Journal of Perinatology (2019) 39:1065–1071
https://doi.org/10.1038/s41372-019-0400-3

ARTICLE

The value of serial newborn screening for congenital hypothyroidism using thyroxine (T4) in the neonatal intensive care unit

Tina O. Findley[1] · Avni Shah[2] · Cynthia Bell[3] · Amir Khan[1]

Received: 12 December 2018 / Revised: 16 April 2019 / Accepted: 27 April 2019 / Published online: 18 June 2019

Abstract

Objective To evaluate the role of serial newborn screening of congenital hypothyroidism using thyroxine (T4) in the neonatal intensive care unit (NICU).

Subjects Newborn screen results were reviewed from a single academic NICU during 2007–2016 ($n = 6100$). Thyroid function levels were reviewed in patients treated for hypothyroidism during that period. Duration of treatment was followed after discharge.

Results Overall incidence of treated hypothyroidism was 1:103 with increasing incidence inversely related to birth weight. Among treated infants ($n = 59$), initial newborn screen demonstrated sensitivity and specificity of 74.1% and 84.9%, respectively; second screen demonstrated rates of 85.7% and 76.1%, respectively. Based on follow-up data, prevalence of permanent congenital hypothyroidism in our NICU population was 1:870 ($n = 7$); two patients would have been missed with a single screen.

Conclusion Abnormal T4 on newborn screening is common for preterm neonates. Higher rates of permanent congenital hypothyroidism highlight the need for screening beyond the newborn screen.

Introduction

Congenital hypothyroidism is the most common cause of preventable intellectual disability, and early detection and treatment has been aided by its inclusion in newborn screening programs since the 1970s. While increasing incidence of congenital hypothyroidism in the overall population has been reported, it is debatable whether we are actually observing a real rise in congenital hypothyroidism [1]. It is well-known that infants born premature and ill neonates have underlying physiology that predisposes them to thyroid dysfunction [2–4]. The timing of newborn screening collection often occurs when the premature infant is acutely ill with conditions known to affect thyroid function including sepsis, respiratory distress syndrome, patent ductus arteriosus, and intraventricular hemorrhage [5–10]. In addition, patients in the neonatal intensive care unit (NICU) are often administered medications that may affect neonatal thyroid function including dopamine, caffeine, morphine, and total parenteral nutrition [7, 11]. The incidence of congenital hypothyroidism in the overall population has increased over time from 1:3010 to 1:1660, with likely contributing factors including improved survival of premature infants at risk for thyroid dysfunction and lowering of screening TSH thresholds with increasing treatment of mild and transient cases of hypothyroidism, although the rate of severe congenital hypothyroidism has remained closer to historic values of 1:3000–4000 [1, 12].

It remains unclear how best to screen for congenital hypothyroidism in the NICU population. In Texas, two serial newborn screens are collected using thyroxine (T4) as the primary screening method. Although various newborn screening programs in the United States use primary T4 to

✉ Tina O. Findley
Tina.O.Findley@uth.tmc.edu

[1] Division of Neonatal-Perinatal Medicine, Department of Pediatrics, McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX, USA

[2] Division of Endocrinology, Department of Pediatrics, McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX, USA

[3] Division of Nephrology, Department of Pediatrics, McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX, USA

screen for congenital hypothyroidism, little is published in the literature regarding the detection rate of serial T4 testing in premature and ill neonates. Our study aim was to evaluate the role of newborn screening using T4 in the NICU.

Materials and methods

We performed a single center retrospective study to review newborn screening results of patients admitted to a large, academic Level IV NICU. Our study included all patients admitted to Children's Memorial Hermann Hospital in Houston, Texas, with two newborn screens over a 9-year period. Institutional review board (IRB) approval was obtained from The University of Texas Health Science Center at Houston and the Texas Department of State Health Services (TDSHS) with waiver of consent.

In Texas all newborns require two newborn screens; one collected at 24 h of life, the second at 10–14 days of life. In our NICU, the timing of the second newborn screen within 10–14 days of life is at the discretion of the bedside nurse. In collaboration with the TDSHS, we collected newborn screening results on all patients who had two newborn screens between 1 July 2007 and 30 June 2016 ($n = 6100$), excluding patients with only one newborn screening result, such as healthy newborns who were discharged soon after birth, critically ill neonates who died within 2 weeks of life, and patients who were transferred to our institution later in their hospitalization. In addition, some patients were excluded in the data system if the demographic information significantly differed on the same patient. The current TDSHS data system links over 90 percent of infants on average. All newborn screening specimens are analyzed at the TDSHS in Austin, Texas. T4 is initially tested in all newborn screening specimens, and first, second, and subsequent repeated newborn screens run in separate batches. Per TDSHS protocol, specimens with the lowest 10% of T4 in each batch are retested for T4 and TSH. In the retested batch, specimens with the lowest 0.5% of T4 in each batch and/or TSH levels greater than a predetermined threshold (generally 30 mIU/L) are considered abnormal [13]. All newborn screening results released by the TDSHS for the purposes of our study were de-identified, providing only their birth year, birth weight, and all thyroid screen results (limited to *normal T4*, *normal T4/normal TSH*, *abnormal thyroid screen: T4 low*, *abnormal thyroid screen: TSH slightly/moderately/very elevated*, or *unsatisfactory*). The start date for data extraction was selected to coincide with when TDSHS began electronically storing newborn screening results. We did not include 212 first newborn screening results and 131 second newborn screening results when calculating the detection rate of each screen individually due to unsatisfactory specimen collections. When calculating the detection rate of the two screenings in tandem, we did not include 69 patients who had unsatisfactory specimens for both newborn screens.

We also conducted a retrospective review of all patients treated with replacement therapy, levothyroxine, for presumed congenital hypothyroidism in the Level IV NICU at Children's Memorial Hermann Hospital, Houston, Texas, during the same 9-year span ($n = 59$). Data collected on each patient included the gestational age at birth, birth weight, newborn screening results, and the level of free T4 and TSH ordered by the physician just prior to initiating medical therapy with levothyroxine to infer what level(s) precipitated treatment. We also noted if any major congenital anomalies and/or syndromes were diagnosed in each patient. Patients were excluded if they were initially treated with levothyroxine at the referring hospital and transferred to our hospital later in their care, or if they had incomplete newborn screening records. The charts of patients who were discharged from the NICU on levothyroxine were reviewed in the outpatient clinic electronic medical record. Electronic charts were reviewed for clinical documentation from the pediatric endocrinology clinic to evaluate date of last visit, if and when thyroid replacement was discontinued, or last dose of thyroid replacement if still on treatment. IRB approval was obtained from The University of Texas Health Science Center at Houston with waiver of consent.

Data analysis was performed using Stata 15 SE. Continuous variables are reported as median (interquartile range) and categorical variables are reported as counts (percentages). Kaplan–Meier curves are used to calculate proportion with transient hypothyroidism over the study period. Follow-up time was defined as time from birth to last newborn screening in patients discharged off treatment or lost to follow-up after discharge, or last clinic date in patients seen at the pediatric endocrinology clinic. A two-sided p-value of 0.05 defined statistical significance.

Results

A total of 6100 neonates with two documented newborn screenings were admitted to Children's Memorial Hermann Hospital NICU between 1 July 2009 and 30 June 2016. We will discuss our results by sub-categories of birth weight as gestational age at birth was not provided by the TDSHS. A total of 923 extremely low birth weight (<1000 g) infants, 859 very low birth weight (1000–1499 g) infants, 2232 low birth weight (1500–2499 g) infants, and 2086 normal birth weight infants (>2500 g) were included in our study cohort.

During the same 9-year period, a total of 59 infants were treated with levothyroxine (Table 1 for characteristics). The

median gestational age at birth was 26 weeks (25–28), and the median birth weight was 725 g (563–1140). Ten patients had conditions associated with thyroid dysfunction including Trisomy 21, Turner syndrome, panhypopituitarism, or underlying maternal thyroid condition (e.g., Grave's disease). The total prevalence of treated hypothyroidism in our NICU was 1:103 with increasing prevalence inversely related to birth weight (Table 2). Among extremely low birth weight infants, the prevalence of treatment was as high as 1:21.

Overall among those treated, 43 infants (72.9%) had an abnormal first newborn screen, 48 infants (81.4%) had an abnormal second newborn screen, and 35 infants (59.3%) had abnormal results for both newborn screens, indicating some results normalized on serial screening. We observed two cases of infants who had normal results for both newborn screens but eventually received medical therapy for hypothyroidism. One case was an infant with Turner syndrome and aortic coarctation born at 34 weeks gestational age who had an elevated TSH (32.4 mIU/L) and normal free T4 (1.21 ng/dl) levels on later thyroid function testing ordered by the physician after the newborn screen. She is still on treatment at under 3 years of age, and whether she will be diagnosed with permanent congenital hypothyroidism is to be determined. The second case was an infant born at 34 weeks gestational age whose twin sibling was detected by newborn screening, and additional thyroid function testing on the infant revealed an elevated TSH (29.6 mIU/L) and normal free T4 (0.81 ng/dl); the twin siblings were lost to follow-up.

Table 1 Characteristics of infants treated for hypothyroidism in the NICU

Total, *n*	59
Sex	
Female, *n* (%)	31 (52.5)
Male, *n* (%)	28 (47.5)
Birth weight (g), median (IQR)	725 (563–1 140)
Gestational age at birth (weeks), median (IQR)	26 (25–28)
Congenital anomalies	
Down syndrome (Trisomy 21), *n*	3
Turner syndrome, *n*	1
DiGeorge syndrome (22q11.2 deletion), *n*	1
Maternal thyroid condition, *n*	3
Panhypopituitarism, *n*	2
Thyroid function prior to initiating medical therapy, median (IQR)	
TSH (mIU/L), median (IQR)	13.8 (7.3–29.6)
Free T4 (ng/dL), median (IQR)	0.79 (0.59–1.05)
Corrected gestational age at initiation of medical therapy (weeks), median (IQR)	37 (32–40)

IQR interquartile range

To determine the probability of detecting and treating transient, mild, and permanent cases of hypothyroidism in our NICU population, we included all infants treated for hypothyroidism and found the initial newborn screen demonstrated sensitivity and specificity of 74.1% and 84.9%, respectively (Table 3). The second newborn screen exhibited improved sensitivity and specificity of 85.7% and 86.7%, respectively. To evaluate if screening rates improved when results were evaluated in tandem, we defined results as "positive" if the patient had abnormal results for both screenings and "negative" if the patient had at least one normal result. For all NICU patients, specificity improved to 93.4%; however, sensitivity rates declined to 62.5% in the overall NICU population with only 40% detected among treated infants born at 1500 g or greater. This could be due to our strict criteria of "positive" results requiring two abnormal screening results.

During the study period, there was no institutional protocol on screening for congenital hypothyroidism after the state newborn screens, and the TSH levels prompting medical therapy varied in our NICU population. We investigated the thyroid function levels ordered by the physician prior to initiation of medical therapy and found that two patients had severe congenital hypothyroidism (defined as TSH ≥ 100 mIU/L), and 17 patients had mild congenital hypothyroidism (defined as TSH 20–99 mIU/L). Two patients with abnormal newborn screens were found to have undetectable TSH levels and low free T4 and were

Table 2 Serial T4 newborn screening results and incidence of hypothyroidism by birth weight category

Birth weight category	Total, *n*	Abnormal first screen, *n* (%)	Abnormal second screen, *n* (%)	Incidence of treated hypothyroidism[a]	Incidence of permanent CH[b]
Overall	6100	926 (15.2)	835 (13.7)	1:103	1:871
Extremely low birth weight	923	460 (49.8)	535 (58)	1:21	1:185
Very low birth weight	859	190 (22.1)	151 (17.6)	1:143	1:430
Low birth weight	2232	170 (7.6)	69 (3.1)	1:319	0
Normal birth weight	2086	106 (5.1)	80 (3.8)	1:695	0

[a]Treated Hypothyroidism defined as receiving treatment for hypothyroidism during NICU hospitalization (total $n = 59$)

[b]Permanent CH, congenital hypothyroidism, diagnosed at 3 years of age (total $n = 7$)

Table 3 Detection rate of hypothyroidism requiring treatment in the NICU by serial T4 newborn screening at 24 h of life and 10–14 days of life

	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %
First newborn screen				
<1500 g	79.2 (65.0–89.5)	63.3 (61.0–65.6)	5.8 (4.2–7.9)	99.1 (98.3–99.5)
≥1500 g	50 (18.7–81.3)	93.5 (92.7–94.2)	1.8 (0.6–4.2)	99.9 (99.7–100.0)
All NICU patients	74.1 (61.0–84.7)	84.9 (83.9–85.8)	4.6 (3.4–6.2)	99.7 (99.5–99.8)
Second newborn screen				
<1500 g	91.3 (79.2–97.6)	61.9 (59.6–64.2)	6.1 (4.5–8.2)	99.6 (99.0-99.9)
≥1500 g	60.0 (26.2–87.8)	96.6 (96.0–97.1)	4.0 (1.5–8.6)	99.9 (99.7–100.0)
All NICU patients	85.7 (73.8–93.6)	86.7 (85.8–87.5)	5.7 (4.3–7.5)	99.8 (99.7–99.9)
T*andem newborn screens*				
<1500 g	67.4 (52.0–80.5)	79.1 (77.1–81.1)	8.1 (5.6–11.3)	98.9 (98.2–99.4)
≥1500 g	40.0 (12.2–73.8)	99.0 (98.7–99.3)	8.9 (2.5–21.2)	99.9 (99.7–99.9)
All NICU patients	62.5 (48.5–75.1)	93.4 (92.8–94.0)	8.2 (5.8–11.2)	99.6 (99.4–99.8)

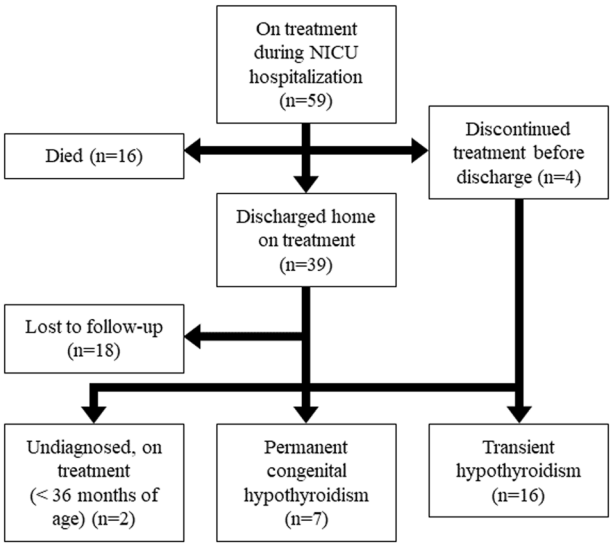

Fig. 1 Flowchart of patients treated for hypothyroidism during NICU hospitalization and treatment outcomes after discharge

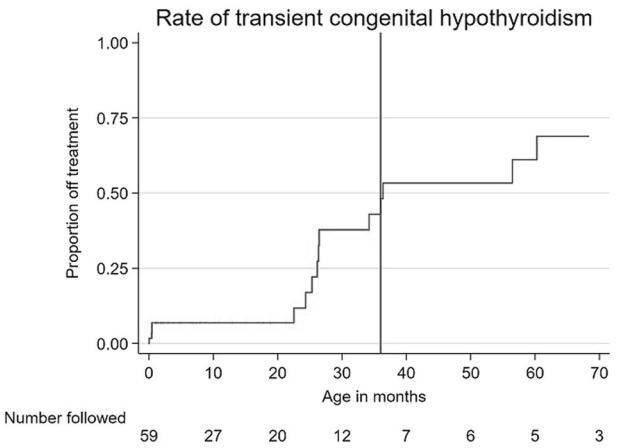

Fig. 2 Kaplan–Meier curve of proportion with transient congenital hypothyroidism

ultimately diagnosed with central hypothyroidism. Prior to initiating medical therapy the median TSH level was 13.8 mIU/L (7.3, 29.6), and the median free T4 level was 0.79 ng/dl (0.59, 1.05). At the time patients were started on levothyroxine, the median corrected gestational age was 37 weeks (32, 40). The mortality rate was 27.1% ($n = 16$), reflecting the degree of critical illness in the treatment group. Of those who survived to discharge, 90.7% ($n = 39$) were discharged home on levothyroxine treatment.

Of the 39 patients who were discharged from the NICU on levothyroxine treatment, 18 were lost to follow-up after discharge (Fig. 1). A total of 16 treated patients eventually had their medication discontinued before hospital discharge or in the outpatient setting and so were diagnosed with transient congenital hypothyroidism. At the time of chart review, seven patients remained on levothyroxine treatment beyond the age of 3 years and were diagnosed with permanent congenital hypothyroidism (Fig. 2). Upon reviewing their newborn screening results, two patients with permanent congenital hypothyroidism had a normal first newborn screen and would have been missed if only a single screening was done.

Discussion

The limitations of primary TSH newborn screening have been well-described and includes failure to detect delayed TSH elevation, central hypothyroidism, and hypothyroxinemia [14]. This is particularly relevant in the NICU as thyroid dysmaturity, illness, and medications have all been

linked to the higher occurrence of delayed TSH elevation and transient hypothyroxinemia (also known as atypical hypothyroidism) in premature and ill neonates [15]. The alternative method of congenital hypothyroidism screening in newborn screening programs uses primary T4 with backup TSH screening. Primary T4 has the advantage of detecting central hypothyroidism but also fails to detect delayed TSH elevation. In addition, false positives are frequently detected in the NICU setting due to transient hypothyroxinemia, as demonstrated in our patient population. In neonates <1500 g at birth, the specificity was ~60%; poor specificity was highlighted in the extremely low birth weight neonates where half of the patients had abnormal newborn screening results. As a result, frequent false positives potentially have the unintended consequence of clinicians disregarding abnormal newborn screening results. An unexpected finding was that for infants ≥1500 g at birth, the newborn screen was poorly sensitive, and this persisted when the two newborn screens were evaluated in tandem. Consequently, normal serial newborn screening results may be falsely reassuring in the premature and ill neonate. Still, studies have shown serial newborn screening increases detection of congenital hypothyroidism, particularly in preterm infants [16–20].

Screening and management of thyroid dysfunction in the premature and ill neonatal population due to conditions such as congenital hypothyroidism, thyroid dysmaturity, and transient hypothyroxinemia continues to garner much discussion and controversy. There are published reports of increasing incidence of congenital hypothyroidism, but when Mitchell et al. investigated the rising incidence in Massachusetts, they reported the incidence of severe congenital hypothyroidism remained stable while increasing numbers were observed in mild and transient cases of congenital hypothyroidism where clinical significance is yet to be determined [1]. However, based on available follow-up data we can conservatively estimate that 1:871 were diagnosed with true or permanent congenital hypothyroidism defined as requiring levothyroxine beyond 3 years of age in our NICU population. These results are contrary to those by Srinivasan et al. who reported that incidence of permanent congenital hypothyroidism, using the same definition, was similar in the term and preterm population [21]. Our NICU patients were overall more premature when compared with the median gestational age of 32 weeks in the study population by Srinivasan et al. and may explain the differences in the incidence of permanent congenital hypothyroidism. Our population appeared comparable to other neonatal study populations as the prevalence of thyroid dysfunction requiring medical therapy during NICU hospitalization was similar to other preterm populations reported by Mandel et al. (1:153 in very low birth weight infants) [15], Bijarnia et al. (1:128 in very low birth weight infants) [17], and Kaluarachchi et al. (1:143 in premature infants born <30 weeks gestation) [22].

The incidence of permanent congenital hypothyroidism is seldom reported in former NICU patients as duration of medical therapy is rarely followed after hospital discharge. The high rate of our patients lost to follow-up in the pediatric endocrinology clinic reflects the challenges to understanding the natural course of hypothyroidism treated in the NICU setting. However, using our most conservative estimate by assuming all patients lost to follow-up were transient cases, the rate of permanent congenital hypothyroidism in our NICU population was still higher than previously reported [1, 21]. Co-existing conditions in NICU patients may increase risk for congenital hypothyroidism, including genetic syndromes (i.e., Trisomy 21), and midline syndromes affecting the pituitary gland (i.e., septo-optic dysplasia). While delayed TSH elevation and attenuated maturation of the hypothalamic-pituitary-thyroid axis in preterm infants have been well-described, whether there are additional mechanisms causing permanent changes to the hypothalamic-pituitary-thyroid axis remains unknown [2–11]. Other contributing factors may include differences in management in the absence of explicit guidelines for premature infants and the diverse background population of Houston. The authors are not aware of unique risk factors for congenital hypothyroidism in Houston, but it is plausible iodine deficiency may be undetected in certain immigrant populations during pregnancy. Nonetheless, our results highlight the importance of closer screening beyond the newborn screen in the NICU.

In an effort to have a more targeted approach for congenital hypothyroidism screening in the NICU, alternative TSH and free T4 reference ranges and nomograms for the premature population have been proposed, as well as age-dependent thresholds for TSH screening [16, 23, 24]. While all state newborn screening programs mandate screening at birth, most states only perform a single screen. Expert opinion generally recommends repeat screening in premature and ill infants [16, 17, 22, 25–28]. However, few guidelines have been published on subsequent management and treatment for the preterm population. Guidelines published by the American Academy of Pediatrics and the European Society for Paediatric Endocrinology focus on healthy, term infants [14, 27]. Since our findings, our institution now routinely screens thyroid function in all preterm infants (<35 weeks gestational age at birth) at 30 days of life or prior to discharge which is more consistent with guidelines by the Clinical & Laboratory Standards Institute and validated in a large Michigan newborn population by Korzeniewski et al. [16, 26].

Some limitations of our study include its retrospective study design at a single institution. Due to the rarity of

congenital hypothyroidism, there is a relatively small sample size of treated congenital hypothyroidism in a large NICU population. Since we selected our cohort of infants treated for thyroid dysfunction by screening for patients treated with levothyroxine, there is the possibility that an infant with congenital hypothyroidism went undiagnosed in the NICU and began treatment after discharge. Also, we relied on the recommendations of the pediatric endocrinologist to initiate treatment with levothyroxine, a salient point as there is no agreed-upon criteria for treatment of thyroid dysfunction in the NICU. Strengths of our study include a large overall study population as well as information on duration of therapy and outcomes when available which allowed us to better define transient versus permanent cases of congenital hypothyroidism.

In conclusion, serial newborn screens with primary T4 is complicated by frequent false positive results, especially in extremely preterm infants, yet is also poorly sensitive for preterm infants weighing at least 1500 g at birth. Both factors can be alarming to families and perplexing to the clinician [29]. The timing of newborn screening often coincides with when the newborn is critically ill and on thyroid-suppressive medications. Coupled with thyroid dysmaturity, this population is at high-risk for hypothyroxinemia and/or delayed TSH elevation, which are transient in most cases, but our study suggests the prevalence of permanent congenital hypothyroidism in the NICU population to be greater than previously reported. For these reasons, we recommend measuring TSH and free T4 at ~30 days of life in the NICU in accordance with an increasing number of experts to avoid missed or late diagnosis of a treatable disease. Additional research is needed in the significance of transient and mild cases of thyroid dysfunction and whether those infants benefit from treatment with replacement therapy.

Acknowledgements We would like to thank our collaborators at the Texas Department State Health Services for their assistance.

Author contributions TF designed the study, drafted the project proposal, coordinated with IRB, collected data, drafted and approved final paper as submitted. AS was involved in design of the study, collected data, and drafted and approved final paper as submitted. CB performed data analysis, drafted and approved the final paper as submitted. AK was involved in designing of the study, reviewed and approved final paper as submitted.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Mitchell ML, Hsu H, Sahai I, the Massachusetts Pediatric Endocrine Work Group. The increased incidence of congenital hypothyroidism: fact or fancy? Clin Endocrinol. 2011;75:806–10.
2. Bongers-Schokking JJ, Schopman W. Thyroid function in healthy normal, low birthweight and preterm infants. Eur J Pedia. 1984;143:117–22.
3. Hashimoto H, Sato T, Horita S, Kobu M, Ohki T. Maturation of the pituitary-thyroid axis during the perinatal period. Endocrinol Jpn. 1991;38:151–7.
4. Biswas S, Buffery J, Enoch H, Bland JM, Walters D, Markiewicz M. A longitudinal assessment of thyroid hormone concentrations in preterm infants younger than 30 weeks' gestation during the first 2 weeks of life and their relationship to outcome. Pediatr. 2002;109:222–7.
5. Franklin RC, Puride GL, O'Grady CM. Neonatal thyroid function: prematurity, prenatal steroids, and respiratory distress syndrome. Arch Dis Child. 1986;61:589–92.
6. LaFranchi S. Thyroid function in the preterm infant. Thyroid. 1999;9:71–78.
7. Williams FLR, Ogston SA, van Toor H, Visser TJ, Hume R. Serum thyroid hormones in preterm infants: associations with postnatal illnesses and drug usage. J Pedia Endocrinol Metab. 2007;90:5954–63.
8. Clemente M, Ruiz-Cuevas P, Carrascosa A, Potau N, Almar J, Salcedo S, et al. Thyroid function in preterm infants 27–29 weeks of gestational age during the first four months of life: results from a prospective study comprising 80 preterm infants. J Pedia Endocrinol Metab. 2007;20:1269–80.
9. Carrascosa A, Ruiz-Cuevas P, Clemente M, Salcedo S, Almar J. Thyroid function in 76 sick preterm infants 30–36 weeks: results from a longitudinal study. J Pedia Endocrinol Metab. 2008;21:237–44.
10. Ryckman KK, Spracklen CN, Dagle JM, Murray JC. Maternal factors and complications of preterm birth associated with neonatal thyroid stimulating hormone. J Pedia Endocrinol Metab. 2014;27:929–38.
11. Filippi L, Cecchi A, Tronchin M, Dani C, Pezzati M, Seminara S, et al. Dopamine infusion and hypothyroxinemia in very low birth weight preterm infants. Eur J Pedia. 2004;163:7–13.
12. Olivieri A, Fazzini C, Medda E. Italian study group for congenital hypothyroidism. Horm Res Paediatr. 2015;83:86–93.
13. Drummond-Borg M, Johnson D. Newborn screening for congenital hypothyroidism: the Texas experience. Tex Med. 2003;99:50–52.
14. American Academy of Pediatrics, Rose SR, American Thyroid Association, RS, Lawson Wilkins Pediatric Endocrine Society. Update of newborn screening and therapy for congenital hypothyroidism. Pediatr. 2006;117:2291–303.
15. Mandel SJ, Hermos RJ, Laron CA, Prigozhin AB, Rojas DA, Mitchell ML. Atypical hypothyroidism and the very low birthweight infant. Thyroid. 2000;10:693–5.
16. Korzeniewski SJ, Kleyn M, Young WI, Chaiworapongsa T, Schwartz AG, Romero R. Screening for congenital hypothyroidism in newborns transferred to neonatal intensive care. Arch Dis Child Fetal Neonatal Ed. 2013;98:F310–315.
17. Bijarnia S, Wilcken B, Wiley VC. Newborn screening for congenital hypothyroidism in very-low-birth-weight babies: the need for a second test. J Inherit Metab Dis. 2011;34:827–33.
18. Ford GA, Denniston S, Sesser D, Skeels MR, LaFranchi SH. Transient versus permanent congenital hypothyroidism after age 3 years in infants detected by the first vs. second newborn screening test in Oregon. Horm Res Paediatr. 2016;86:169–77.

19. McGrath N, Hawkes CP, Mayne P, Murphy NP. Optimal timing of repeat newborn screening for congenital hypothyroidism in preterm infants to detect delayed thyroid-stimulating hormone elevation. J Pedia. 2019;205:77–82.
20. Silva SA, Chagas AJ, Goulart EM, Silva GA, Marçal LV, Gomes MN, et al. Screening for congenital hypothyroidism in extreme premature and/or very low birth weight newborns: the importance of a specific protocol. J Pedia Endocrinol Metab. 2010;23:45–52.
21. Srinivasan R, Harigopal S, Turner S, Cheetham T. Permanent and transient congenital hypothyroidism in preterm infants. Acta Paediatr. 2012;101:e179–182.
22. Kaluarachchi DC, Colaizy TT, Pesce LM, Tansey M, Klein JM. Congenital hypothyroidism with delayed thyroid-stimulating hormone elevation in premature infants born at less than 30 weeks gestation. J Perinatol. 2017;37:277–82.
23. Adams LM, Emery JR, Clark SJ, Carlton EI, Nelson JC. Reference ranges for newer thyroid function tests in premature infants. J Pedia. 1995;126:122–7.
24. Imamoglu EY, Gursoy T, Hayran M, Karatekin G, Ovali F. Nomogram-based evaluation of thyroid function in appropriate-for-gestational-age neonates in intensive care unit. J Perinatol. 2015;35:204–7.
25. Gruñeiro-Papendieck L, Chiesa A, Mendez V, Santilli A, Prieto L. Efficacy of congenital hypothyroidism neonatal screening in preterms less than 32 weeks of gestational age: more evidence. J Pedia Endocrinol Metab. 2005;18:373–7.
26. CLSI. CLSI document I/LA31-A.. Newborn screening for preterm, low birth weight, and sick newborns; approved guideline. Wayne, PA: Clinical and Laboratory Standards Institute; 2009.
27. Léger J, Olivieri A, Donaldson M, Torresani T, Krude H, van Vliet G, et al. European society for paediatric endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. Horm Res Paediatr. 2014;81:80–103.
28. LaFranchi S. Screening preterm infants for congenital hypothyroidism: better the second time around. J Pedia. 2014;164:1259–60.
29. Schmidt JL, Castellanos-Brown K, Childress S, Bonhomme N, Oktay JS, Terry SF, et al. The impact of false-positive newborn screening results on families: a qualitative study. Genet Med. 2012;14:76–80.