The Impact of Transient Hypothyroidism on the Increasing Rate of Congenital Hypothyroidism in the United States

abstract

The reported incidence rate of primary congenital hypothyroidism (CH) has been increasing in the United States over the past 2 decades. We have considered the possibility that the inclusion of cases of transient hypothyroidism has inflated the reported incidence rate of CH. Assessing the effects of cases of transient hypothyroidism on the incidence rate is problematic, because the definitions, diagnostic criteria, and differentiation from transient hyperthyrotropinemia vary widely among state newborn screening programs. Among the 4 etiologies for transient hypothyroidism (maternal thyrotropin receptor–blocking antibodies, exposure to maternal antithyroid medications, iodine deficiency, and iodine excess), there is little evidence of increases in the incidence rate from thyrotropin receptor–blocking antibodies. Exposure to antithyroid drugs could contribute significantly to the incidence rate of transient CH, given the high estimated incidence of active maternal hyperthyroidism. Iodine deficiency or excess in the United States seems unlikely to have contributed significantly to the incidence rate of CH, because the secular trend toward lower iodine intake among women of reproductive age in the 1980s and 1990s seems to have plateaued, and perinatal iodine exposure has presumably declined as a result of recommendations to discontinue using iodine-containing disinfectants. Although the female-to-male sex ratio among newborns with thyroid agenesis or dysgenesis (the most common causes of CH) is typically 2:1, analysis of the sex ratio of newborns diagnosed with presumed CH in the United States suggests that a substantial proportion might have transient hypothyroidism or hyperthyrotropinemia, because the sex ratio has been well below the expected 2:1 ratio. Combined ultrasonography and ^{123}I scintigraphy of the thyroid gland are effective tools for identifying cases of thyroid agenesis and dysgenesis and can help to differentiate cases of transient hypothyroidism from true CH. Imaging is also a vital component in evaluating children who, at 3 years of age, undergo a trial of discontinuation of levothyroxine treatment to test for persistence of hypothyroidism. Ultimately, thyroid gland imaging, in conjunction with long-term follow-up studies that appropriately assess and report whether there was permanence of hypothyroidism, will be necessary to address the true incidence rate of CH and any contribution to the observed rate by transient cases of hypothyroidism or hyperthyrotropinemia. *Pediatrics* 2010;125:S54–S63

AUTHORS: John S. Parks, MD, PhD,[a] Michelle Lin, MD,[a] Scott D. Grosse, PhD,[b] Cynthia F. Hinton, PhD, MS, MPH,[b] Margaret Drummond-Borg, MD,[c,d] Lynette Borgfeld, MT,[c] and Kevin M. Sullivan, PhD, MPH, MHA[e]

[a]Division of Pediatric Endocrinology, Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia; [b]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia; [c]Department of State Health Services, Austin, Texas; [d]Cook Children's Physician Network, Fort Worth, Texas; and [e]Department of Epidemiology, Rollins School of Pubic Health, Emory University, Atlanta, Georgia

KEY WORDS

transient hypothyroidism, hyperthyrotropinemia, thyrotropin receptor–blocking antibodies, antithyroid drugs, iodine, thyroid imaging

ABBREVIATIONS

CH—primary congenital hypothyroidism
NBS—newborn screening
TRBAb—thyrotropin receptor–blocking antibody
T4—thyroxine
TSH–thyrotropin
NNSIS—National Newborn Screening Information System
UI—urinary iodine
NHANES—National Health and Nutrition Examination Survey
CI—confidence interval

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Address correspondence to John S. Parks, MD, PhD, Division of Pediatric Endocrinology, Emory Children's Center, 2015 Upper Gate Dr, Atlanta, GA 30322. E-mail: jparks@emory.edu

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The purpose of this review was to consider whether the inclusion of newborns with transient forms of thyroid dysfunction have contributed to the reported increase in the incidence rate of primary congenital hypothyroidism (CH) in the United States.[1] For detailed discussions of the increasing incidence rate, see the articles by Olney et al[2] and Hinton et al.[3] We initially examined the various definitions of transient hypothyroidism used by different state newborn screening (NBS) programs. We reviewed the 4 recognized causes of transient hypothyroidism: exposure to maternal thyrotropin receptor–blocking antibodies (TRBAbs); exposure to antithyroid drugs; iodine deficiency; and iodine excess. We evaluated deviation from the expected 2:1 female-to-male sex ratio among newborns with reported CH as an indicator of potential misclassification of cases of transient hypothyroidism as permanent. We discussed ultrasound and radioisotope imaging of the thyroid gland as strategies for distinguishing between transient and permanent hypothyroidism. Finally, we reviewed the recommendations to reevaluate thyroid status and diagnosis among children with presumed CH after 3 years of treatment to determine if the hypothyroid state identified through NBS is permanent.

DEFINITIONS OF TRANSIENT HYPOTHYROIDISM

The definition of transient hypothyroidism in the medical literature is variable. According to a 2006 report of the American Academy of Pediatrics, which provided specific recommendations to guide the confirmatory process for newborns with a positive newborn screen result for hypothyroidism, the definition of transient hypothyroidism is abnormal screening values (low thyroxine [T4] and elevated thyrotropin [TSH] concentrations) resulting from one of the causes of transient hypothyroidism but normal serum T4 and TSH concentrations on a subsequent serum test at 1 to 2 months of age.[4] This definition implies that a definitive diagnosis of transient hypothyroidism can be achieved within the first 2 months of life, at which time the causes of transient hypothyroidism (see below) have generally resolved. Transient hypothyroidism should be distinguished from a false-positive screening test, in which the latter is an abnormal screening-test result but a normal second-screen or serum-test result. In addition, false-positive results have no identified cause for the initial positive screening-test result, such as hypothyroxinemia of prematurity or one of the causes of transient hypothyroidism or transient hyperthyrotropinemia.

In contrast, although hyperthyrotropinemia (normal T4 and elevated TSH concentrations on confirmatory laboratory testing) also can be transient, this condition generally requires a longer time frame to distinguish between permanent and transient cases. There are heterogeneous etiologies for hyperthyrotropinemia, including delayed maturation of the hypothalamic-pituitary axis, increased TSH response to thyroid-releasing hormone, and presence of antithyroid antibodies, thyroid morphology abnormalities, or thyroperoxidase or thyrotropin receptor gene-sequence variations.[5,6] Some of these etiologies overlap with the 4 recognized causes of transient hypothyroidism, whereas others account for permanent cases of hyperthyrotropinemia. Given the transient nature of many cases of hyperthyrotropinemia, there is controversy whether thyroid hormone therapy should be initiated.[7,8] However, for those neonates started on treatment with levothyroxine, a trial off therapy at 3 years of age is recommended to distinguish those with transitory forms of hypothyroidism from those with true CH who require lifetime treatment.[4,9]

Authors of many surveillance or research studies do not distinguish between transient hypothyroidism and transient hyperthyrotropinemia and have defined all such cases as transient hypothyroidism. For example, in a study in Italy, researchers examined children with CH at 3 years of age and classified all who were no longer hypothyroid as having had transient hypothyroidism.[10] A study in Scotland distinguished cases of true CH from transient TSH elevation, which encompassed cases of both transient hypothyroidism and transient hyperthyrotropinemia.[11] Therefore, depending on the definition of transient hypothyroidism, there are likely to be significant differences between the reported incidence rates of this condition. Although the definition of transient hypothyroidism varies, the crucial reliable distinguishing factor between true CH and transitory forms of hypothyroidism is withdrawal of treatment after 3 years of age and assessment of thyroid function. Whether such examinations are conducted can result in significant differences in the reported incidence rate of CH.

There is little agreement among NBS programs in the United States on the definition of transient hypothyroidism. Current definitions are listed on the National Newborn Screening Information System (NNSIS) Web site.[12] All of them relate to dictionary definitions of "transient" as "remaining in place only a brief time" or "passing with time, ie, not permanent." These definitions provide wide latitude for interpretation and differ with respect to (1) whether an initial diagnosis of hypothyroidism is based on a screening test or a confirmatory serum test result, (2) whether both T4 and TSH

TABLE 1 Definitions and Reported Cases of Transient Hypothyroidism in 2008

State NBS Program	Definition	Cases of Transient Hypothyroidism, *n*	Cases of CH, *n*	Transient Hypothyroidism/CH Ratio
California	High TSH returns to normal in newborn period	3	305	0.01
Florida	Elevated TSH on initial test; normal TSH and free T4 when on T4 therapy	4	57	0.07
Kansas	Temporarily decreased thyroid level and temporarily elevated TSH	3	32	0.09
Michigan	Children treated for CH but came off treatment in ≤3 y	1	51	0.02
Tennessee	Defined by individual endocrinologist	0	35	0.00
Texas	Low T4 with normal or high TSH on first and/or second screen, correcting to normal T4 and TSH by 6 wk of age	16	207	0.08
Virginia	Low T4 and elevated TSH at time of screening, with normal follow-up testing results without treatment	171	39	4.36
All states and territories	Variable	290	1727	0.17

Data are according to those reported in reference 12.

concentrations must be abnormal, (3) the time allowed for concentrations to normalize on subsequent serum tests, and (4) whether the identified newborns are placed on levothyroxine replacement. Several examples of the definition of transient hypothyroidism used by state NBS programs, as well as the 2008 numbers of newborns with transient hypothyroidism and CH, are listed in Table 1. It is unfortunate that most programs do not provide enough detail to determine if the initial abnormal test result that prompted a diagnosis of presumed CH was based on a filter-paper screening test or a serum test.

At the time of our review, the California program defined transient hypothyroidism as a high TSH concentration (presumably serum concentration, although not stated) that returns to normal during the newborn period (presumably 28 days), whereas the Texas program specified a return to normal by 6 weeks of age. The Virginia program, with a ratio of 4.87 transient hypothyroidism cases for every case of CH, seemed to include cases in which the abnormal screening results were not confirmed by follow-up filter-paper or serum tests; these cases would have been classified as "false-positive" or being absent of thyroid disease in other states. The Texas program has a definition that is similar to that of the Virginia program but reported only 16 cases of transient hypothyroidism, because the program did not include any case of an abnormal first screen with a normal second screen or any case of an abnormal screen with normal serum T4 and TSH concentrations on the initial confirmatory test. The Tennessee program and many other states left the definition of transient hypothyroidism to the individual endocrinologist. The Michigan program defined children with transient hypothyroidism as those who were "treated with congenital hypothyroidism but came off treatment in less than or equal to 3 years;" this program's definition was the only one that implied a need for long-term follow-up to make the diagnosis.

Overall, there were 290 cases of transient hypothyroidism and 1727 cases of presumably permanent CH reported by state NBS programs to the NNSIS in 2008, for a ratio of transient hypothyroidism to presumed-permanent CH of 0.17:1.00, although the ratio for individual programs varied from 0.0:1.0 to 4.4:1.0.[12] The female-to-male ratio was 0.7:1.0 for transient hypothyroidism and 1.4:1.0 for CH.[12] Given the highly variable definitions from state to state, it is problematic to interpret accurately the incidence rate or geographical distribution of transient hypothyroidism on the basis of the NNSIS data.

CAUSES OF TRANSIENT HYPOTHYROIDISM

There are 4 recognized causes of transient hypothyroidism (Table 2): transplacental passage of TRBAbs; transplacental passage of antithyroid drugs used to treat maternal hyperthyroidism; iodine deficiency; and iodine excess. Each can impair fetal production of thyroid hormone. Some forms of thyroid dyshormonogenesis caused by mutations in *DUOXA2* or *DUOX2* can

TABLE 2 Maternal or Neonatal Causes of Transient Neonatal Hypothyroidism

Cause	Duration of Effect	^{123}I Imaging Result	Ultrasound Imaging Result
TRBAbs[a]	Months	Blocked	Normal
Antithyroid medications[b]	Days	Normal	Normal
Iodine deficiency[b]	Variable	Normal	Normal
Iodine excess[a]	Variable	Blocked	Normal

[a] Uptake of radioiodine (or ^{99}Tc-pertechnetate) might be blocked partially or completely under conditions of exposure to TRBAbs or excess iodine, but the thyroid usually can be identified in a normal location by ultrasonography.
[b] Radionuclide and ultrasound imaging under conditions of exposure to antithyroid medications or iodine deficiency generally disclose a normally located thyroid gland.

cause transient hypothyroidism,[13] but these rare causes are not discussed here. It is interesting to note that the underlying etiology of transient hypothyroidism is not determined in many cases.

Thyrotropin Receptor–Blocking Antibodies

TRBAbs develop in the context of maternal autoimmune thyroid disease, such as Graves disease, chronic lymphocytic thyroiditis, and acquired hypothyroidism. They represent a subset of immunoglobulin G antibodies directed against the thyrotropin receptor on the plasma membrane of thyroid follicular cells. These antibodies cause hypothyroidism in the fetus and newborn by transplacental passage and blockage of the access of thyrotropin to fetal thyrotropin receptors. As with CH, serum T4 concentration is low and TSH concentration is high.

TRBAb testing should be considered for all newborns with a maternal history of hypothyroidism. Because of the blocking antibodies, the thyroid gland cannot be visualized by ^{123}I or ^{99}Tc scans, but the gland should be demonstrable in the normal anatomic location by ultrasonography.

Hypothyroidism caused by TRBAbs eventually resolves with the disappearance of maternal antibodies from the infant's circulation. The half-life of immunoglobulin G is on the order of 4 weeks, so thyroid hormone–replacement needs to be continued for 3 to 6 months.

Hypothyroidism caused by TRBAbs is uncommon and occurs in 1% to 2% of all newborns with hypothyroidism or 1 in 180 000 live births.[5] There is no evidence that this form of transient hypothyroidism has made a major contribution to the observed increase in the reported incidence rate of CH.

Antithyroid Drugs and Treatment of Maternal Hyperthyroidism

Propylthiouracil and methimazole, both used in the management of maternal hyperthyroidism, cross the placenta and inhibit fetal thyroid hormone production. The objective of medical management of Graves disease during pregnancy is to maintain maternal T4 concentrations in the upper part of the normal range for each stage of gestation. Newborns who are known to be at risk for hypothyroidism because of maternal antithyroid-drug exposure should have serial measurements of T4 and TSH over the first week or two of life, with the expectation that drug effects causing low T4 and elevated TSH concentrations will resolve within this interval.

The frequency of active maternal hyperthyroidism has been estimated to be from 1 in 1000 to 1 in 200.[14] This is much higher than the overall reported frequency of transient hypothyroidism. It is possible that many cases of transient hypothyroidism caused by maternal use of antithyroid drugs have not been reported to state NBS programs.

Iodine Deficiency

Iodine is an absolute requirement for maternal, fetal, and postnatal thyroid hormone synthesis. Newborns affected with iodine deficiency have low T4 and high TSH concentrations. With radioisotope imaging, there is avid uptake of ^{123}I by a normally located gland. Treatment involves iodine replacement until normal iodine balance is achieved.

On a global basis, iodine deficiency is the most common cause of transient hypothyroidism, particularly in preterm newborns.[15–17] Preterm newborns are at higher risk because they have been prematurely deprived of the maternal supply of thyroid hormone, as well as iodine, which leads to inadequate accumulation of iodine in the thyroid gland compared with that of term newborns. Hypothyroidism represents a form of the broader category of iodine-deficiency disorders, which include endemic goiter, hypothyroidism, cretinism, decreased fertility rate, increased infant mortality, and intellectual disability.[18] There is extreme variation in iodine deficiency among countries and among regions within the same country. For example, in central Africa, where iodine deficiency exists in tandem with a dietary excess of thiocyanate, which inhibits transport of iodide into the thyroid gland, a study showed that up to 10% of newborns had cord blood T4 concentrations of <3 μg/dL and TSH concentrations of >100 mU/L.[19] Results of an Italian study indicated that the overall incidence rate of CH detected by screening was 1 in 3200, but in several districts historically affected by iodine deficiency there was an incidence rate of >1 in 2000; more than half (58%) of the case newborns in these districts had normally located thyroid glands and transient hypothyroidism.[20] A report from Krakow, Poland, showed the importance of public health policies for preventing transient hypothyroidism.[21] The incidence rate of transient hypothyroidism was 1 in 3920 from 1985 through 1991, but it declined in the community to 1 in 48 474 from 1992 through 2000, during which time iodized salt was reintroduced.

Commonly used measures of iodine insufficiency include urinary iodine (UI) concentration and the proportion of NBS specimens with a TSH concentration of >5 mU/L.[22] The World Health Organization criterion for assessing the iodine nutrition status of a population

using casual urine specimens is based on the median UI concentration.[22] For a population of pregnant women, a median UI concentration of <150 μg/L is considered indicative of iodine deficiency, and a median UI concentration of 150 to 249 μg/L is considered adequate; for nonpregnant women, the values are <100 and 100 to 199 μg/L, respectively.

In the United States, iodine nutrition has been evaluated in the National Health and Nutrition Examination Survey I (NHANES I) (1971–1974), NHANES III (1988–1994), and NHANES 2001–2006.[23–25] For pregnant women, the median UI concentrations for the 3 NHANES studies were 327 μg/L (95% confidence interval [CI]: 259–396), 141 μg/L (95% CI: 124–180), and 153 μg/L (95% CI: 105–196), respectively; for nonpregnant women aged 15 through 44 years, the median values were 293 μg/L (95% CI: 271–313), 127 μg/L (95% CI: 120–135), and 129 μg/L (95% CI: 118–130), respectively. These values indicate a decline in iodine nutrition from NHANES I to NHANES III and an apparent stabilization thereafter. Applying the World Health Organization criterion based on median UI concentration to pregnant women in the NHANES III would have identified that population as having iodine deficiency. For the NHANES 2001–2006, the median UI concentration was 153 μg/L, just over the cutoff value of 150 μg/L, but the lower confidence limit of 105 μg/L would indicate that iodine deficiency likely exists in a portion of this population.

Dried-blood-spot TSH concentrations are often used as an indirect measure of iodine deficiency at the population level,[26] but this process requires that specimens be collected at least 72 hours after birth, because TSH concentrations values first surge and then decrease rapidly during the first several postnatal days.[27] Consequently, the percentage of neonatal thyrotropin concentrations of >5 mU/L in newborn specimens collected by US NBS programs cannot be used for this purpose. Umbilical cord blood specimens have also been used to assess iodine deficiency at the population level, although such specimens are not routinely collected and may not be an appropriate indicator of iodine deficiency in the United States. In 1 study, a high prevalence of elevated TSH concentrations was found at study sites in Bangladesh, Guatemala, and Atlanta, Georgia; values were >5 mU/L in 84%, 58%, and 82% of neonatal cord blood specimens, respectively, which suggests severe iodine deficiency at all sites.[28] The median UI values among pregnant women at each of the sites were 96, 120, and 105 μg/L, respectively, which indicates that the pregnant women at all 3 study sites had insufficient iodine intakes on average. However, the authors suggested that the elevated newborn TSH concentrations in the US samples might have been due, in part, to β-iodine antiseptic exposure among 98% of the mothers for intravenous access, bladder catheterization, or epidural anesthesia (see "Iodine Excess") rather than true chronic maternal iodine deficiency.

Although maternal iodine deficiency certainly exists in the United States, its prevalence does not seem to have increased over the past 2 decades, so it is unlikely that transient hypothyroidism caused by iodine deficiency has contributed significantly to the observed increase in the reported incidence rate of CH. However, certain elements of the population might be at higher risk, particularly when borderline iodine nutrition is combined with exposure to goitrogens (inhibitors of thyroid gland function that interfere with iodine uptake) such as perchlorate and organochlorines, so assessing for transient hypothyroidism among offspring of this group of women definitely bears further study.

Iodine Excess

The Wolff-Chaikoff effect involves transient inhibition of T4 synthesis by excessive plasma concentrations of inorganic iodine. The effect lasts for ~10 days and is followed by an escape from suppression with resumption of normal iodine organification and normal thyroid peroxidase function. Iodine excess can be associated with the use of iodine-containing antiseptics, contrast agents, and certain drugs (including amiodarone) and ingestion of seaweed. Iodine passes freely from the maternal to the fetal circulation system and also can be transmitted through breast milk. Because most newborn exposure to iodine occurs during labor and delivery or postnatally, elevated TSH concentrations might not be evident in specimens taken on the first or second day after birth. The newborn with transient hypothyroidism caused by excessive iodine exposure will have low T4 and high TSH concentrations, generally after 2 to 3 days of age, as in other forms of hypothyroidism. ^{123}I imaging will fail to show a thyroid gland, because excess iodine blocks ^{123}I uptake, although ultrasonography will show a gland in the normal location that might or might not be enlarged.

Results of several studies have indicated that transient hypothyroidism is more common among newborns in hospitals that use iodine for skin disinfection than in those that use chlorhexidine.[29–31] The incidence rate of transient hypothyroidism was especially high in a Berlin, Germany, hospital that used povidone-iodine for cleansing of the umbilical stump.[31] In contrast, a prospective controlled study from a NICU in Massachusetts

did not demonstrate a difference in mean T4 or TSH concentrations between newborns who had routine skin cleansing with povidone-iodine versus those for whom chlorhexidine was used.[32] However, topical iodine exposure during the birthing process cannot be excluded as a cause of transient hypothyroidism in the United States, because preterm newborns and those born in iodine-deficient regions (who, among the latter, already have low T4 and high TSH concentrations resulting from iodine deficiency) might be more susceptible to the Wolff-Chaikoff effect of topical iodine exposure.

Iodine-containing radiologic contrast agents are also a source of free iodine. A study from Germany revealed that such contrast agents can compromise thyroid function among preterm newborns.[33] However, the authors also reported that the use of either of 2 contrast agents was not as disruptive to thyroid function among preterm newborns as the use of an iodine-containing antiseptic for long-term skin care.

Dietary iodine excess is a major issue in Japan because of ingestion of kombu, a type of seaweed, as a vegetable and incorporated in soups and food additives. In 1 study, nearly half of the newborns recalled for thyroid evaluation after screening had a history of excessive maternal iodine ingestion of 2300 to 3200 μg/day.[34] Levothyroxine replacement was used among 75% of the newborns because of persistent elevations of TSH concentration, which the authors hypothesized was a result of consumption of iodine by the infants and susceptibility to the inhibitory effect of iodine. Treatment was generally continued until 2 years of age.

Treatment with the antiarrhythmic drug amiodarone can alter thyroid function.[35] The drug is used among pregnant women and among newborns with congenital heart disease. It contains 37% iodine by weight, and its structure resembles T4. It can cause either hypothyroidism or hyperthyroidism through interaction with the thyroid hormone receptor. These effects can persist for many months after exposure.

Numerous studies that have evaluated the effects of topical iodine exposure on preterm newborns have each recommended that routine use of iodine-containing antiseptics be avoided in this population.[31,33,36–38] Therefore, it is reasonable to assume that the use of these products in NICUs has declined, so it seems unlikely that iodine excess can account for the reported increase in the incidence rate of CH in the United States. Nevertheless, questioning about iodine exposure continues to be an important part of the medical history for newborns with positive screen results for hypothyroidism, and iodine excess from procedure-related exposure should be suspected when newborns from a particular hospital have a high rate of elevated TSH concentrations.

SEX RATIOS AND TRANSIENT HYPOTHYROIDISM

The reported (from studies of European, Australian, and Canadian newborns[10,11,39–41]) female-to-male sex ratio among case infants with true CH is ~2:1. The ratio was even higher (2.4:1.0) among newborns with CH caused specifically by thyroid aplasia or ectopy.[39] According to results from studies in Italy, the female-to-male ratio was 2:1 among newborns with thyroid dysgenesis, which accounted for ~75% of all newborns with CH; 1:1 among newborns with CH with eutopic (normally positioned and normal-appearing) glands; and 0.5:1.0 among newborns with transient hypothyroidism.[10,42] In a Scottish study, the female-to-male sex ratio was 2.2:1.0 among 224 newborns with definite CH and 1:1 among 88 newborns with transient hypothyroidism.[40] In the United States there have been no systematic long-term follow-up studies to evaluate the sex ratio among newborns with transient versus permanent hypothyroidism. However, the sex ratio among newborns with CH seems to vary significantly according to race or ethnicity (see the article by Hinton et al[3]), so deviations from the expected 2:1 ratio might be expected in the United States in contrast to that in the more homogeneous populations in Europe, Australia, and Canada.

We conducted a study of the sex ratios among neonates with presumed CH in the United States by using NBS data for the period 1993–2000, obtained from the National Newborn Screening and Genetics Resource Center and previously validated by the reporting programs. For newborn boys or girls, the odds of being diagnosed with CH were estimated by using a negative binomial distribution to account for extra-Poisson variation using SAS 9.2 (SAS Institute, Inc, Cary, NC). For all states combined, the odds ratio for case infants was determined to be 1.56:1.00 (female-to-male). An analysis according to state showed that the sex ratio was not uniform among state NBS programs. The majority of states had a sex ratio of $<$1.9:1.0, although 13 states had sex ratios of $\geq$1.9:1.0. The most recent NNSIS data in 2008 showed a female-to-male ratio in the United States of 1.4:1.0 for newborns with presumed CH, which is still substantially lower than the expected 2:1 ratio. This observed sex ratio was inconsistent with the experience of NBS programs in other countries, which consistently reported 2 or more girls for each boy

diagnosed with true CH. This observation raises the possibility that a significant proportion of newborns in the United States reported to have CH after NBS and confirmatory testing do not, in fact, have true CH but could have transient hypothyroidism or transient hyperthyrotropinemia, which has a much lower female-to-male ratio of ~1:1. Additional studies will be necessary to evaluate this hypothesis.

THYROID IMAGING AND TRANSIENT HYPOTHYROIDISM

Thyroid imaging is very helpful in distinguishing transient hypothyroidism from true CH. Demonstration of a thyroid gland of normal size in the normal anatomic position (eutopy) identifies newborns who are more likely to have a transient condition. Most newborns with CH have no demonstrable thyroid gland (agenesis), an ectopic gland located along the path of embryonic descent of the thyroid, or a hypoplastic gland. In a recent study from Scotland, the proportions among newborns with true CH were 31% with agenesis, 32% with ectopy, 22% with hypoplasia, and 14% with eutopic thyroid glands but dyshormonogenesis (defects in the synthesis of thyroid hormones).[11] In contrast to true CH, most newborns with transient hypothyroidism are expected to have eutopic thyroid glands. Although thyroid imaging results rarely are reported for newborns with transient hypothyroidism, 1 study that evaluated 9 newborns with hyperthyrotropinemia revealed 78% with eutopic glands, 22% with ectopic glands, and none with thyroid agenesis.[43] Because newborns with true CH can have eutopic thyroid glands and newborns with transient hypothyroidism can have ectopic glands, the imaging result alone is not sufficient to distinguish true CH from transient hypothyroidism. Therefore, all children diagnosed with hypothyroidism, except those with confirmed thyroid aplasia, should receive a trial off of therapy at 3 years of age to determine if the hypothyroidism is transient.

Combined ultrasound and radioisotope scanning are complementary tools for evaluating the thyroid gland because isotope scanning can fail to recognize the gland among newborns with TRBAbs or iodine excess and ultrasound might fail to detect very small or ectopic glands.[44] Scintigraphy with ^{123}I is preferred over the use of ^{99}Tc-pertechnetate because it is more sensitive, provides a quantitative estimate of iodine uptake, and allows the use of the perchlorate-discharge test to identify iodination defects.[43,45]

ASSESSMENT OF PERMANENCE OF HYPOTHYROIDISM

NBS programs typically classify infants as having transient hypothyroidism or true CH within the first few months of life. However, an equally important group of children is those who were treated for 2 or 3 years before being taken off treatment, reevaluated, and found to have normal thyroid function. It is unfortunate that the proportion of children who make up this category is rarely reported.

Traditionally, it has been uncommon for a state NBS program to receive long-term follow-up information about children who were placed on levothyroxine treatment. However, the Texas NBS program has had the advantage of close collaboration between a number of pediatric endocrinologists and the state follow-up program. In this program, when a child's diagnosis was changed from presumed-permanent CH to transient hypothyroidism, or vice versa, these endocrinologists would notify the follow-up program of the change. However, even with long-term follow-up, in recent years only a small number of diagnoses have been changed from presumed CH to transient hypothyroidism: 2 cases among 225 cases of CH in 2004, 2 cases among 224 cases of CH in 2005, and none so far among 212 cases of CH in 2006. However, during this time period only 64% of infants were followed-up and reported on by endocrinologists in the first year of life, after which the percentage decreased to 26%, either because of incomplete reporting by endocrinologists or follow-up exclusively by primary care physicians. Other possibilities for the decline in the number of cases for which follow-up information was reported to the NBS program include removal from treatment by the parent or determination of transient hypothyroidism by the primary care physician. These observations illustrate many of the difficulties of obtaining the final classification of children with presumed CH through long-term follow-up.

One recent study evaluated a standardized protocol to assess the permanence of presumed CH at a pediatric endocrinology clinic in Indiana.[9] Children with presumed CH who were eligible for the study were those with an anatomically normal thyroid gland on imaging; those without previous diagnostic imaging; or those who did not have imaging but had relatively mild abnormalities in T4 and TSH concentrations despite apparent thyroid agenesis on technetium scans. There was no mention of whether absence of TSH elevation during treatment was a criterion for the study. T4 treatment was discontinued for 4 weeks before having thyroid-function tests and a thyroid ultrasound. Those with an abnormal thyroid ultrasound result underwent a technetium scan. Children with a normal thyroid ultrasound result but abnormal thyroid-function tests had a perchlorate-discharge test. Children with normal results had repeat

thyroid-function tests 4 and 6 months later. Of the 33 children in the study, 27% had dysgenesis or agenesis of the thyroid gland, 36% had a defect in the iodination of tyrosine residues on thyroglobulin (organification defect) or other forms of dyshormonogenesis, and 36% were euthyroid and remained euthyroid at 4 and 6 months. Thus, more than one-third of the eligible children for the study were found to have had a transient form of hypothyroidism, although the majority had hyperthyrotropinemia on confirmatory testing for the abnormal NBS test result. These results provide a rational and effective protocol for establishing the definitive diagnosis and the permanence of hypothyroidism. However, although comprehensive, this approach is not the only one. A study in Toronto, Ontario, Canada, 2 decades earlier concluded that after 3 years of age, a 3-week withdrawal of thyroid hormone alone was sufficient for adequate and safe confirmation of permanent hypothyroidism.[46]

In contrast, a report from China suggested that a longer period of withdrawal from thyroid hormone is necessary for a definitive diagnosis.[47] Among 1144 children with presumed CH, 157 required only a low maintenance dose of levothyroxine to maintain normal T4 and TSH concentrations. These 157 children underwent withdrawal of treatment at 2 to 3 years of age; 90% eventually achieved normal TSH concentrations, although the TSH concentration remained elevated in 25% of them at 1 month, 4% at 2 months, and <1% at 10 months after discontinuing treatment. The remaining 15 children (10%) had high concentrations of TSH while off treatment and were restarted on levothyroxine. The authors concluded that the optimal observation period for determining if thyroid function is normal while off treatment is 2 to 3 months. The fact that one-quarter of the children had persistent TSH elevations even after 1 month off treatment might have reflected an elevated proportion of children in China with iodine deficiency and a prolonged period of recovery of normal thyroid function. The shorter withdrawal time of 1 month generally is regarded as appropriate for use in the United States; however, in the absence of a comparable large-scale study in the United States, it is not certain.

CONCLUSIONS

Transient hypothyroidism certainly exists in the United States, although a precise definition for the condition is lacking, and there is great variability among state NBS programs as to which newborns are classified with this condition, as well as the reported incidence rate of transient hypothyroidism. Some confusion arises regarding the differentiation of transient hypothyroidism from transient hyperthyrotropinemia, which might represent a continuum along a scale of thyroid dysfunction. It seems likely that the 4 etiologies of transient hypothyroidism (TRBAbs, antithyroid drugs, iodine deficiency, and iodine excess) have not had substantial changes in prevalence over time and, therefore, have not contributed significantly to the increasing incidence rate of CH in the United States. However, it is important to consider these etiologies in every case of neonatal hypothyroidism because newborns who had both maternal and fetal thyroid hormone concentrations compromised, as can be the case with TRBAbs or iodine deficiency, will have significant future risk of mental impairment despite early diagnosis and management of transient hypothyroidism. It is clear that newborns diagnosed with presumed-permanent CH in the United States do not follow the expected 2:1 female-to-male sex ratio, which indicates a high likelihood that newborns with transient hypothyroidism or hyperthyrotropinemia are being misclassified as having true CH, thus perturbing the ratio. It seems that the use of thyroid gland imaging, in conjunction with long-term follow-up studies that appropriately assess and report whether there is permanence of hypothyroidism, will be necessary to determine the true incidence rate of CH and any contribution of transient hypothyroidism to the reported increasing incidence rate of CH.

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