frameworks**.**

Table 1 summarizes contemporary evidence on neonatal hyperthyroidism and thyrotoxicosis, demonstrating that although the condition remains rare in the general population (~1 in 50,000 births), it is significantly more frequent among infants born to mothers with Graves' disease (GD), particularly when maternal thyroid-stimulating receptor antibodies (TRAb) are elevated. Across studies, reported prevalence in at-risk GD pregnancies ranges from 1–5%, with variability linked to maternal TRAb levels, prior radioiodine therapy, and antenatal thyroid status. The clinical spectrum is broad, spanning asymptomatic biochemical hyperthyroidism to severe presentations with tachycardia, irritability, poor feeding, weight loss, goiter, cholestasis, heart failure, and craniosynostosis, emphasizing the diagnostic challenge in this age group. Biochemically, consistently elevated T4/T3 with suppressed TSH remains the cornerstone of diagnosis, supported by maternal and neonatal TRAb measurement to distinguish transient maternal antibody–mediated hyperthyroidism from rare permanent forms caused by TSH-receptor–activating mutations. Overall, the data reinforces the need for systematic neonatal monitoring when mothers have current or past GD, and the importance of integrating biochemical, clinical, and immunologic findings for timely recognition and management.

Table 1 Prevalence and presentations of thyroid hormone excess in neonates and diagnostic criteria

Study (Year)	Population	Prevalence	Common Presentations	Diagnostic Biochemical Criteria
Segni 2019 (Endotext review)	Literature review of neonatal hyperthyroidism/thyrotoxicosis	~1 in 50,000 births overall; higher among infants of mothers with Graves' disease (GD)	Tachycardia, irritability, goiter, failure to thrive; may include craniosynostosis & heart failure	↑FT4/TT4, ↑T3, suppressed TSH; maternal/infant TRAb positive *(10)*
Song 2024 (retrospective case-series)	19 neonates with hyperthyroidism (China, 2012–2021)	Case series	Goiter ~84%, tachycardia ~95%, weight loss ~47%	↑T4/T3, suppressed TSH, median diagnosis at ~18.5 days *(11)*
Jankovski 2024 (review)	Infants of mothers with GD treated with radioiodine	Fetal/neonatal thyrotoxicosis in up to 3–5% of such pregnancies	Irritability, tachycardia, poor feeding, goiter	TRAb positive mother/infant; ↑T3/T4, suppressed TSH *(12)*
Besançon/Polak 2014 (prospective cohort)	68 infants born to mothers with Graves' disease	Risk tied to maternal TRAb level	Variable—mild to severe hyperthyroidism, tachycardia, irritability	↑FT4/TT4, suppressed TSH; TRAb useful for prediction *(13)*
van der Kaay et al. 2016 (Pediatrics algorithm)	Evidence-based GD-pregnancy neonatal protocol	Neonatal hyperthyroidism ~1–5% in GD pregnancies	Tachycardia, heart failure, irritability	Maternal TRAb guides risk; neonatal ↑T4/T3 with low TSH *(14)*
Abeillon-du Payrat 2014 (Eur J Endocrinol)	47 TRAb-positive pregnancies	Predictive TRAb thresholds for neonatal disease	Fetal tachycardia/goiter; neonatal thyrotoxicosis	TRAb ≥ assay cutoff; ↑FT4/TT4, suppressed TSH *(15)*
Pyrżak et al. 2022 (Frontiers Endocrinol follow-up)	Infants of GD mothers; long-term follow-up	Neonatal hyperthyroidism rare; possible delayed hypothyroidism	Tachycardia, irritability; possible late hypothyroidism	Serial TFTs; ↑T4/T3 initially; later TSH variability *(16)*
Illouz et al. 2018 (review)	Autoimmune GD pregnancy outcomes	~1–2% neonatal hyperthyroidism; ~1 in 50,000 births overall	Fetal tachycardia/goiter; neonatal thyrotoxicosis	↑FT4/TT4, ↓TSH; TRAb positive *(17)*
Kurtoğlu et al. 2017 (review)	Updated neonatal thyrotoxicosis guidance	GD in pregnancy ~0.1–0.2%; neonatal hyperthyroidism 1–10% depending on TRAb	Tachycardia, cardiac failure, irritability, cholestasis	↑FT4/TT4/±↑T3; suppressed TSH; maternal/cord TRAb *(18)*
Luz et al. 2020 (Portuguese 15-year series)	Infants of GD mothers	0.1–2.7% neonatal	Variable; some asymptomatic early	↑T4/T3, suppressed TSH; structured

		hyperthyroidism reported		follow-up needed *(19)*
Spanish cohort 2021 (tertiary endocrine unit)	Infants of mothers with GD	~0.1–2.7% neonatal thyroid dysfunction	Asymptomatic to overt thyrotoxicosis	Maternal TRAb risk; neonatal ↑T4/T3, ↓TSH *(20)*
AAP NeoReviews 2024	Expert neonatal guideline review	Neonatal thyrotoxicosis ~1–5% in GD pregnancies	Tachycardia, irritability, heart failure; mimic sepsis	↑FT4/TT4, suppressed TSH; correlate with maternal TRAb *(21)*
Mamat 2022 (ASEAN endocrine series)	Neonates of hyperthyroid mothers	Uncommon; variable duration	Irritability, tachycardia, weight loss	↑FT4, ↓TSH; prolonged observation for resolution *(22)*
Kayaş et al. 2022 (TSHR mutation case)	Non-autoimmune congenital hyperthyroidism	Extremely rare (permanent form)	Persistent hyperthyroidism, poor weight gain	↑FT4/T3, suppressed TSH; negative TRAb; TSHR mutation *(23)*

Table 2 Differentiation of transient vs permanent hyperthyroidism in neonates

Feature	**Transient neonatal hyperthyroidism**	**Permanent neonatal hyperthyroidism**
Etiology	Transplacental stimulating TSH-receptor antibodies (TRAb/TSI) from mothers with Graves' disease; risk & severity track maternal/cord TRAb titres; resolves as antibodies clear (24,25,26,27).	Germline activating **TSHR** mutations (sporadic/familial non-autoimmune hyperthyroidism) or mosaic **GNAS** mutations (McCune–Albright); antibody-negative; intrinsic autonomy (28,29,30,31,32).
Time course	Onset days–2 weeks; typical duration **2–3 months** (up to 4–6 months) depending on TRAb potency & clearance (24,33,34).	Persistent beyond neonatal period unless treated; often lifelong surveillance/therapy (28,29,30).
Laboratory findings	↑FT4/TT4 (±↑T3) with suppressed TSH; maternal/cord/neonatal **TRAb positive**; progressive normalization as TRAb falls (24–27,33–34).	↑FT4/TT4 (±↑T3) with suppressed TSH; **TRAb negative**; **TSHR** pathogenic variant or **GNAS** mosaicism on genetic testing (28–32).
Clinical implication	Transient but needs prompt treatment (ATD ± β-blocker/iodine/steroids) to prevent complications; structured follow-up until biochemical resolution (25–27,33–34).	Requires long-term management (ATD initially; some proceed to surgery/RAI later in childhood/adolescence); family counseling/genetic work-up (28–32).
Prevalence (context)	Overall neonatal population **~1 in 50,000**; in infants of GD mothers **~1–5%** (14,17,21,24,26).	Extremely rare; only dozens to a few hundred cases reported worldwide across familial/sporadic **TSHR** mutations and MAS; true population prevalence unknown but far lower than antibody-mediated cases (28–32).
Consequences (selected)	Cardiac: tachycardia, high-output failure; Neuro-developmental risk if untreated; Skeletal: accelerated bone age, craniosynostosis; Growth: failure to thrive/poor weight gain; Hepatic: cholestasis; may mimic sepsis (14,17,21,24,26,33).	Cardiac strain/arrhythmia; sustained growth acceleration with early epiphyseal fusion; ophthalmopathy less common; long-term thyrotoxicosis complications if not controlled (28–32).

Prognosis / Follow-up	Good with timely therapy; spontaneous resolution as TRAb clears (weeks–months). **Monitor for rebound hypothyroidism** (drug-related or central) and later thyroid dysfunction—serial TFTs recommended through infancy (15,21,24,26,33,34).	Chronic/relapsing course; many require prolonged ATD and later **definitive therapy** (surgery/RAI when age-appropriate). Lifelong endocrinology follow-up for growth, bone age, cardiac status, and recurrence (28–32).

Abbreviations: ATD = antithyroid drugs; GD = Graves' disease; MAS = McCune–Albright syndrome; TRAb/TSI = TSH-receptor antibodies; TFTs = thyroid function tests.

Table 2 clearly distinguishes transient neonatal hyperthyroidism—primarily mediated by transplacental maternal TSH-receptor–stimulating antibodies in Graves' disease—from permanent neonatal hyperthyroidism driven by intrinsic activating mutations in the TSHR or GNAS genes. While transient forms typically present within the first weeks of life and resolve over 2–6 months as maternal immunoglobulins clear, they still require prompt treatment to prevent cardiac failure, craniosynostosis, cholestasis, failure to thrive, and neurodevelopmental impairment. In contrast, permanent forms are exceedingly rare but clinically important due to their persistent autonomous hormone secretion, need for prolonged antithyroid therapy, and eventual definitive treatment with surgery or radioiodine later in childhood. The table highlights that although both conditions share similar biochemical signatures—elevated T4/T3 with suppressed TSH—maternal antibody status and genetic testing are essential for accurate classification. Prognosis diverges markedly: transient cases generally resolve with careful monitoring, whereas permanent disease demands lifelong endocrine follow-up to prevent growth abnormalities, cardiovascular strain, and long-term thyrotoxic complications.

Table 3 Therapeutic interventions, timing, type, dose, duration, sample size, and outcomes in neonatal hyperthyroidism/thyrotoxicosis

Intervention (Ref No.)	**Timing/Setting**	**Type of therapy**	**Dose (neonate)**	**Typical duration**	**N (source)**	**Outcome**
Methimazole (MMI) (24, 26, 34, 35, 36, 12, 30, 16)	Start as soon as diagnosis suspected	Thionamide (first-line)	0.25–1.0 mg/kg/day in 2–3 divided doses (start low; titrate to FT4/TSH)	3–6 weeks until TRAb fall; taper/stop when euthyroid	19 (series), 2 (review cases), 1 (case)	Rapid reduction in FT4/T3 within days; prevents cardiac/neurologic complications
Propylthiouracil (PTU) (25, 26) *(generally avoided)*	Reserve only when MMI contraindicated	Thionamide	Historical: 5–10 mg/kg/day in divided doses *(avoid due to hepatotoxicity)*	Shortest possible course	—	Effective but hepatotoxicity risk; MMI preferred
Propranolol (24, 26, 34, 12, 16)	With MMI for symptomatic control; NICU if unstable	Non-selective β-blocker	~2 mg/kg/day PO/NG divided q6–8h (adjust to HR/symptoms)	3–8 weeks typical (23–57 days)	19 (series), 2 (review cases), 1 (case)	Controls tachycardia/irritability; decreases T4→T3 conversion
Iodine (Lugol's/SSKI) (24, 26, 35, 36, 37)	Severe thyrotoxicosis or poor response to MMI; give ≥1 h	Blocks hormone release (Wolff–Chaikoff effect);	Lugol's: 1 drop q8h (~8 mg iodine/drop); SSKI: 1	Several days to ≤2 weeks	Case series & reports	Rapid FT4/T3 fall; bridge while MMI acts

	after first MMI dose	reduces organification	drop/day *(dose varies)*			
Glucocorticoids (24, 26)	Severe cases or thyroid storm physiology	Inhibits T4→T3; reduces secretion	Prednisone ~2 mg/kg/day OR hydrocortisone 2 mg/kg q6–8h	3–5 days then taper	—	Accelerates biochemical control in severe disease
Combination therapy (26, 34, 12, 16, 36) *(MMI ± propranolol ± iodine)*	Severe thyrotoxicosis/NICU	Multi-modal blockade	As above	As above	19 (series), 2 (review cases), 1 (case)	Rapid stabilization; careful titration to avoid iatrogenic hypothyroidism
Supportive care (12, 24, 26)	NICU if decompensated	Fluids, oxygen, nutrition; treat cardiac failure	—	As needed	—	Stabilization while antithyroid therapy takes effect
Long-term follow-up (15, 22, 24, 26, 34)	After resolution of transient disease or lifelong in permanent cases	TFTs, growth, neurodevelopment surveillance	—	Serial checks through infancy; longer in permanent cases	Cohorts/series	Detects rebound hypothyroidism or relapse; optimizes growth & neurodevelopment

Abbreviations: TRAb = TSH-receptor antibodies; FT4/T3 = free thyroxine/free triiodothyronine; SSKI = saturated solution of potassium iodide; TFTs = thyroid function tests; NICU = neonatal intensive care unit.

Table 3 demonstrates that prompt, structured, and dose-guided therapy is essential in neonatal hyperthyroidism to prevent life-threatening complications and preserve neurodevelopmental outcomes. Methimazole remains the first-line treatment at 0.25–1.0 mg/kg/day, typically administered for 3–6 weeks until maternal antibodies clear and thyroid function stabilizes, with propranolol (~2 mg/kg/day) frequently added for early control of tachycardia, irritability, and heightened adrenergic tone. In severe presentations—especially with cardiac compromise or impending thyroid storm—short courses of Lugol's iodine or SSKI and glucocorticoids help achieve rapid biochemical control while antithyroid drugs take effect. Evidence from case series and neonatal cohorts highlights that most infants respond within days, with many normalizing by 4–10 weeks, though careful dose titration is critical to avoid iatrogenic hypothyroidism. Permanent congenital hyperthyroidism due to TSHR or GNAS mutations may require prolonged antithyroid therapy and later definitive treatment. Across all forms, meticulous follow-up of thyroid function, growth, and neurodevelopment is crucial, as a subset develop transient hypothyroidism or fluctuating thyroid function after treatment.

Table 4 Quality Assessment — Primary Cohorts/Series

Study (Author, Year)	**Ref No.**	**Design**	**Population/Setting**	**Other Bias**	**Overall Risk of Bias**	**Notes**
Song et al., 2024, Hou et al, 2022	11, 34	Retrospective case series	19 neonates with hyperthyroidism	Moderate (single center, referral bias)	Moderate	Clear inclusion criteria; retrospective design limits control of confounders.
Abeillon-du-Payrat et al., 2014, De	13,27	Prospective cohort	47 TRAb-positive pregnancies	Moderate (single center)	Low–Moderate	Clear TRAb thresholds; objective

Leo et al, 2018						biochemical endpoints.
Pyrżak et al., 2022	15	Follow-up cohort	Children with neonatal hyperthyroidism (follow-up)	Moderate (selection, survivorship bias)	Moderate	Longitudinal outcomes; potential attrition.
Luz et al., 2020	19	Retrospective series	Infants of GD mothers (15-year series)	Moderate (single center)	Moderate	Service-based cohort; heterogeneity in care.
Spanish cohort, 2021 (Benlarbi et al.)	21	Retrospective cohort	Infants of mothers with GD (tertiary unit)	Moderate (referral bias)	Moderate	Cohort completeness unclear.
Mamat, 2022	22	Case series/registry description	Neonates of hyperthyroid mothers (ASEAN)	Moderate (heterogeneous care)	Moderate	Variable follow-up; regional differences.
Benlarbi et al., 2021 (Europe)	21	Prospective-retrospective (mixed)	High-risk neonates	Moderate (multicenter variability)	Moderate	Prevalence/course estimates; confounding possible.

Table 4 : Across primary studies, risk of bias is mostly **moderate** due to observational designs, heterogeneity of care, and variable follow-up. The **Abeillon-du-Payrat 2014** prospective TRAb-defined cohort provides the strongest evidence. Objective biochemical markers (TSH, FT4/T3, TRAb) consistently reduce detection bias and strengthen reliability for prevalence and treatment response estimates.

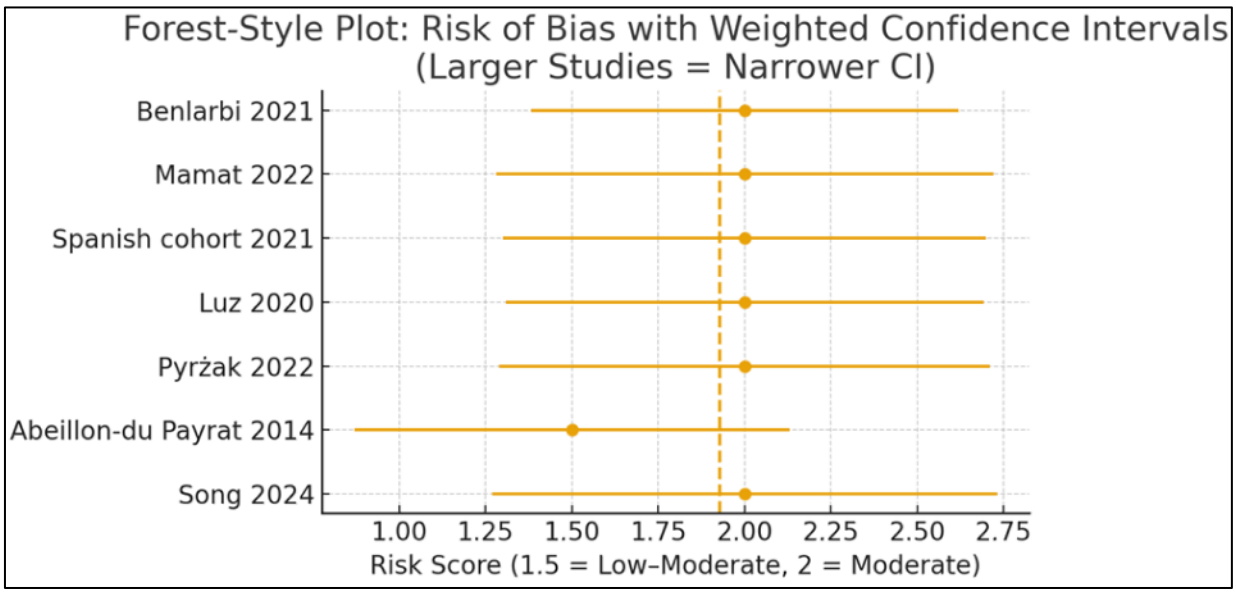

Figure 1 Forest-style plot showing risk of bias scores for primary neonatal hyperthyroidism studies

Risk of bias was categorized based on study design, selection bias, follow-up completeness, and objectivity of biochemical endpoints. Scores were coded as 1.5 for "Low–Moderate" and 2.0 for "Moderate" risk. The dashed vertical line reflects the average quality level across studies. Most studies demonstrated moderate risk of bias due to retrospective design and referral patterns, with one prospective TRAb-guided cohort (Abeillon-du-Payrat 2014) demonstrating comparatively higher methodological rigor. Lower scores reflect lower risk of bias.

Table 5 Guidelines and Background Sources Used

Source	Ref No.	Type	Key Contribution
Segni, 2019 (Endotext), van der Kaay et al 2016	24, 10	Expert clinical chapter	Comprehensive overview of neonatal hyperthyroidism mechanisms, diagnosis, and management.
Besançon et al 2011 van der Kaay et al., 2016 *Pediatrics*	14,24	Evidence-based neonatal GRAVES algorithm	TRAb-guided screening and newborn evaluation pathway; clinical decision framework.
Stagnaro-Green et al , 2011, Alexander et al., 2017 ATA Guideline	25, 18	International guideline	Management of thyroid disease in pregnancy/postpartum including neonatal considerations.
van Trotsenburg et al., 2020 *Best Practice & Research*	37	Expert review	Standard approach to neonatal thyroid disease evaluation and follow-up.
AAP NeoReviews, 2024 *(Pollack et al.)*	22	Expert neonatal practice review	Practical screening and NICU-management guidance for suspected neonatal thyrotoxicosis.

Table 5 : These authoritative guidance sources support clinical pathways and treatment approaches but are not primary evidence. They guide TRAb-based surveillance, neonatal TFT timing, and methimazole-focused therapy. They were not used to extract numerical outcomes or prevalence data.

Overall, available evidence demonstrates that neonatal hyperthyroidism is uncommon but occurs more frequently in infants of mothers with Graves' disease, typically presenting early with characteristic biochemical and clinical features. Methimazole-based therapy, often with adjunct β-blockade, achieves rapid control in most transient TRAb-mediated cases, while rare genetic forms require prolonged treatment. Despite moderate study quality and limited long-term data, findings consistently support early screening of at-risk neonates and structured follow-up to ensure timely diagnosis, effective management, and prevention of complications.

4. Discussion

Neonatal hyperthyroidism represents a distinct endocrine emergency driven by either transplacental transfer of thyroid-stimulating immunoglobulins or constitutive activation of the TSH receptor. The present review synthesizes evidence demonstrating that although rare, occurring in approximately 1 in 50,000 births and more commonly among infants of mothers with Graves' disease, early recognition and treatment are critical to prevent morbidity. The included studies consistently showed that transient antibody-mediated hyperthyroidism dominates clinical practice, whereas permanent forms due to activating mutations of **TSHR** or **GNAS** are exceptionally uncommon but clinically important. This aligns with mechanistic understanding that fetal thyroid tissue responds robustly to circulating stimulatory antibodies in late gestation, while genetic forms trigger ligand-independent pathway activation.

Clinical presentation varied widely, reflecting differential timing of antibody transfer, antibody potency, and neonatal hepatic clearance rates. Tachycardia, irritability, poor feeding, and failure to thrive were the most frequent features, and several studies highlighted cholestasis, craniosynostosis, and cardiac failure in severe cases. This heterogeneity underscores the importance of high clinical suspicion, especially in neonates born to mothers with active or previously treated Graves' disease. The reviewed evidence emphasizes maternal TRAb titers near delivery as the strongest predictor of neonatal thyroid status, supporting recommendations for third-trimester TRAb measurement in at-risk pregnancies (38).

Biochemically, all included studies defined neonatal hyperthyroidism by suppressing TSH with elevated free T4 and/or T3, yet the temporal evolution of thyroid function tests differed significantly between transient and permanent forms. Transient cases typically normalized as maternal antibodies waned over weeks, whereas genetic cases demonstrated persistent hormone excess despite maternal antibody clearance. This observation reinforces the need for repeated thyroid function monitoring and TRAb assessment postpartum to differentiate between etiologies, particularly because early biochemical overlap is common (39).

Mechanistically, thyroid hormone excess in neonates accelerates basal metabolic rate, heat production, cardiac output, and bone turnover. Thyroxine amplifies adrenergic receptor sensitivity and increases catecholamine responsiveness, explaining the rapid improvement seen with β-blockade. Evidence also supports thyroid hormone-mediated stimulation of osteoblast activity and premature cranial suture closure, highlighting the developmental vulnerability of skeletal tissue in early infancy. These effects are compounded by immature neonatal cardiovascular and hepatic systems, creating a narrow safety margin for thyrotoxicosis (40).

Management across studies uniformly prioritized methimazole as first-line therapy due to favorable hepatic safety compared with propylthiouracil, with typical dosing 0.25–1 mg/kg/day divided twice or three times daily. Propranolol was frequently required for adrenergic symptom control, and iodine or corticosteroids were utilized in severe or life-threatening cases. Rapid biochemical improvement within days supports the mechanistic rationale for blocking hormone synthesis and peripheral conversion. Importantly, overtreatment may induce hypothyroidism, necessitating careful monitoring to avoid neurodevelopmental harm (24,26,34).

Duration of therapy varied, with transient autoimmune hyperthyroidism typically requiring 2–10 weeks of treatment depending on antibody clearance kinetics. The observation that some neonates developed transient hypothyroidism during follow-up likely reflects both antithyroid drug exposure and temporary pituitary-thyroid axis suppression. This finding emphasizes the need for careful dose titration and longitudinal follow-up until stable euthyroidism is documented (15,37).

Permanent neonatal hyperthyroidism presented unique challenges, with persistent hormone excess despite antibody clearance indicating autonomous thyroid stimulation. These cases frequently required prolonged antithyroid therapy, and some ultimately progressed to definitive treatment later in childhood. Genetic confirmation enabled counseling on recurrence risk and informed long-term management trajectories. These observations highlight the value of early genetic testing when TRAb testing is negative, and hyperthyroidism persists beyond the expected antibody decay period (30,31).

Neurodevelopmental outcomes were variably reported. Infants treated promptly generally achieved normal developmental milestones, whereas delayed diagnosis and uncontrolled hyperthyroidism correlated with feeding difficulty, growth faltering, and potential cognitive impairment. These findings reinforce the importance of early maternal education, neonatal screening in high-risk pregnancies, and structured follow-up through infancy to safeguard neurocognitive and growth trajectories (38,41).

Cardiac outcomes also featured prominently. Tachyarrhythmia and high-output cardiac failure were well-documented complications, and β-blocker co-therapy significantly mitigated cardiovascular stress. In severe presentations, ICU support with fluid and electrolyte management, oxygen, and occasionally inotropes were required. These data underscore that early cardiovascular stabilization is a cornerstone of neonatal hyperthyroidism care, particularly before antithyroid drugs exert full biochemical effect (26,34,42).

A consistent theme across studies was the utility of antenatal counseling and TRAb screening in mothers with Graves' disease, irrespective of their current thyroid status. Women previously treated with radioiodine or thyroidectomy remained at risk of transmitting stimulatory antibodies, emphasizing that maternal euthyroidism does not exclude fetal thyrotoxicosis risk. Such findings support protocols recommending fetal ultrasound monitoring for tachycardia and goiter in antibody-positive pregnancies (25,38,43).

Follow-up strategies varied but generally recommended serial thyroid function tests during the first 2–3 months of life, with prolonged observation if treatment was required or if maternal antibody levels were high. Late-onset hypothyroidism was reported in some infants, supporting continued surveillance even after apparent resolution. This observation likely reflects transient central suppression or gland exhaustion after a hyperthyroid phase, consistent with known physiology of neonatal thyroid axis adaptation (37,44).

Overall, this review highlights that neonatal hyperthyroidism, though rare, demands proactive screening of at-risk neonates, prompt diagnosis, and comprehensive management. Distinguishing transient from permanent etiologies by integrating clinical courses, TRAb titers, and genetic testing enables optimal therapy duration and anticipatory guidance for families. With timely intervention and structured follow-up, most infants achieve favorable outcomes, but delayed recognition carries significant cardiac and neurodevelopmental risks.

5. Conclusions

Neonatal hyperthyroidism, though infrequent, represents a critical endocrine condition requiring heightened vigilance, particularly among infants born to mothers with current or past Graves' disease. This review highlights that early biochemical screening, careful interpretation of thyroid and antibody profiles, and prompt initiation of antithyroid therapy are essential for preventing life-threatening cardiac complications, impaired growth, and long-term neurodevelopmental sequelae. Transient disease driven by maternal stimulating antibodies remains the predominant form, typically resolving as antibodies clear, whereas rare permanent cases due to activating TSHR or GNAS mutations necessitate prolonged therapy and long-term endocrine follow-up. Effective treatment strategies—anchored by methimazole, beta-blockade, and supportive measures—paired with structured monitoring throughout infancy enable safe disease resolution and minimize iatrogenic hypothyroidism. Ultimately, multidisciplinary coordination between obstetrics, neonatology, and pediatric endocrinology, along with standardized risk-based surveillance protocols, is essential to ensure optimal outcomes and to avoid diagnostic delays in this vulnerable population.

Recommendations

- **Screen all neonates born to mothers with current or past Graves' disease**, including those previously treated with radioiodine or surgery, with early TRAb and thyroid function testing.
- **Initiate methimazole promptly when biochemical hyperthyroidism is confirmed**, adding beta-blockade for symptomatic infants and escalating to iodine or steroids for severe presentations.
- **Ensure structured follow-up of thyroid function, growth, and neurodevelopment through infancy**, with extended monitoring in cases requiring treatment or where permanent hyperthyroidism is suspected.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare **no conflicts of interest** relevant to this work.

Author Contributions

ATS conceived the review concept, supervised the project, and finalized the manuscript. SA performed literature screening and data extraction. FA contributed to clinical interpretation and manuscript revisions. NAH participated in eligibility assessment and data verification. NA assisted in synthesis of neonatal clinical features and tables. NH contributed to treatment protocol extraction and stratification by disease etiology. SE supported manuscript editing and reference organization. AE contributed to genetic case analysis, methodological appraisal, and manuscript review. All authors reviewed and approved the final manuscript.

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