Optimal Timing of Repeat Newborn Screening for Congenital Hypothyroidism in Preterm Infants to Detect Delayed Thyroid-Stimulating Hormone Elevation

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Objectives To evaluate the timing of a delayed rise in thyroid-stimulating hormone (TSH) levels in preterm infants with congenital hypothyroidism, and to determine whether cases of congenital hypothyroidism would be missed by using current consensus guidelines of repeat screening at approximately 2 weeks of age or 2 weeks after the first screening.

Study design The study was performed over a 13-year period (January 2004-December 2016). Whole-blood TSH samples were collected between 72 and 120 hours after birth. Repeat samples were collected weekly in preterm infants until the infant was term-corrected (37 weeks' gestation). Patients were followed up to determine whether congenital hypothyroidism was permanent or transient.

Results Twenty-seven (50.9%) preterm infants born at <33 weeks of gestation who were diagnosed with congenital hypothyroidism had delayed TSH elevation and would not have been detected on first newborn screen. Twelve of these infants (40.7%) with delayed TSH elevation had decompensated hypothyroidism at diagnosis (free thyroxine [FT4] <10 pmol/L), and 4 had severe congenital hypothyroidism (FT4 <5.5 pmol/L) at diagnosis. If screening had been repeated only at 2 weeks of life, 13 infants (48%) with delayed TSH elevation would not have been identified. Of the 27 infants with delayed TSH elevation, 6 (22%) have permanent congenital hypothyroidism, and another 12 will be reevaluated at age 3 years.

Conclusion Repeat screening for congenital hypothyroidism in preterm infants is necessary to avoid missing cases of congenital hypothyroidism with delayed TSH elevation. Repeat screening once at 2 weeks of life will miss infants with delayed TSH elevation and decompensated permanent congenital hypothyroidism. *(J Pediatr 2019;205:77-82).*

Congenital hypothyroidism affects approximately 1 in 2000-4000 births[1-4] and is a preventable cause of neurodevelopmental disability. Newborn screening programs have increased the rate of early detection of this condition and almost eradicated the neurologic complications. The reported incidence of congenital hypothyroidism has significantly risen during the past 2 decades.[5-7] Suggested factors contributing to this rise are the change in thyroid-stimulating hormone (TSH) screening cutoff levels over time and increasing survival of preterm infants.[5,8]

A unique form of congenital hypothyroidism has been described in preterm infants. This atypical form of hypothyroidism is characterized by a delayed elevation in TSH concentration, such that preterm infants pass their first newborn screening test but are detected on repeat screening.[9] The timing of this elevation, although variable, occurs between 2 and 6 weeks in most cases.[10] Although a small percentage of these infants have thyroid dysgenesis, the majority have a structurally normal thyroid gland.[10]

Several studies have recommended repeating newborn screening in preterm neonates to identify those with delayed elevations in TSH concentration.[11,12] This approach reflects a concern that primary congenital hypothyroidism may be masked due to the suppression of TSH secretion caused by hypothalamic-pituitary immaturity, medication administration, and effects of serious neonatal illness.[13] The utility of the second screening, its timing, and the optimal TSH cutoff to be used remain subjects of active debate.[10,14,15] The most recent European congenital hypothyroidism screening consensus guidelines recommend a strategy of second screening in preterm and low birth weight infants at approximately 2 weeks of age, or 2 weeks after the first screening test was performed.[16] The guidelines published by the American Academy of Pediatrics[17] in 2006 acknowledge a disproportionate incidence of delayed TSH rise and congenital hypothyroidism in very low birth weight infants (incidence 1 in 250 births) and low birth weight infants (incidence 1 in 1589 births). Although they do not provide recommendations on when and how often to repeat screening in these infants, they state that some screening programs routinely screen

FT4	Free thyroxine
TSH	Thyroid-stimulating hormone

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again at 2 weeks and 6 weeks and recommend initiating thyroid hormone replacement if hyperthyrotropinemia persists at 6 weeks of age.

Newborn screening of preterm infants for congenital hypothyroidism in the Republic of Ireland consists of whole-blood TSH measurement at 72-120 hours and then repeat whole-blood TSH measurement weekly until 37 weeks corrected gestational age or discharge from the hospital. The aims of this study were to review these national screening data to determine the timing of the delayed TSH rise in infants with congenital hypothyroidism, and to determine whether cases of congenital hypothyroidism would be missed by using current European consensus guidelines of repeat screening at approximately 2 weeks of age or 2 weeks after the first screening.

Methods

The Ethics Committee of the Children's University Hospital, Temple St approved this study. The population-based, prospective records of the Republic of Ireland's National Newborn Bloodspot Screening Program for congenital hypothyroidism, coordinated from the Children's University Hospital, Temple Street were reviewed.

Screening for congenital hypothyroidism in the Republic of Ireland consists of collection of whole-blood samples on filter paper following a heel-prick between 72 and 120 hours after birth. Whole-blood TSH concentration is measured by AutoDELFIA Immunoassay (PerkinElmer, Waltham, Massachusetts), and this assay has been used throughout the study period. In patients with a whole-blood TSH concentration >15 mU/L, serum TSH and free thyroxine (FT4) are requested, and the patient is referred for evaluation to a pediatric endocrinologist. If the whole-blood TSH level is between 8 and 15 mU/L, a second newborn screen sample is requested within a recommended time frame of 7 days. If this repeat measurement is >8 mU/L, serum TSH and FT4 concentrations are measured and the patient is referred for assessment. Unlike other screening programs, the newborn screening program has used the same assay and a consistent screening whole-blood TSH cutoff for preterm infants of 8 mU/L since the program's inception in 1979. In the preterm population, even if the initial whole-blood TSH is normal, repeat whole-blood TSH samples are collected weekly until the infant is term-corrected (37 weeks of gestation) or until the infant is discharged to home from the neonatal intensive care unit.

Term infants with positive screens for congenital hypothyroidism are called to attend the National Screening Centre for scintigraphy. Because preterm infants in neonatal intensive care units are unable to attend for scintigraphy, thyroid ultrasonography is arranged as soon as is practical. Congenital hypothyroidism is then classified as thyroid dysgenesis (athyreosis, ectopy, and hypoplasia) or normal/hyperplastic gland based on imaging. Follow-up care is provided either by a pediatric endocrinologist or a local pediatrician, according to local availability and family preference.

Patient Population

All preterm infants (≤33 weeks of gestation) diagnosed with congenital hypothyroidism and treated with levothyroxine in the Republic of Ireland between 2004 and 2016 were identified. A gestational age of 33 weeks was selected as a cutoff for this study to ensure follow-up TSH screening data for at least 4 weeks after delivery. Age at first screening, TSH concentration on newborn screen, thyroid function test results at diagnosis, sex, gestation, ethnicity, comorbidities, thyroid imaging results (if performed), presence of medical iodine exposure, and family history of thyroid disease were recorded for all patients.

Determination of Transient and Permanent Congenital Hypothyroidism in Patients with Early and Delayed TSH Elevation

In cases in which a normal gland in situ was confirmed or no imaging was performed in the neonatal period, the pediatric endocrinologist or local pediatrician treating the patient was contacted. If the patient had not required an increase in levothyroxine dose over time, a trial off levothyroxine was performed after age 3 years. This involved discontinuing levothyroxine and repeating thyroid function tests after 2 weeks, then 4 weeks later, and then 6 weeks later (ie, 3 months after discontinuing levothyroxine). If thyroid function tests remained normal, the patient was classified as having transient congenital hypothyroidism. If the plasma TSH concentration was >10 mU/L following complete withdrawal of treatment, permanent congenital hypothyroidism was diagnosed. If plasma TSH increased slightly (5.5-10 mU/L), the patient was followed and, if the mild hyperthyroptropinemia persisted, reevaluated with a thyrotropin-releasing hormone test to confirm primary hypothyroidism and restarted on levothyroxine. Patients who had dysgenesis on imaging or increasing levothyroxine dose requirements in childhood did not undergo a trial off treatment.

Statistical Analyses

All statistical analyses were performed with SPSS 22.0 (IBM, Armonk, New York, New York). Data are presented as median and absolute range. The Mann-Whitney *U* test was used to compare groups of non-normally distributed data, and the independent-samples *t* test was used for normally distributed data. A *P* value <.05 was considered statistically significant.

Results

Between January 2004 and December 2016, a total of 898 424 infants were screened for congenital hypothyroidism in the Republic of Ireland, and of these, 586 infants were treated for congenital hypothyroidism (incidence, 1:1533 births). A total of 53 infants (11%) were <33 weeks of gestation. Gestational age in the preterm cohort ranged from 23 to 33 weeks (median, 29 weeks), and median birth weight was 1.2 kg (range, 0.46-3.16 kg). The median serum TSH concentration at diagnosis was 78.3 mU/L (range, 13.3-1122 mU/L), and median FT4 concentration was 8.9 pmol/L (range, 1.0-18.7 pmol/L) (**Figure**).

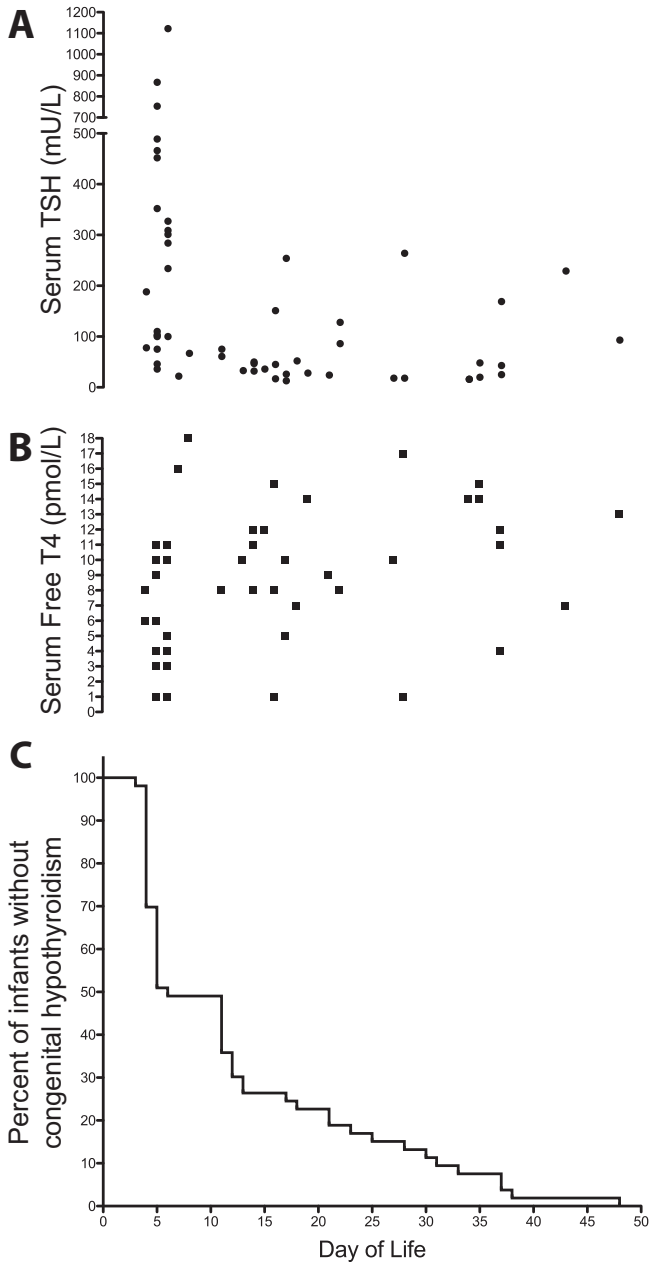

Figure. Serum TSH (**A**) and FT4 (**B**) concentrations at diagnosis in preterm infants according to age at detection of congenital hypothyroidism. **C,** Kaplan-Meier plot including all preterm infants who were diagnosed with congenital hypothyroidism, demonstrating the percentage of infants not yet diagnosed with congenital hypothyroidism over the first 50 days. Note that within the first 10 days, one-half of the infants were not yet diagnosed with congenital hypothyroidism.

Thyroid imaging was performed in 37 infants (68.5%), of whom 28 had a normal gland in situ, 6 had athyreosis, 1 had an ectopic gland, and 2 had a hypoplastic gland. All infants with thyroid dysgenesis were identified on the first newborn screen. Seven infants had abnormal thyroid function following exposure to iodine, including 1 infant who had trisomy 21 and 6 infants who developed thyroid dysfunction after surgery for necrotizing enterocolitis, of whom 3 died in the neonatal period from complications of necrotizing enterocolitis.

Incidence of Delayed TSH Elevation

Twenty-seven (50.9%) of the preterm infants born at <33 weeks of gestation who were diagnosed with congenital hypothyroidism had delayed TSH elevation and would not have been diagnosed on the first newborn screen at 72-120 hours. Characteristics of the infants with delayed TSH elevation are presented in **Table I**. Of the infants who had an initial normal whole-blood TSH on the newborn screen, a delayed TSH rise was detected between 8 and 48 days (median, 13 days). Twelve infants (40.7%) with delayed TSH elevation had decompensated hypothyroidism at diagnosis (FT4 <10 pmol/L), and 4 had severe congenital hypothyroidism (FT4 <5.5 pmol/L) at diagnosis.[18] Thirteen infants with delayed TSH elevation had a structurally normal thyroid gland, 8 were unclassified, and 6 had exposure to iodine, all of whom underwent surgery for necrotizing enterocolitis. One infant had trisomy 21. Had current European consensus guidelines[16] been followed and TSH level been repeated only at 2 weeks of life, 13 infants (48%) with delayed TSH elevation would not have been detected, because TSH concentration at 14 days of age was normal. Seven of these infants had decompensated hypothyroidism with a low FT4 concentration when diagnosed with congenital hypothyroidism at a median age of 30 days (range, 17-48 days). If the

Table I. Characteristics of patients treated for congenital hypothyroidism with normal initial newborn TSH screen and delayed TSH elevation

Age at first elevated screen, d	Newborn screen TSH, mU/L	Serum TSH at diagnosis, mU/L	FT4 at diagnosis, pmol/L	Diagnosis
25	9	18.9	17.5	Normal gland
23	9	18.3	15.9	Normal gland
11	32	47	12.1	Normal gland
13	12	13.3	10.7	Normal gland
17	18	20.4	14.6	Normal gland
11	18	61.5	8.4	Normal gland
14	11	24	9.1	Normal gland
22	55	86.9	8.8	Normal gland
8	10	75	8.1	Normal gland
37	12	25.3	12.3	Normal gland
12	18	36.7	12.2	Normal gland
11	26	32	11.1	Normal gland
13	24	45.8	8.9	Normal gland
38	59	229	7.3	Iodine exposure
30	11	16.3	14.9	Iodine exposure
11	8	16.3	14.9	Iodine exposure
33	13	48	15	Iodine exposure
37	56	169	4.9	Iodine exposure
11	130	151	1.5	Iodine exposure
12	13	29	14.5	Unclassified
31	18	43.5	11.5	Unclassified
11	8	26	10.9	Unclassified
12	18	52.5	7.2	Unclassified
22	240	128	8.1	Unclassified
25	58	264	1	Unclassified
10	42	254	2	Unclassified
48	70	93.6	13.5	Unclassified

Table II. Characteristics of patients diagnosed on first newborn screen and patients with delayed TSH elevation diagnosed on repeat screening

Characteristics	Total (n = 53)	Diagnosed on first TSH screen (n = 26)	Delayed TSH elevation (n = 27)	*P* value
Sex, male:female, n	1:1	1:1.36	1.45:1	**.005**
Birth weight, kg, median (range)	1.2 (0.46-2.47)	1.47 (0.51-2.47)	0.87 (0.46-2.3)	**<.001**
Gestational age, wk, median (range)	29 (23-33)	30 (23-33)	28 (24-33)	**.005**
Whole-blood TSH at diagnosis, mU/L, median (range)	26 (8-500)	140 (9-500)	17.9 (8-240)	**<.001**
Serum TSH at diagnosis, mU/L, median (range)*	78 (11-1122)	149 (14.7-1122)	47 (11-229)	**.002**
Serum FT4 at diagnosis, pmol/L, median (range)†	8.9 (1.0-18.8)	6.3 (1.0-18.8)	10.9 (1.5-18.2)	.029

Significant *P* values are in bold type.
*Reference range, 0.1-5.5 mU/L.
†Reference range, 10-22 pmol/L.

final repeat screen was taken at age 4 weeks, congenital hypothyroidism would not have been detected in 7 infants (26% of patients with delayed TSH elevation). These 7 infants had normal whole-blood TSH levels at day 28 that later became elevated, and 2 of 7 (28%) had decompensated hypothyroidism at the time of congenital hypothyroidism diagnosis.

Characteristics of Preterm Infants Diagnosed on First Newborn Screening TSH vs Those with Delayed TSH Elevation Diagnosed on Repeat Screening

Infants with delayed TSH elevation were born at an earlier gestational age (median, 28 weeks vs 30 weeks; $P = .005$) and had a lower birth weight (median, 0.87 kg vs 1.47 kg; $P < .001$). Infants with delayed TSH elevation had a lower median whole-blood and serum TSH concentration at diagnosis ($P = .002$) (**Table II**), likely reflecting the fact that all infants with thyroid dysgenesis were detected on the first newborn screen.

Incidence of Permanent Congenital Hypothyroidism in Patients with Early and Delayed TSH Elevation

Of the 53 preterm infants treated with congenital hypothyroidism between 2004 and 2016, 15 were aged <3 years at the time of this study and were not eligible for a trial off treatment to determine whether they had transient or permanent congenital hypothyroidism. Three infants died in the neonatal period, and we were unable to contact the families of 6 infants for follow-up. Of the remaining 29 infants, 18 (62%) had permanent congenital hypothyroidism and 11 (38%) had transient congenital hypothyroidism. Of those with permanent congenital hypothyroidism, 9 (50%) had thyroid dysgenesis and 7 (39%) had increasing levothyroxine dose requirements over the first 3 years. Another 2 infants (11%) failed a trial off levothyroxine treatment. Of those 27 infants with normal TSH concentration on initial newborn screen but subsequent delayed TSH elevation, 6 (22%) had permanent congenital hypothyroidism (4 had increasing levothyroxine dose requirements over time and 2 failed a trial off treatment) and 8 (29%) had transient congenital hypothyroidism. One infant died in the neonatal period, and the remaining 12 patients will be reevaluated at age 3 years.

Discussion

In this study, we have found that repeat screening for congenital hypothyroidism in preterm infants is necessary to avoid missing cases of permanent and decompensated hypothyroidism. One-half of the preterm infants diagnosed with congenital hypothyroidism were not diagnosed on initial newborn screening. Among the infants with delayed TSH rise, >40% had decompensated hypothyroidism at diagnosis, and >20% had permanent congenital hypothyroidism. Along with emphasizing the importance of repeat TSH screening in preterm infants, we have also demonstrated that repeat screening once at 2 weeks or 4 weeks of age is insufficient to detect all cases of congenital hypothyroidism with delayed TSH elevation. Based on these data, we recommend that congenital hypothyroidism screening protocols for preterm infants include measurement on days 3-5 and at 1 week, 2 weeks, 4 weeks, and term-corrected gestational age.

Repeat screening of preterm infants has not been adopted by all screening programs.[19] The utility of serial testing has been questioned on the basis of low yield,[20] the possibly transient nature of most detected cases,[21] and conflicting long-term neurodevelopmental outcome data.[21] However, we have shown that many patients have decompensated hypothyroidism at diagnosis and have permanent congenital hypothyroidism. Our data are consistent with studies showing a high incidence of delayed TSH rise, particularly in very low birth weight infants.[9,22] In addition, many of these infants have permanent congenital hypothyroidism.[10,23] Suggested approaches to frequency of screening have included measurement at 2 weeks[24] or 1 month[25] to screen for delayed TSH elevation. Had these approaches been applied to our patient population, 13 infants (48%) with delayed TSH elevation would have been missed by a 2-week-only screen, 7 of whom had decompensated hypothyroidism. Similarly, a single second screening test at 1 month would have resulted in delayed diagnosis of congenital hypothyroidism in many infants with decompensated congenital hypothyroidism. Of the 27 preterm infants with a delayed TSH rise, 13 (48%) were detected between 8 and 13 days of life. Nearly one-half of the infants had a delayed TSH elevation before age 2 weeks, so waiting until 2 weeks would have delayed their diagnosis.

One-quarter of the infants with delayed TSH elevation in our cohort had been exposed to iodine during surgery for necrotizing enterocolitis, and 4 of these infants had an elevated TSH level after 28 days of age. Three of these infants had severe decompensated hypothyroidism at diagnosis. This finding highlights the need for repeat screening and close monitoring of infants exposed to iodine.[26] In these infants, TSH elevation was identified between 3 and 26 days (median, 18 days) after iodine exposure; thus, exposed infants may need to be monitored for up to 1 month following exposure. Whether the iodine exposure was the cause of these infants' transient hypothyroidism cannot be stated with certainty, however.

The main strengths of our study are the availability of weekly whole-blood TSH screening results in a cohort of preterm infants over a 12-year period using the same assay, with a stable screening TSH cutoff of 8 mU/L and detailed follow-up data on treated patients. In the Irish protocol, the last TSH screening in preterm infants was performed at term-corrected gestational age; thus, it is not possible to determine whether any infants developed congenital hypothyroidism with delayed TSH elevation after this period. However, we are not aware of any infant who was diagnosed with congenital hypothyroidism after term-corrected gestational age. At our center, thyroglobulin is not currently measured. Some studies suggest that a diagnosis of athyreosis should be validated by measuring thyroglobulin.[27,28]

In conclusion, repeat screening for congenital hypothyroidism in preterm infants is necessary to avoid missing cases with delayed TSH elevation. Delayed TSH elevation is common in this cohort and is seen in one-half of preterm infants with congenital hypothyroidism. Repeat screening once at 2 weeks of life will miss a significant number of infants with delayed TSH elevation and decompensated permanent congenital hypothyroidism and repeat screening only at 4 weeks will delay the diagnosis of decompensated hypothyroidism in the first 2 weeks. We recommend initial screening at 72-120 hours with repeat screening at 1 week, 2 weeks, 4 weeks, and term-corrected gestational age or discharge from hospital. Infants exposed to iodine should be monitored for up to 1 month after exposure to identify delayed TSH elevation following exposure. ■

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50 Years Ago in *The Journal of Pediatrics*

Maternal and Congenital Rubella before 1964: Frequency, Clinical Features, and Search for Isoimmune Phenomena

White LR, Sever JL, Alepa FP. J Pediatr 1969;74:198-207.

Maternal rubella infection can lead to a spectrum of anomalies referred to as congenital rubella syndrome. During the rubella epidemic in the US between 1964 and 1965, 20 000 children were born with congenital rubella syndrome and another 8000 were either stillborn or died as neonates.[1] White et al assessed 30 059 pregnancies occurring before 1964 and identified rubella infection in 25 of them during this nonepidemic phase. This was expected to result in birth of 7-15 infants with congenital rubella syndrome per 100 000 pregnancies. They also concluded that the clinical features of these infants were not significantly different from those born in the epidemic phase, negating the proposed "supervirulent viral hypothesis" for the epidemic. They also refuted the theory that maternal IgG antibodies had anything to do with the fetal or neonatal immune competence.

Now 50 years later, our understanding of the clinical features and immune response to maternal rubella infection has not changed; but the incidence of congenital rubella syndrome has declined globally. Given the dreaded sequelae of maternal rubella, the Pan American Health Organization (PAHO) resolved to eliminate rubella and congenital rubella syndrome in the Americas by 2010. Introduction of rubella-containing vaccines into routine vaccination, high immunization coverage, mass vaccination of adolescents and adults, and stringent surveillance enabled the Americas to achieve this target[2]; Europe followed in 2015. Currently, rates of congenital rubella syndrome are highest in Africa and southeast Asia, where 42 countries are yet to introduce routine rubella vaccination. With a 97% reduction in rubella cases between 2000 and 2016, the world has something to cheer about. However, as of August 9, 2018, 2 cases of rubella infection have been reported from Mexico and another 513 cases from the European region.[3] Surveillance is needed as importation of rubella cases from endemic regions continues to threaten the so-called "rubella-free" nations.

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