Screening for Congenital Hypothyroidism in Newborns: A Literature Update for the U.S. Preventive Services Task Force

Prepared by:
David Meyers, M.D.
Stephen Haering, M.D., M.P.H.
Agency for Healthcare Research and Quality
Rockville, Maryland

Corresponding Author:
David Meyers, MD
Center for Primary Care, Prevention, and Clinical Partnerships
Agency for Healthcare Research and Quality (AHRQ)
540 Gaither Road
Rockville, MD 20850
Office phone: 301-427-1634
e-mail: David.Meyers@AHRQ.hhs.gov

AHRQ Publication No. 08-05109-EF-1
March 2008

This report is based on research conducted by staff at the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD. The investigators involved have declared no conflicts of interest with objectively conducting this research. The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

This report may be used, in whole or in part, as the basis for the development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

Suggested Citation: Meyers D, Haering S. Screening for Congenital Hypothyroidism in Newborns:A Literature Update for the U.S. Preventive Services Task Force. AHRQ Publication No. 08-05109-EF-1. Rockville, MD: Agency for Healthcare Research and Quality, 2008.

Structured Abstract

Objective
Left untreated, congenital hypothyroidism can result in mental retardation, growth failure and other neuropsychological complications. The U.S. Preventive Services Task Force (USPSTF) commissioned this literature update as it prepared to reissue its 1996 recommendation statement in support of universal screening of newborns for the disorder.

Methods
Staff of the Agency for Healthcare Research and Quality (AHRQ) performed a targeted search of the medical literature from January 1, 1995, to September 15, 2006 and consulted with subject matter experts. The main goal of the review was to identify significant trials that would call into question the evidence base upon which the USPSTF's previous recommendation was based.

Results
No randomized controlled trials of screening for congenital hypothyroidism were identified. Recent studies have focused on identifying the proper timing and dosage of thyroid replacement to optimize outcomes. Variation in screening strategies and definitions results in wide ranges for estimates of the false positive rate in congenital hypothyroidism screening programs. Recent qualitative studies have begun to document the consequences of false-positive results for families.

Conclusions
There continues to be strong support in the field for universal congenital hypothyroidism screening. Current areas of interest include determining optimal screening strategies and tests, including the potential contribution of repeat testing and screening for central hypothyroidism.

Screening for Congenital Hypothyroidism in Newborns: A Literature Update for the U.S. Preventive Services Task Force

Introduction

In the U.S., primary congenital hypothyroidism (CH) occurs in about 1 of every 3,000-4,000 newborns.[1] In infants with CH, brain damage may begin during the first weeks after birth even before most cases are clinically recognizable; untreated CH results in numerous well-known complications with irreversible mental retardation being the most worrisome. Other effects of untreated CH include growth failure and neuropsychological complications, including motor abnormalities, learning disabilities, and speech disorders. In 1996 the United States Preventive Services Task Force (USPSTF) recommended "screening for congenital hypothyroidism with thyroid function tests performed on dried-blood spot specimens for all newborns, optimally between days 2 and 6, but in all cases before newborn nursery discharge (A recommendation)[2]."

In 2006, the USPSTF decided to update its recommendation statement on screening for congenital hypothyroidism. Noting that the 1996 recommendation was made on a strong evidence base and that it would take large, high-quality studies or evidence of substantial harms to overturn the current recommendation, the USPSTF chose to perform a reaffirmation update for this topic. The USPSTF performs reaffirmation updates for older recommendation statements that remain USPSTF priorities, are within the scope of the USPSTF, and for which there is compelling reason for the USPSTF to have a current recommendation statement.

To assist the USPSTF in updating its 1996 recommendation on screening for congenital hypothyroidism, staff at the Agency for Healthcare Research and Quality (AHRQ) performed a literature search and consulted with subject area experts. The goal of this targeted review was to find new, high-quality evidence regarding the benefits and potential harms of screening for congenital hypothyroidism. Thirty-eight studies were initially identified. No studies on benefits and three studies relating to potential harms were found to meet review inclusion criteria, and the latter are included in the following review.

Evidence of the benefits of screening for congenital hypothyroidism

Since the 1950s the medical community has known that thyroid hormone replacement decreases the occurrence of mental retardation in infants with congenital hypothyroidism. During the early 1970s screening tests were developed, and by the late 1970s screening programs for congenital hypothyroidism were instituted across the United States and around the world. The work of the New England Congenital Hypothyroidism Collaborative in the late 1970s and early 1980s provided evidence from a prospective population-based study that screening in conjunction with early initiation of thyroid replacement improves cognitive and neuropsychological outcomes in children with congenital hypothyroidism when compared to therapy instituted after the manifestation of clinical signs and symptoms of the disorder. In the conclusion of their 1981 paper in the

journal *The Lancet*, they concluded that "…it is obvious now … that all newborn infants must be screened for hypothyroidism."[3] In 1996, the USPSTF based its recommendation on the significant evidence that early detection through screening and treatment improved important clinical outcomes for children with congenital hypothyroidism.

Our review identified no new randomized controlled trials of screening for congenital hypothyroidism. Recent studies have focused on identifying the proper timing and dosage of thyroid replacement to optimize outcomes.

Evidence of the harms of screening for congenital hypothyroidism

In 1996, the USPSTF noted that false positive results are common in U.S. screening programs, and that studies of the effects on families of falsely positive screening tests were limited by methodologic flaws. [2] Our review found three recent articles related to the potential harms of screening for congenital hypothyroidism: two identified the rates of false positives [4, 5] and one explored the effects on family dynamics of a false positive neonatal screening result. [6]

Kwon and Farell utilized data from the Council of Regional Networks for Genetic Services from 1990 to 1994 to determine the sensitivity, specificity, and positive predictive values for three hereditary metabolic disorders and two congenital endocrinopathies. They reported a positive predictive value of 1.77% for the 1993 cohort and 1.91% for the 1994 group. They further noted that congenital hypothyroidism screening contributed nearly two-thirds of the over 90,000 false positive results from the battery of five tests in both 1993 and 1994 in this large U.S. data set.[4] This positive predictive value is much lower than that reported in most other studies. A CDC expert reviewer noted that the positive predictive value in current screening programs is thought to be 3-4% (S. Grosse, 10/7/06). A recent update by the American Academy of Pediatrics (AAP) on screening and treatment for congenital hypothyroidism reports false positive rates for a variety of small studies of currently utilized testing strategies for CH ranging from 2 to 12 infants recalled for further testing for every case of CH identified[7].

Lanting and colleagues published an analysis comparing three screening strategies for congenital hypothyroidism based on the six years of data supplied by the Dutch Health Administration. The data set included screening results and diagnostic findings for all children screened for CH in the Netherlands in addition to pediatric clinical records allowing identification of false negative and false positive cases. The investigators found that a screening strategy commonly used in the U.S. would have resulted in 572 infants being followed and the identification of 371 cases of CH.[5] This equates to recalling 3 newborns for further testing to identify 2 cases of CH. However, these results likely do not reflect the current U.S. experience due to potential differences between cut-off points used by different screening programs.

Gurian and colleagues examined the impact of false positive results of screening tests for biochemical genetic disorders on parental stress, family relationships, and perceptions of a child's health. Compared with parents who received true negative results, both mothers

and fathers who had received a false-positive newborn screening result scored higher on a standardized assessment of parental stress (Parenting Stress Index – short form) and its 'difficult child' and 'parent-child dysfunctional interaction' subscales. The study was limited due to sample differences: children in the control group had an average age of 6 months, whereas children in the false-positive group averaged 13 months of age. The results of the study did not change when socioeconomic and marital status were controlled for. The team noted the possibility of a 'nocebo' effect – the potential for a false positive screening test result to engender stress among parents by creating expectation of illness in an otherwise healthy child. The authors call for improved communication (including risk communication), parent education, and timely follow-up reporting to ease the stress and anxiety related to false-positive screening results.[6]

No studies of longer term outcomes or of health outcomes related to false positive results were identified.

Recent recommendations from other groups

In September 2006, the American Academy of Pediatrics, in conjunction with the American Thyroid Association, and the Lawson Wilkins Pediatric Endocrine Society published an "Update of Newborn Screening and Therapy for Congenital Hypothyroidism."[7] Additionally, the AAP published an update of its 1996 "Newborn Screening Fact Sheets" with CH information reflecting the updated guideline.[1] These documents call for universal newborn screening for congenital hypothyroidism. While laying out the advantages and disadvantages of different screening tests, these guidelines do not recommend a specific screening regimen.

In 1999, the European Society of Paediatric Endocrinology published its "Revised Guidelines for Neonatal Screening Programmes for Primary Congenital Hypothyroidism" and called for universal newborn screening for congenital hypothyroidism in conjunction with other newborn screening initiatives.[8]

The American Academy of Family Physician recommends screening for congenital hypothyroidism.[9]

Current issues in screening for congenital hypothyroidism

While screening is required in all 50 states and the District of Columbia, the testing methods differ. There is no current consensus on the optimal screening method for CH. In the U.S., most states either screen for elevated TSH with follow-up testing for low T_4 or employ a primary T_4 method with TSH backup. Some jurisdictions test both TSH and T_4 for all newborns and some are considering a TSH-only screen due to improved test characteristics using newer test techniques.

Screening programs in the U.S. are designed to detect cases of primary congenital hypothyroidism. These screening programs miss many, and at times all, infants with central hypothyroidism, a less common condition where the main problem is in the

brain's regulation of the thyroid gland and not in the thyroid gland itself. While the AAP quotes a prevalence of 1 in 50,000 for central congenital hypothyroidism[7], Lanting and colleagues found a rate of 1 in 16,000 over six years of expanded screening in the Netherlands.[5] Given that the clinical outcomes of untreated central CH may be similar to that of primary, thyroid-based CH; that treatment of central CH leads to improved outcomes; and that early, pre-clinical treatment of central CH with replacement therapy would be expected to lead to further improved outcomes, the U.S. may want to consider expanded screening strategies that incorporate central CH screening. In their comparison of different screening techniques, Lanting and colleagues found that the incremental cost for an expanded screening program using low T_4/TBG (T_4 binding globulin) ratio in addition to low T_4 and high TSH (a screening strategy that identifies central as well as primary hypothyroidism) over a more narrow primary T_4 with follow-up TSH program was $11,206 per case detected.[5]

References

1. Kaye CI; Committee on Genetics, Accurso F, La Franchi S, Lane PA, Hope N, Sonya P, G Bradley S, Michele A LP. Newborn Screening Fact Sheets. *Pediatrics* 2006;118(3):e934-63.
2. U.S. Preventive Services Task Force. Screening for Congenital Hypothyroidism. In: *Guide to Clinical Preventive Services*, 2nd edition. Alexandria, VA: International Medical Publishing; 1996:503-507.
3. New England Congenital Hypothyroidism Collaborative. Effects of Neonatal Screening for Hypothyroidism: Prevention of Mental Retardation by Treatment Before Clinical Manifestations. *The Lancet* 1981:1095-1098.
4. Kwon C, Farrell PM. The magnitude and challenge of false-positive newborn screening test results. *Arch Pediatr Adolesc Med* 2000;154(7):714-718.
5. Lanting CI, van Tijn DA, Loeber JG, Vulsma T, de Vijlder JJ, Verkerk PH. Clinical effectiveness and cost-effectiveness of the use of the thyroxine/thyroxine-binding globulin ratio to detect congenital hypothyroidism of thyroidal and central origin in a neonatal screening program. *Pediatrics* 2005;116(1):168-173.
6. Gurian EA, Kinnamon DD, Henry JJ, Waisbren SE. Expanded Newborn Screening for Biochemical Disorders: The Effect of a False-Positive Result. *Pediatrics* 2006;117(Number 6):1916-1922.
7. American Academy of Pediatrics. Update of Newborn Screening and Therapy for Congenital Hypothyroidism. *Pediatrics* 2006;117(6):2290-2303.
8. Revised guidelines for neonatal screening programmes for primary congenital hypothyroidism. Working Group on Neonatal Screening of the European Society for Paediatric Endocrinology. *Horm Res* 1999;52(1):49-52.
9. American Academy of Family Physicians. Policy Statement on Newborn Screening. Issue Brief 2006;2006(October 5):1-12.