Thyroid Function in the Neonatal Intensive Care Unit

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INTRODUCCIÓN

La unidad de cuidados intensivos neonatales (UCIN) presenta desafíos únicos para el screening de rutina universal tiroideo en el recién nacido para la detección temprana y tratamiento del hipotiroidismo congénito, y la interpretación de las pruebas de función tiroidea recolectadas (PFT).

Los bebés prematuros nacen antes de la maduración del eje hipotálamo-hipófisis-tiroides y son propensos a hipotiroidismo con retraso en el aumento de la hormona estimulante de la tiroides (TSH) y el hipotiroidismo transitorio. Además, la enfermedad afecta la interpretación de PFT de pretérmino y neonatos enfermos a término. Este artículo revisa el desarrollo del eje hipotalámico-pituitario-tiroideo fetal y neonatal normal, así como las indicaciones y el momento adecuado de la prueba de la hormona tiroidea en la UCIN, la medicación, artefactos y condiciones que pueden afectar los resultados de la prueba tiroidea, asi como la interpretación de la prueba tiroidea en la UCIN, evidencia a favor y en contra de proporcionar hormona tiroidea a pacientes con RCIU que tienen PFT límite, y reevaluación de seguimiento de neonatos con RCIU con hipotiroidismo, para diferenciar el hipotiroidismo transitorio del permanente.

Le invitamos a leer el texto completo en inglés.

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KEYWORDS

• Congenital hypothyroidism • Neonatal intensive care unit • Preterm infants
• Thyroid screening • Thyroid function testing • Thyroid testing artifacts

KEY POINTS

- Neonatal illness and prematurity may necessitate additional thyroid function screening to ensure early detection and treatment of hypothyroidism, and may alter the results and interpretation of thyroid function tests.
- Preterm infants are prone to transient hypothyroidism with delayed thyroid stimulating hormone (TSH) rise because of immaturity of the hypothalamic-pituitary-thyroid axis at birth.
- Transiently low total thyroxine (T4) and triiodothyronine (T3) levels are common during periods of neonatal illness in term and preterm infants.

INTRODUCTION

The neonatal intensive care unit (NICU) presents unique challenges to routine universal newborn thyroid screening for early detection and treatment of congenital hypothyroidism, and the interpretation of collected thyroid function tests (TFTs).[1] Preterm infants are born before hypothalamic-pituitary-thyroid axis maturation and are prone to hypothyroidism with delayed thyroid-stimulating hormone (TSH) rise and transient hypothyroidism.[2,3] In addition, illness affects the interpretation of TFTs of preterm and term sick infants.[4,5]

This article reviews normal fetal and neonatal hypothalamic-pituitary-thyroid axis development, indications for and timing of thyroid hormone testing in the NICU, medication artifacts and conditions that may affect thyroid test results, thyroid test interpretation in the NICU, evidence for and against providing thyroid hormone to NICU

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patients who have borderline TFT, and follow-up retesting of NICU infants with hypothyroidism, to differentiate transient from permanent hypothyroidism.

NORMAL IN UTERO AND POSTNATAL HYPOTHALAMIC-PITUITARY AXIS DEVELOPMENT

During the first trimester, the fetus must derive all of its thyroid hormone supply from the mother.[6] Maternal unbound thyroxine (free T4) levels increase in early pregnancy when placental human chorionic gonadotrophin, structurally similar to TSH, exhibits a weak TSH-like effect.[7] Free T4 remains elevated throughout pregnancy and is actively transported across the placenta via thyroid hormone transporters.[8,9] Although total thyroxine (T4) levels in the fetal compartments are 1/100th of maternal levels, the unbound and active fraction, free T4, is elevated relative to adults.[8,10] Iodine is also actively transported across the placenta.[11] Within the brain, type 2 and type 3 deiodinases locally convert T4 to T3, which is critical to embryonic neural cell development.[6,12]

The thyroid is the earliest endocrine structure to develop. The thyroid placode, an enlargement of the embryonic endoderm, is noted by embryonic day 22.[13] The developing thyroid begins to collect and store iodine by 10 to 12 weeks.[14] Thyroid follicles have developed by the time the fetal thyroid begins to secrete hormones into the circulation at approximately 16 weeks.[6,11] The parafollicular cells (C-cells), the neuroendocrine cells in the thyroid that produce calcitonin, develop separately. These cells differentiate from the ectoderm and move into the interfollicular connective tissue during thyroid gland development.[15] The hypothalamus develops in the first and second trimesters and it begins to take on an adult-like appearance between 24 and 33 weeks.[16,17]

T4 and free T4 serum concentrations continue to rise until they reach adult levels by 36-weeks' gestation.[18] Thyroxine-binding globulin, the primary carrier of bound T4 in the bloodstream, also rises during the second half of pregnancy.[19] However, serum concentrations of T3 and free T3 remain low throughout fetal development before a late surge prior to term.[18]

At birth, TSH, T3, and free T4 levels rapidly rise within the first postnatal half-hour.[18] However, this rise is attenuated in preterm infants because of hypothalamic-pituitary-thyroid axis immaturity. The degree of rise correlates inversely with gestational age and in the most extremely preterm infants, thyroid hormone levels decrease in the hours following birth.[20]

APPROPRIATE INDICATIONS FOR AND APPROPRIATE TIMING OF THYROID HORMONE TESTING

Congenital hypothyroidism is the most common disorder that is screened for on universal newborn metabolic screens. All infants hospitalized within the NICU should receive an initial thyroid screening test within several days of birth.[19,21] Usually this is done as part of government-mandated and -sponsored universal newborn metabolic screening. The test should be collected after 24-hours postnatal age, whenever possible, which reduces the false-positive rate especially in preterm NICU patients.[21,22] If government-sponsored metabolic screens must be collected before 24-hours because of blood transfusions that would interfere with screening results, it is important to always repeat a second screen after 24-hours postnatal age.

It must be remembered that infants may develop congenital hypothyroidism even if the initial screen within the first several days after birth had normal TSH and T4.

NICU patients, including preterm infants and acutely ill infants, are at high risk for hypothyroidism with delayed TSH rise.[3] Compared with more mature infants, the prevalence of congenital hypothyroidism is higher in very low birth weight (VLBW) (<1500 g) neonates.[2,4,23] VLBW infants reportedly have a 14-fold higher incidence of transient hypothyroidism compared with infants that are greater than 1500 g at birth, although levels of permanent hypothyroidism are similar in preterm and term infants.[4,24,25] Most VLBW newborns with congenital hypothyroidism initially have a normal government newborn screening test and subsequently have a delayed TSH elevation.[4,24–26]

The 2014 European Society for Pediatric Endocrinology Consensus Guidelines on Screening, Diagnosis, and Management of Congenital Hypothyroidism[5] state that a second screening may be required for preterm neonates born at a gestation less than 37 weeks, for infants with a birthweight less than 1500 g, for ill and preterm neonates admitted to the NICU, if the initial specimen collection was collected in the first 24 hours postnatal, or if there are multiple births which may have permitted mixing of blood secondary to twin-twin transfusion. The guidelines recommend that a repeat specimen should be collected at 2-weeks postnatal age or 2 weeks after the first screen was obtained.[5] These factors have led most newborn screening programs to recommend rescreening of preterm infants. However, there are no standardized guidelines currently in place and the indications and timing for rescreening remain debatable. Some recommend rescreening at 2 weeks[1]; others at 4 weeks[27] and 6 weeks.[2] Within the United States, some states recommend an additional government newborn screen via dried blood spot, whereas others recommend obtaining in-house serum TFT as a repeat screen. In the absence of a universal repeat screening protocol for preterm infants, it is critical that clinicians obtain a serum TSH and free T4 whenever there is a clinical concern for potential thyroid disorder.[1]

ARTIFACTS AND CONDITIONS THAT MAY AFFECT THYROID FUNCTION TEST INTERPRETATION

A variety of issues can affect the TFTs. The most common are associated with prematurity, illness, medications, and maternal thyroid disease.

Iodine

Preterm infants born at less than 32 weeks are vulnerable to thyroid dysfunction because of the effects of iodine.[28] The normal human defense mechanism against iodine overload, called the Wolff-Chaikoff effect, prevents overproduction of thyroid hormone once serum iodine reaches a critical level by stopping the uptake of iodine and iodination of tyrosine.[28] However, Wolff-Chaikoff is not typically mature until 36 to 40 weeks' gestation. Immaturity of the thyroid gland, increased permeability of the skin, and decreased renal clearance of iodine in preterm infants also contribute to iodine-associated thyroid dysfunction.[28–30] Iodine overload can be caused by iodinated disinfectants, iodinated contrast media, and high maternal iodine concentrations (prenatally through skin disinfection with povidone iodine used in C-section, vaginal douching, epidural/spinal anesthesia, or postnatally through breast milk).[28,31] If iodine overload is suspected, urinary iodine levels should be measured and the TFTs closely monitored. In a recent systematic review, the incidence of transient hypothyroidism/hyperthyrotropinemia in iodine-exposed infants ranged from 12% to 33%[28,29] depending on the laboratory values used to classify hypothyroidism. Some defined hypothyroidism as a TSH greater than 20 mIU/L and some as TSH greater than

30 mIU/L,[28] with a definition of hyperthyrotropinemia for TSH greater than or equal to 10 but less than or equal to 20 mIU/L.[28]

Nonthyroidal Illness

Nonthyroidal illness (NTI), otherwise also known as sick euthyroid syndrome, can cause changes in serum levels of thyroidal hormones in the absence of classical thyroidal disease. The classic picture seen in NTI is low serum total T3, normal to low total T4, elevated reverse T3, and normal TSH levels. These alterations are believed to be adaptive for the individual and the severity of illness has been correlated with the magnitude of changes observed.[32] In newborn infants, a low T3 is the most frequent change that is seen and an elevation of reverse T3 is not always observed. The low levels of T3 are thought to be an adaptive response to stress to save energy, reduce the metabolic rate, and protect the body from hypercatabolism caused by illness.[33–35] The lower the total T3 value, the poorer the prognosis for infant survival and the more metabolically adaptive it may be for the infant to have the low T3 level. When clinical recovery occurs, a rise in TSH should be followed by an increase in serum T3.[32] Illness severity can also have an impact. Sick premature infants have an attenuated hypothalamic-pituitary-thyroid axis response secondary to immaturity. With critical illness, they are exposed to a variety of agents known to affect TFT. In cases of neonatal sepsis or septic shock, thyroid hormone levels may have a possible prognostic value but further studies need to be completed. Interleukin-6 and other inflammatory cytokines, components of the acute phase response during illness, have been implicated in the pathogenesis of NTI. Low levels of total T3 and T4 are associated with illnesses and adverse outcomes including respiratory distress syndrome, sepsis, and mortality.[36]

Medications

Several medications are known to affect TFT results. Dopamine is an adrenergic neurotransmitter that inhibits TSH secretion by means of adenylyl cyclase. This blockage may be caused by gene expression inhibition for the B subunit of TSH leading to an inhibition of nocturnal TSH peak amplitude.[34] Dopamine also suppresses T4 secretion. Once dopamine is discontinued, an immediate increase in T4 levels can occur.[37,38]

Steroid or glucocorticoid use can lead to a reduction in T3 and an elevation of reverse T3 approximately 12 hours after starting the medication.[34] Steroid use can also reduce the TSH response and peripheral conversion of T4 to T3.[37] Arai and colleagues[37] demonstrated that infants undergoing steroid exposure at 2 weeks of age had significantly lower TSH levels than those without steroid exposure.

Metoclopramide, a dopamine receptor antagonist, is used to prompt gastric emptying in neonates with gastrointestinal dysmotility issues and can induce a significant TSH release resulting in transient thyroid dysfunction.[39]

Aminophylline, caffeine, and the active metabolite theophylline are used as respiratory stimulants for neonatal apnea. These medications can increase the expression of TSH and thyroglobulin, which then can result in thyroid dysfunction.[39]

Heparin used intravenously or subcutaneously, even in very small doses, such as to keep a cannula patent, can cause competition for the thyroid hormone binding sites on thyroid binding globulin and artifactually increase the serum free thyroid hormone levels. Therefore it is best to avoid measuring the free T4 during this time but if clinically indicated, then obtain the blood sample greater than 10 hours after the last injection of

heparin and analyze the sample without delay. If displacement is suspected, measure total T4 along with TSH and thyroid binding globulin to help confirm the patient's thyroid status.[40–42]

Maternal Factors

Maternal TSH receptor blocking antibodies and maternal thyroid medications can also affect the TFTs in the neonate leading to a higher likelihood of having transient disease. Therefore, it is important to try to identify mothers with severe autoimmune thyroid disease so that the neonate's thyroid function can be closely monitored.[43,44] Maternal iodine deficiency and maternal iodine excess (either through nutritional supplements, iodine-rich seaweed, kelp, brassica vegetables) can also cause inadequate thyroid hormone levels.[30,45] Although less common in industrialized nations, iodine deficiency is the most common cause of congenital hypothyroidism worldwide.[5]

INTERPRETATION OF TESTS OF THYROID FUNCTION

The interpretation of TFTs in sick and preterm infants is complex. Although there are numerous reasons for abnormal TFT results in preterm neonates, the most common is immaturity of the hypothalamic-pituitary-thyroid axis. The feedback loop of the hypothalamic-pituitary-thyroid axis is not fully developed, which results in delayed TSH rise in response to serum levels of thyroid hormones. Other common reasons for abnormal screening results in hospitalized neonates, apart from true permanent congenital hypothyroidism, include exposure to certain, commonly used drugs in the neonatal period, inability to regulate iodine balance, and postnatal illnesses.[2]

TSH elevation is common in preterm infants within the first postnatal month when they are critically ill and have possible exposure to various medications. This often makes it unclear if initial TSH elevations are caused by permanent hypothyroidism, persistent hyperthyrotropinemia (elevated TSH with normal T4), or transient hypothyroidism.[2,4,23,25] As preterm infants recover from hypothyroxinemia (low free T4 level with normal TSH level), some have mild transient serum TSH level elevation before reaching a new equilibrium. When followed over time, the TSH returns to normal in most and is considered a normal response to the physiologic hypothyroxinemia seen in healthy preterm infants.[4] Some preterm infants have greater and more persistent delayed TSH elevation. This is either transient or permanent. There do not seem to be any clinical or laboratory characteristics that reliably predict whether the hypothyroidism will be transient or permanent. Woo and colleagues[4] analyzed LBW infants with initial low screening T4 and normal TSH. On repeat screenings, 85% had moderate TSH elevation that normalized spontaneously without treatment at an average of 42 days. The other 15% with higher TSH values were started on treatment.[4]

There are currently no universal standards in place for values used to signify a positive congenital hypothyroidism result based on TSH. When newborn screening was initiated, a blood spot TSH value of 30 mIU/L was the cutoff. Then in the 1990s, the cutoff point was lowered to 20 mIU/L. Following documented cases of congenital hypothyroidism that were missed, studies were performed using a TSH threshold of 10 mIU/L.[46] Mengreli and colleagues[46] found that 65% of preterm infants with permanent congenital hypothyroidism were detected using a TSH cutoff value of greater than 10 mIU/L on the first newborn screen. However, the call-back rate for positive screens with this lower TSH cutoff value was increased 10-fold from baseline to 1.2%.[46]

Some have suggested that if a lower TSH threshold were used, a second TSH screen might not be necessary.[47]

The mean T4 is lower in VLBW infants relative to infants weighing greater than 1500 g. This is most likely secondary to low thyroid binding globulin levels and increased incidence of NTI (sick euthyroid syndrome).[4] Gestational age and birth weight specific reference ranges have been published to aid clinicians in their interpretation of TFT in hospitalized preterm infants. Sun and colleagues[24] established reference intervals for VLBW infants (mean gestational age, 27.9 weeks; mean birthweight, 992 g) at 3 to 6 weeks of age: the normal free T4 range is 0.85 to 1.7 ng/dL and TSH range is 1.14 to 11.04 mIU/L.

EVIDENCE FOR AND AGAINST PROVIDING THYROID HORMONE TO NEONATAL INTENSIVE CARE UNIT PATIENTS WHO HAVE BORDERLINE THYROID FUNCTION TESTS

It is well known that thyroid hormones are required for normal human brain development and that replacement of thyroid deficiency in full-term infants is indicated as early as possible to prevent neurodevelopmental problems.[1] However, the treatment indications and guidelines for hospitalized infants with transient or mild thyroid abnormalities continue to be debated.

Universal Levothyroxine Supplementation for Very Low Birth Weight Preterm Infants

Because transient hypothyroidism is common in preterm infants due to hypothalamic-pituitary-thyroid axis immaturity, it was hypothesized that routinely supplementing all VLBW preterm infants with levothyroxine (L-T4) would improve neurodevelopment. However, multiple randomized trials showed no benefit. Van Wassenaer and coinvestigators[48] found universal thyroxine supplementation to infants born at less than 30 weeks' gestation had no effect on 24-month neurodevelopmental outcomes. A multicenter, double-blind randomized placebo-controlled trial by Ng and colleagues[49] that assessed the effects of L-T4 supplementation for all less than 28 weeks' gestation infants, found no apparent effect on brain size and growth at 36 weeks' postmenstrual age. Van Wassernaer-Leemhuis and colleagues[50] performed a multicenter, phase 1 clinical trial of differing doses of thyroid hormone supplementation for infants born at less than 28 week's gestation and assessed 3-year neurodevelopmental outcomes. There were no differences in cognitive, motor, and neurologic development in the treated versus the nontreated groups, nor were there adverse outcomes in the treated group.

Although rare, L-T4 supplementation has been associated with adverse effects. Kawai and colleagues[51] found in a nationwide surveillance study that late-onset circulatory collapse was reported in 0.5% of infants that received L-T4. It was hypothesized that L-T4 may have increased the relative adrenal insufficiency of prematurity and thus the risk of late-onset circulatory collapse in VLBW infants. If L-T4 is used in VLBW infants, close monitoring of blood pressure and adrenal function should occur.[51]

Transient Hypothyroidism

Transient hypothyroxinemia (low free T4 level with normal TSH) is common in preterm neonates and has been associated with later neurodevelopmental deficiency.[52,53] However, the exact serum levels of free T4 needed to achieve optimal brain maturation have not been quantified and there is no universal consensus on an age or free T4 level cutoff at which treatment should be mandatory.[54] It is possible that low thyroid

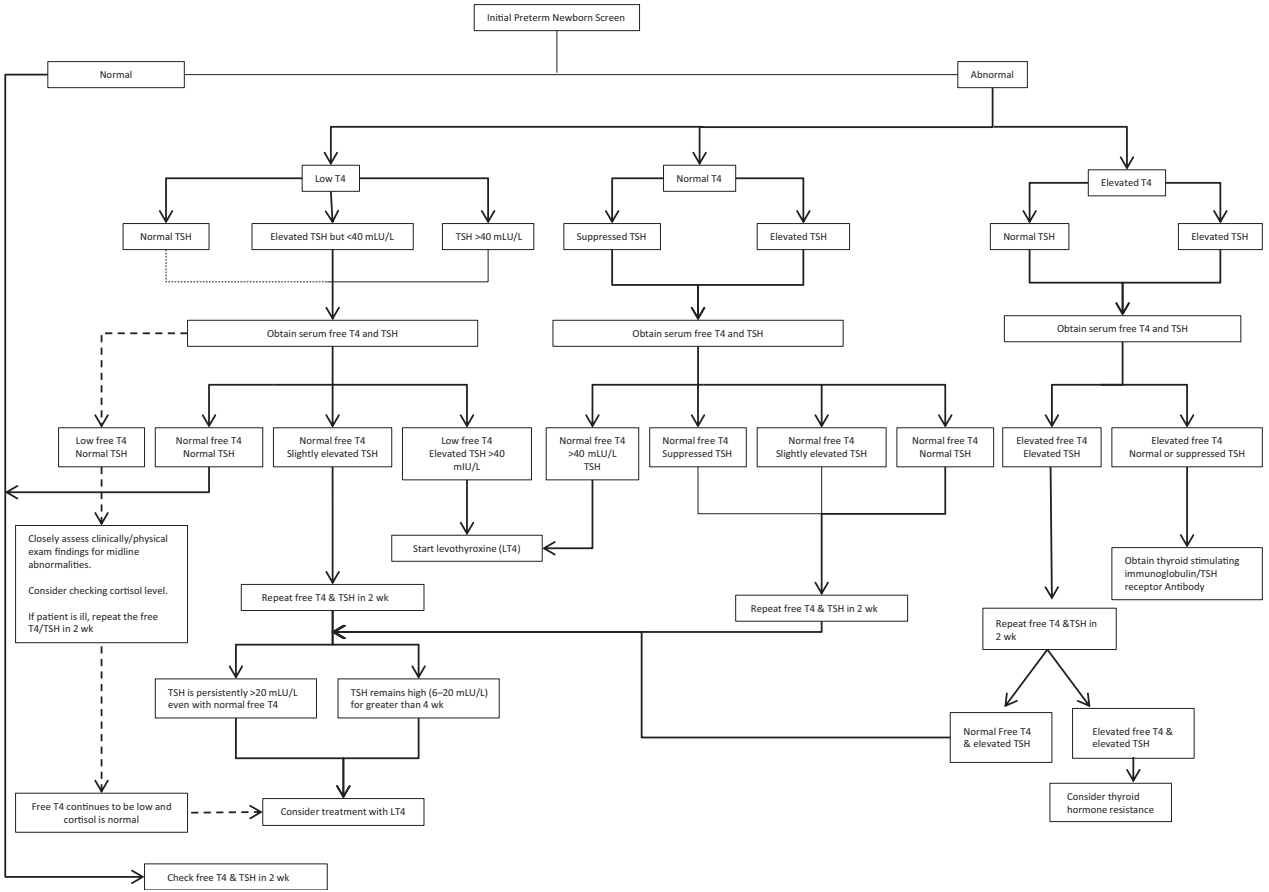

Fig. 1. Flowchart to assist in decision making for rescreening and treating hypothyroidism in preterm infants.

hormone levels are a normal physiologic attempt to protect the sick infant by reducing the metabolic rate during a time of illness.[37]

Transient congenital hypothyroidism with delayed TSH rise is also common in preterm infants.[1] The benefit of treating premature infants with transient TSH elevations with L-T4 is unclear. Some researchers recommend that neonates, even with transiently elevated TSH values (>50 mIU/L), should be promptly treated with L-T4 because of intellectual disability risk.[2] Woo and colleagues[4] found that at 18-month follow-up, VLBW infants with a history of congenital hypothyroidism with delayed TSH elevation had similar growth and neurodevelopment as compared with matched control subjects without hypothyroidism. However, they noted significantly more head circumferences measuring less than 10th percentile in infants with hypothyroidism with delayed TSH elevation.[4]

Uchiyama and colleagues[55] performed an unmasked, multicenter randomized clinical trial of L-T4 supplementation in VLBW infants with transient hypothyroxinemia of prematurity. Infants with TSH less than 10 mIU/L and free T4 less than 0.8 ng/L were randomized to L-T4 supplementation or placebo between 2 and 4 weeks of age. L-T4 treatment did not affect growth or neurodevelopmental outcome at 18 months and 3 month of age.[55,56]

Fig. 1 presents a flowchart to assist in decision making for rescreening and treating hypothyroidism in preterm infants. Given the complexity of TFT evaluation in sick and preterm neonates, we recommend consultation with a pediatric endocrinologist when deciding when to begin treatment and for planning follow-up. Regardless of initial treatment decision, close monitoring of patients with borderline elevated TSH values is important because persistent or permanent hypothyroidism is noted in a subset of infants.[2]

WHEN TO RETEST TO ASSESS PERMANENCY OF HYPOTHYROIDISM

The American Academy of Pediatrics[1] recommends assessing the permanency of congenital hypothyroidism in children treated with L-T4 if the initial TSH was less than 50 mIU/L without an increase in TSH during therapy following the newborn period. Assessment for permanent congenital hypothyroidism should be performed after 3 years of age, by either a trial off therapy for 30 days or a 50% reduction in the dose of L-T4 for 30 days. Subsequent repeat TFTs should be collected to assess the effects. If the TFTs were normal after the 50% L-T4 dose reduction, then medication should be discontinued for 30 days and the TFTs repeated. If the TSH is elevated off of therapy, this would be compatible with hypothyroidism.

SUMMARY

Compared with healthy term newborns, infants hospitalized within NICUs are more likely to have abnormal TFTs because of illness and prematurity. Because of an immature hypothalamic-pituitary-thyroid axis, preterm infants may present with congenital hypothyroidism with a delayed TSH rise that is undetected on initial postnatal screening tests. Therefore, repeat screening several weeks after birth is recommended.[5] Congenital hypothyroidism in NICU patients may be transient, and consultation with a pediatric endocrinologist is recommended when deciding when to begin treatment. Regardless of initial treatment decisions, it is important to closely follow serum TSH and free T4 levels to exclude the possibility of permanent hypothyroidism.

Best Practices

What is the current practice?

Newborn screening for congenital hypothyroidism

All newborns including those hospitalized in NICUs should receive TSH and T4 based screening for congenital hypothyroidism in the first several days after birth. Screens should be collected after 24-hours postnatal age unless earlier screen collection is necessitated by blood transfusion. Screens collected before 24 hours should be repeated, because the results have high likelihood of being false positive.

What changes in current practice are likely to improve outcomes?

- Thyroid screening tests should be repeated in sick and preterm NICU patients at several weeks postnatal age to evaluate for congenital hypothyroidism with delayed TSH rise.
- It is important to closely follow abnormal serum TSH and free T4 levels in 2-week intervals, to assess for permanent hypothyroidism.
- If the TSH is greater than 40 mIU/L, start levothyroxine therapy (10–15 μg/kg orally daily; intravenous dose is ~50% of oral dose)
- If the TSH is elevated but less than 40 mIU/L, repeat the free T4 and TSH levels.
- If the TSH is persistently elevated at 4-weeks postnatal age, consider levothyroxine therapy (10–15 μg/kg orally daily; intravenous dose is ~50% of oral dose)
- Once levothyroxine therapy is initiated, repeat the free T4 and TSH in 4 weeks to assess adequacy of the dose.
- Consider a trial off therapy at 3 years of age in those individuals who had a normal free T4 with an elevated TSH, to determine whether lifelong therapy is needed.

Is there a clinical algorithm?

The most common clinical recommendations for neonatal screening, diagnosis, and treatment of congenital hypothyroidism are those of the American Academy of Pediatrics and the European Society for Paediatric Endocrinology.

Data from Rose SR, Brown RS, Foley T, et al. Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics 2006;117(6):2290–303; and Leger J, Olivieri A, Donaldson M, et al. European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. J Clin Endocrinol Metab 2014;99(2):363–84.

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