Prevalence of Congenital Hypothyroidism—Current Trends and Future Directions: Workshop Summary

abstract

In response to published newborn-screening data that have shown an increase in the incidence (birth prevalence) rate of primary congenital hypothyroidism (CH) in the United States, a workshop was held in Atlanta, Georgia, on February 27 and 28, 2008, to examine this issue. Topics of the meeting included pathophysiology, medical management, and follow-up of CH; transient hypothyroidism (etiology, clinical implications, management, and changes in prevalence); risk factors for CH; laboratory approaches to newborn screening for CH; state-specific evaluations of trends in incidence rates of CH; and concluding discussions on future directions to resolve outstanding issues. Through presentations and discussion, gaps in knowledge were identified, such as the lack of consistent definitions for CH and transient hypothyroidism and the effects of preventable risk factors on incidence rates of CH. One outcome of the meeting was a series of accompanying articles that examined (1) trends in the incidence rates of CH in individual states and nationally, (2) effects of newborn-screening practices on CH-incidence rates, (3) the contribution of transient hypothyroidism to CH-incidence rates, and (4) future research directions. In this summary, we briefly touch on the topics of these articles and examine highlights of other presentations from the workshop that illuminated the secular trends in reported CH-incidence rates in the United States.
In 2007, Harris and Pass published newborn-screening data from New York and the United States that showed an increase in the incidence (birth prevalence) rates of primary congenital hypothyroidism (CH) over the past 2 decades (New York: 1 in 3378 to 1 in 1414 births; United States: 1 in 4098 to 1 in 2370 births). Several potential reasons for these trends in CH-incidence rates were discussed in their article, but the lack of definitive explanations and the need for clarification about an appropriate public health response, if any, led to understandable concerns among public health officials, clinicians, and others in the newborn-screening community. In preliminary discussions, leading concerns included the changing and inconsistent definitions for CH and transient hypothyroidism. However, several other factors that required further examination emerged (e.g., the potential effects of risk factors with changing frequencies in the US population, such as race and ethnicity and rates of preterm birth; evolving screening methods; and shifting practices related to management of children identified by newborn screening). Subsequently, a workshop planning committee was formed and included representatives from the National Newborn Screening and Genetics Resource Center and 2 federal agencies: the Health Resources and Services Administration and the Centers for Disease Control and Prevention (CDC). These groups cosponsored a workshop that was held in Atlanta, Georgia, on February 27 and 28, 2008, entitled “Prevalence of Congenital Hypothyroidism: Current Trends and Future Directions.” In this overview we provide a summary of the issues addressed at the workshop and briefly describe the presentations, the details of which are largely incorporated in other articles in this supplemental issue of *Pediatrics*. Most notably, the future research directions set forth by workshop participants are detailed in the article by Shapira et al.

The overall goal of the workshop was to present participants with detailed background information about CH and data on incidence rates to develop future approaches to resolve the questions surrounding the magnitude of and potential explanations for the increasing CH-incidence rates, whether real or artifactual. At the outset, the workshop organizers compiled the following list of issues to address potential explanations for the reported data trends:

- changes in practice that might have occurred in the follow-up and medical management of screen-positive cases identified by newborn screening, including the primary care provider’s perspective;
- transient hypothyroidism: etiology, clinical implications, management, and changes in prevalence;
- epidemiology and risk factors for CH, such as preterm birth, genetic factors, sex, race and ethnicity, prenatal iodine intake, and autoimmunity (also co-occurring trends in these factors over the past 3 decades); and
- changes in laboratory approaches to newborn screening for CH, including laboratory methods and screening paradigms.

To concentrate on these issues, the planning committee drew from a multidisciplinary group of speakers and invited participants (see the list of workshop participants at the beginning of the supplement), which included endocrinologists, epidemiologists and public health professionals, health services researchers, laboratory staff, medical geneticists, primary care providers, and state newborn-screening program professionals.

### Overview of CH Pathophysiology, Medical Management, and Follow-up: Presentations by Mitchell, Foley, and Van Meter

Normal fetal and neonatal thyroid functions are well established, and details of these physiologic processes have been reviewed in a number of articles. During gestation, the fetus relies at least in part on maternal thyroid hormone. There is typically a surge in thyrotropin (TSH) ~30 minutes after birth to a peak of ~70 mIU/L (or as high as 90 mIU/L) before concentrations decline to normal when the newborn is ~3 to 5 days of age. To identify newborns with CH for the purpose of early treatment, newborn-screening programs measure TSH or thyroxine (T4) concentrations, or both, in dried blood spots obtained from neonates. Hypothyroidism detected in newborns can be either permanent or transient, and a discussion of the challenges in defining and distinguishing the 2 forms follows. Congenital (permanent) defects of thyroid location or structure, which affect most newborns with CH, are characterized by an ectopic gland, an absent gland (thyroid aplasia or agenesis), or thyroid hypoplasia. Scanning studies of newborns with CH typically have revealed that ectopic disorders account for the majority of such defects. Dyshormonogenesis (an inborn error of metabolism) involves defects in T4 synthesis and accounts for ~10% to 20% of newborns with CH. Other causes, which could total another 10% of screen-positive newborns, include resistance to TSH (thyrotropin receptor defects) and the causes of...
transient hypothyroidism: maternal thyrotropin-blocking antibodies, exposure to maternal antithyroid medications, iodine deficiency, and iodine excess.

Newborn screening for CH began with pilot programs in the 1970s and shortly thereafter became widespread and eventually universal in the United States.\(^5\) Identification of primary hypothyroidism, which is the focus of newborn screening for congenital hypothyroidism, is reflected by elevated TSH and low serum free T4 concentrations. Transient hypothyroidism also involves an initially elevated TSH concentration and low or normal T4 level but normal T4 and TSH concentrations on subsequent measurement. Central hypothyroidism can be detected by newborn-screening programs that test T4 as the principal analyte. Medical management begins with confirmatory serum thyroid-function tests to confirm the diagnosis according to established algorithms such as the guidelines formulated by several professional organizations that were published in 2006.\(^5\) Some clinicians also order thyroid imaging by either ultrasound or radionuclide studies. The goal of early identification through newborn screening and follow-up is to normalize the T4 concentration within 24 hours and the TSH concentration within 1 week. Long-term management involves administering oral daily levothyroxine; monitoring of adherence to medication administration and adequacy of dose with serum testing of TSH and free T4 concentrations; monitoring of linear growth; conducting neuropsychological evaluations; and, in cases in which it is not known whether the condition is permanent, discontinuing therapy on a trial basis when the child is 3 years of age.\(^5,14\) Variables that affect medical and neuropsychological outcomes for persons with CH include the severity of CH at diagnosis, age at diagnosis and onset of therapy, dose of levothyroxine, and adherence to medication administration and monitoring. Published guidelines have indicated that monitoring of thyroid hormone concentrations should be performed at specified intervals, with higher frequencies at younger ages, and after any change in medication dosage or pharmaceutical source of medication.\(^5\) There is increasing global interest in expanding screening of CH to detect central hypothyroidism among all newborns, as well as delayed-onset CH that occurs among preterm infants.\(^9\)

Little is known about the management of CH by primary care providers; the most recent data came from a survey in Wisconsin of physicians of record for 500 newborns who screened positive during 1984 and 1985.\(^10\) It is unclear how many primary care providers interact with pediatric endocrinologists, are aware that infants should be treated with crushed tablets slurried in formula, or follow the published 2006 guidelines on clinical management. Population-based data also are needed regarding how many affected children are assessed for educational performance during school years.

**TRANSIENT HYPOTHYROIDISM: PRESENTATIONS BY PARKS, GEURIN, AND GROSSE**

The article by Parks et al\(^11\) explores issues and data related to transient hypothyroidism, such as variations in definitions, risk factors, incidence rates from various sources, and trends over time for all of these factors. This topic was a major focus of the workshop because of suspected variations in the relative frequencies of true CH versus transient hypothyroidism according to state and time period. At the workshop, data were presented that indicated wide variations in the frequency of transient hypothyroidism between state newborn-screening programs, which seemed most likely to be the result of how programs tallied cases of transient hypothyroidism versus “normals” (screen-positive results ultimately reported as neither true CH nor transient hypothyroidism). Ideally, such classification would be based on a precise definition of transient hypothyroidism and prospective follow-up data collected when screen-positive children are at least 2 or 3 years of age, which is the typical window for a trial of discontinuation of therapy to assess the nonpermanence of presumed CH.

One distinguishing factor between permanent CH and transient hypothyroidism is the female-to-male ratio. Numerous European, Australian, and Canadian studies have reported a ratio for true CH cases of ~2:1\(^5,7,12–14\) whereas the ratio among cases of transient hypothyroidism is 1:1 or lower.\(^6,14,15\) There have been no systematic long-term follow-up studies of the sex ratio among newborns with transient versus permanent hypothyroidism in the United States.

Evidence was presented at the workshop, based on an analysis of health insurance claims data, that showed that many US children diagnosed with and treated for CH stop having prescriptions filled well before the age at which trial discontinuation is recommended.\(^16\) Furthermore, it was reported that those children who stopped treatment comprised roughly equal numbers of boys and girls, which is characteristic of transient hypothyroidism.

An alternative approach to classifying cases of CH is through the systematic use of imaging of the thyroid. This practice is standard in Quebec, Canada, where no increase in the incidence rate of thyroid dysgenesis has
been found. Imaging analyses have been done in limited clinical settings in the United States, without reporting of secular trends in incidence rates.10,17

**DATA ON RISK FACTORS FOR CH AND LABORATORY APPROACHES: PRESENTATIONS BY SHAPIRA, THERRELL, MEI, HERTZBERG, HINTON, van der HAAR, AND BLOUNT**

The authors of 3 recent epidemiologic studies from California, Western Australia, and Italy have provided published data on risk factors for CH. Waller et al18 reported on risk factors in California from 1990 to 1998. The overall incidence rate was ~1 in 2800 births; the rate was lower among non-Hispanic black/African American newborns and higher among Hispanic newborns compared with the rate among white newborns. The female-to-male ratio was ~2:1 among white, Hispanic, Filipino, and Chinese newborns but lower among other racial and ethnic groups. Newborns with birth weights of <2000 or ≥4500 g were at elevated risk. This U-shaped curve in incidence rates according to birth-weight category was consistent, even when the data were stratified according to race/ethnicity and sex. Kurinczuk et al reported on 1981–1998 data from Western Australia.15 They excluded patients with transient hypothyroidism (analyzing CH only, the approximate incidence rate was 1 in 3400 births from 1981 through 1998). Girls had more than twice the risk than did boys. The authors also observed a U-shaped curve in incidence rates with birth weight and with gestational age (≤≤37 or ≥41 weeks of gestation). Approximately 10% of affected newborns had another birth defect, which is approximately twice the frequency of birth defects among the general population. The risk for cardiac defects particularly was elevated. Finally, Medda et al19 examined records of 140 Italian newborns with CH and 15 with transient hypothyroidism compared with those of matched control newborns. Thyroid-scan results were available for 71% of newborns with CH, of whom 58% had ectopic glands. Preterm births were more common among newborns with transient hypothyroidism and those with CH. A parental history of hypothyroidism was associated with both transient hypothyroidism and CH. Maternal hypothyroidism was associated with transient hypothyroidism, and paternal hypothyroidism was associated with CH. Medda et al reported an elevated female-to-male ratio only for CH, not for transient hypothyroidism.

In their article, Hinton et al19 report an analysis of secular trends in CH-incidence rates in the United States from 1991 to 2000 and in 4 states (California [1983–2007], Texas [1992–2006], New York [1987–2007], and Massachusetts [1976–2007]) according to race and ethnicity, sex, and low birth weight. At a national level, from 1991 to 2000, CH-incidence rates increased significantly only among white newborns, although a limitation of this finding is that, during this time period, an unknown proportion of infants with Hispanic ethnicity were included in the white racial category. Studies that included later time periods in California (2000–2007) and Texas (1992–2006), in which Hispanic infants with CH were differentiated from non-Hispanic white infants, did show significant increases in the incidence rate of CH among Hispanic infants. The possible influence of changes in newborn-screening methodology on CH-incidence rates needs to be examined. Such an influence was observed in Western Australia, where the incidence rate from 1981 to 1987 was 1 in 5745 births; however, after screening methods changed (lower TSH cutoff), the incidence rate was 1 in 2828 births from 1988 to 1998.15 In an analysis of US data from 1991 to 2000, detailed in the article by Hertzberg et al,20 changes in testing methods for the T4 or TSH analytes did not account for the overall increase in the national CH-incidence rate, although the increasing rate was associated partly with changes in T4 assay methodologies. An effect of changing cutoff points for positive screens was not observed, which (according to CDC-compiled data from 1997–2000) have not varied much in aggregate for T4 or TSH. In addition, although more state laboratories have changed to a TSH assay for the initial screening test (2 laboratories in 1991 compared with 12 laboratories in 2000), this change in screening methodology was not associated with the increasing CH-incidence rate.

Concerns have been raised about the possible influence of inadequate prenatal iodine intake on thyroid function among offspring. A marked reduction in median urinary iodine concentrations among pregnant women was observed in the United States between national surveys conducted during 1971–1974 and 1988–1994; however, between the latter period and a new survey conducted during 2001 and 2002, the direction of change was stable to slightly upward.21 Thus, no decrease in iodine intakes was observed in association with recent increases in the incidence rate of CH, although iodine might have played a role in increasing trends observed before the early 1990s. Another recent publication reported that a majority of table salt samples taken from US volunteers had iodine measurements below the content recommended by the US Food and Drug Administration.22
A related research question is whether perchlorate exposure from environmental sources could affect thyroid functioning, particularly in a background of low iodine intakes. Researchers at CDC and elsewhere have refined assays to measure perchlorate in dried blood spots and other biological samples and found that, in a representative US sample, perchlorate exposure was widespread but below the reference dose. Additional studies are needed to determine if common but low-level perchlorate exposures, inadequate iodine intake, or both might be contributing to recent trends in CH-incidence rates in the United States.

**STATE-SPECIFIC EVALUATIONS OF TRENDS IN INCIDENCE RATES OF CH: PRESENTATIONS BY HARRIS, PASS, EATON, LOREY, GEURIN, AND FEFFERMAN**

Data from individual states have provided an opportunity for detailed, record-based analyses of trends and risk factors for CH. Updated data from New York presented at the workshop showed a persistent increase, as in the original publication that stimulated the meeting. Hinton et al incorporated detailed information from the presentations of data from New York, California, Massachusetts, and Texas. A common but not universal pattern in these data was periods of increase with intervals of stable incidence rates. In Massachusetts, it was reported that although low birth weight newborns had a higher incidence rate of CH, increases in incidence rates also occurred among newborns of normal birth weight. Another important finding, given the increased relative number of Hispanic births during the time period of interest, was confirmation of higher incidence rates of CH in California and Texas among Hispanic newborns. Finally, in some of these 4 states, changes in screening practices occurred, with varying influence on the rates of CH identification.

Clinical data from individual treatment centers are not population based and, therefore, do not provide direct evidence of secular trends; however, such data can provide more detailed information about medical aspects of CH, such as diagnostic imaging and long-term follow-up, that might help to interpret trend data. The Kaiser-Permanente Medical Care Program in California has provided a unique perspective by virtue of the large birth population it serves and its use of coordinated diagnostic, treatment, and preventive services. Scintigraphy has been reported among >200 northern California newborns with CH, with an overall proportion of 43% with normal appearing thyroid glands. As among the statewide population, Hispanic and female newborns had higher incidence rates of CH than non-Hispanic and male newborns, respectively. Moreover, as discussed in the Hinton et al article, abnormal scan results were more frequent among Hispanic and female newborns, which reinforces the underlying heterogeneity of CH according to sex and ethnicity. Kaiser follow-up data presented from southern California indicated that ~15% of newborns initially treated were eventually classified as having had transient hypothyroidism, and initial TSH values were not predictive of who would turn out to have transient hypothyroidism.

**FUTURE DIRECTIONS TO RESOLVE OUTSTANDING ISSUES: PRESENTATION BY THERRELL AND DISCUSSION LED BY SHAPIRA**

The concluding presentations and discussions at the workshop focused on 2 main areas: summarizing gaps in knowledge and brainstorming about future projects to address these gaps. The article on the concluding session by Shapira et al provides a detailed review of a number of issues that remained unresolved or in need of updated information:

- consistent definitions of and diagnostic criteria for permanent and transient hypothyroidism;
- correct classification of transient hypothyroidism and exclusion of such cases from CH-incidence-rate calculations;
- trends in the incidence rate of CH and transient hypothyroidism based on strict definitions of the screening and confirmatory diagnostic criteria for the conditions;
- effects of modifiable and nonpreventable risk factors on the incidence rate of CH; and
- differences in follow-up and treatment of CH based on the type of medical provider.

A number of ideas for future research were offered at the workshop, with specific mechanisms for carrying out these projects, and discussed by Shapira et al:

- long-term follow-up of infants with CH to evaluate effects on the CH-incidence rate from maternal or infant factors and to determine the number of cases of true CH versus transient hypothyroidism;
- other follow-up studies (prospective or retrospective) that link permanent versus transient outcomes to initial diagnostic criteria;
- evaluation of the relation between newborn and maternal (prenatal) thyroid-function tests; and
- pilot projects to document practices in confirmation and man-
agreement of CH by primary care providers and endocrinologists by using common data elements.

CONCLUSIONS
At the end of the 2-day workshop in Atlanta, the invited participants had not identified a single cause for the reported increases in CH-incidence rates. Indeed, they pointed to a number of factors that need further examination through analysis of existing data or prospective studies, most notably changes in diagnostic and treatment practices by clinicians. Some of these efforts are underway already. Public health action to address the issue will require a better understanding of trends and identification of confirmed environmental etiologies or other preventable risk factors that might be responsible for the occurrence of CH.

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