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Maternal Screening for Hypothyroidism and Thyroiditis Using Filter Paper Specimens

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Abstract

Background and Objective: Hypothyroidism and autoimmune thyroiditis are more prevalent than previously considered in women during pregnancy and the postpartum, and are associated with adverse effects on the mother and her fetus. We determined the efficacy and accuracy of screening women for primary hypothyroidism and autoimmune thyroiditis by testing TSH and two thyroid antibodies (TAb): thyroperoxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb), in eluates of filter paper specimens collected during early pregnancy and the postpartum.
Methods: We enrolled 494 first-trimester pregnant women with no exclusion criteria into a prospective study to detect primary hypothyroidism and autoimmune thyroiditis. Finger stick blood was applied to filter paper, dried in room air, eluted, and promptly tested for TSH and TAb. A total of 178 of the pregnant women (36%) were tested in the early postpartum. Women with abnormal results had confirmatory serum tests.
Results: It was found that 91 pregnant women (18.4%) and 43 postpartum women (24.2%) had abnormal TSH values (>4.0 mU/L) and/or positive TAb; 140 pregnant women (28.3%) had TSH values >2.5 mU/L. All subjects with TSH values >4.0 mU/L tested positive for TAb. Eighteen women (3.6%) who tested normal during pregnancy tested abnormal in the postpartum.
Conclusions: This study confirms that TSH and TPOAb measured in eluates of blood-spotted filter paper specimens are excellent screening tests to detect primary hypothyroidism and autoimmune thyroiditis in pregnant and postpartum women. Results are very comparable to serum data in this population published in the literature.

Introduction

Autoimmune thyroid diseases and primary hypothyroidism are common diseases in adults, especially among women.[1–7] One-fourth of otherwise healthy women between the ages of 44 and 54 years have thyroid antibodies (TAb) in serum.[1] Approximately 2% of pregnant women have elevated serum TSH levels between 15 and 18 weeks of gestation, and 0.3% have symptomatic hypothyroidism; an estimated 5–18 % of women between the ages of 15 and 45 years have thyroid antibodies and autoimmune thyroid diseases.[2–4] Furthermore, an estimated 80% of pregnant women with elevated TSH levels at 17 weeks of gestation have high titers of thyroid peroxidase antibodies (TPOAb).[3] The global prevalence of postpartum thyroid dysfunction ranges from 4.4% in Asia to 5.7% in the United States and is 5.7 times more likely to occur in women with thyroid antibodies.[8]

Early pioneering studies by Dr. Evelyn Man[9] confirmed an association between hypothyroidism and adverse outcomes of pregnancy for mother and/or her fetus.[1–7,10–13] Maternal primary hypothyroidism was prevalent among pregnant women; the IQ of the progeny of these women was significantly lower than that of matched controls.[9] Cases of maternal autoimmune thyroiditis causing transient congenital

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hypothyroidism with cretinism and permanent mental retardation as well as neonatal deaths were reported to be caused by transplacentally acquired thyrocytotoxic factors, probably immunoglobulin-mediated thyrocytotoxicity.[13,15–17] Most cases are caused by TSH-receptor blocking antibodies that adversely affect the fetus by transplacental transport.[13]

As a result of serum screening studies, a scientific panel[14] recommended TSH measurements in women who are pregnant or wish to become pregnant and who have these risk factors: (1) family or personal history of thyroid disease, (2) physical findings or symptoms suggestive of goiter or hypothyroidism, (3) diabetes mellitus type 1, or (4) a personal history of specific autoimmune disorders.[4] Whether an entire population of women who wish to become pregnant or are diagnosed as pregnant should be screened remains controversial. Recent studies from Europe, China, and the United States compared the case-finding approach of the high-risk pregnant women to universal screening for pregnant women at their first prenatal visit.[5,18–24] They reported that one-third of women with hypothyroidism in the United Kingdom,[18] 55% in the Czech Republic,[19,23] 81.6% in China,[20] and 80.4% in the United States[21,22] would have been missed by the case-finding approach.

An additional concern has been the cost-effectiveness of maternal universal screening for hypothyroidism and thyroiditis.[10] Compared to serum specimen collections by venipuncture, dried blood spotted (DBS) filter paper specimens collected by finger prick are more cost-effective for newborn screening programs in the detection of congenital hypothyroidism and many other disorders.[25] Therefore, in order to maximize cost-effectiveness and testing simplicity, yet retain detection accuracy, adaptation of the neonatal screening model for an adult population would be appropriate to screen for maternal primary hypothyroidism and thyroiditis.[4,26–28]

The objective of this study is to confirm the validity of the dried blood spotted (DBS) filter paper specimen as a very practical and accurate method to detect autoimmune thyroiditis and primary hypothyroidism in pregnant women. Using this method of testing women early in pregnancy enables detection and treatment of thyroid disorders to prevent the known obstetrical complications of pregnancy from thyroid disease. Various populations of women, especially women living in nonurban areas with limited access to healthcare facilities, would be able to be screened. Furthermore, the use of our cost-effective specimen collection and analytic methods, combined with analysis by high-volume, population screening laboratories, considerably reduces the cost for screening, as previously suggested.[11]

We report our experience of screening pregnant women for primary hypothyroidism and autoimmune thyroiditis using the measurement of TSH, TPOAb, and thyroglobulin antibodies (TGAb) in eluates of DBS filter paper specimens collected by finger prick[29–30] as early in pregnancy as possible, and again during the first three months postpartum.

Materials and Methods

Women newly diagnosed as pregnant were recruited from obstetrical centers and offices of private obstetricians. There were no exclusion criteria since every woman is at risk for thyroid disease during pregnancy. Women with known thyroid disease were included since thyroxine requirements increase in early pregnancy, and without recognition and an increase in thyroxine dose, a mother and fetus may be at an increased risk for complications. After the study was explained to the patient, an informed consent approved by the respective Institutional Review Board was obtained, signed, and witnessed. As early in pregnancy as possible and again approximately 6 weeks postpartum, blood specimens were collected by finger prick; drops of blood were placed into one to four circles (1 cm diameter) on S&S-Whatman 904 filter paper; the filter paper specimens were allowed to dry in room air, placed in glassine envelopes, and promptly tested for TSH, TPOAb, and TGAb, as previously described.[29–30] The validity of the assays that were adapted for use in adults was reported previously in detail.[29–30]

Specifically, TSH was measured in eluates from DBS specimens and in serum using the AutoDELFIA™ Neonatal hTSH kit (PerkinElmer, Inc., Wallac, Turku, Finland) and the same procedure as for neonatal testing with the time-resolved fluoroimmunoassay kit.[29] The only adaptations were to prepare five standards and controls with an adult hematocrit of 35%–45%.[29] The range for the standards was between 2.9 and 27 mU/L since our interest in adults ranged between 1 and 20 mU/L. The TSH standard at 100 IU was obtained from Scantibodies™ Laboratories, Inc. (Santee, CA 97071, USA). Blood with 35% hematocrit was obtained from the Oregon Health Sciences University. Phosphate-buffered saline (PBS) was obtained from Gibco BKL, Life Technologies™ (Grand Island, NY 14072, USA), and albumin was obtained as Albuninar® (Centeon L.b.c., Kankakee, IL 60901, USA).[29]

TPOAb and TGAb were ELISA assays that were originally developed by RSR Limited in Cardiff, UK. These reagents for both serum and DBS TPOAb and TGAb assays were purchased from KRONUS (Boise, Idaho) as Kalibre ELISA TGAb (KR7280) and TPOAb (KR7260) kits.[30] DBS controls were prepared using heparin-treated whole blood from individuals with and without high antibody titers. These blood specimens were spotted onto the same filter paper used for the TSH assay and allowed to dry in room air for 4 hours.[29,30] They were stored in plastic bags containing desiccant and were stable for more than 2 years at $-15°C$.[30]

TSH values in normal adults were found to be <4 mU/L Serum; the sensitivity of the DBS assay was 0.743 with correlation coefficients = 0.99 for the full range of the assay between <0.7 to 160 mU/L and 0.878 for values <11 mU/L.[29] TAb values were positive whenever their values for TPOAb were >2 U/mL Serum (sensitivity at 0.68 U/mL Serum) and >3 U/mL Serum for TGAb (sensitivity >1.4 U/mL Serum)[30] (Table 1). There were 494 women who participated in the study during pregnancy. In addition, we recruited and tested 178 (36%) volunteers from our original cohort during their first 3 postpartum months.

Women with TSH values >4 mU/L were contacted and scheduled for a serum TSH determination at a commercial laboratory. When the screening TSH was normal, but thyroid antibodies were positive, a second DBS filter paper specimen for repeat testing was collected within 1–2 months. With patient approval, results of thyroid testing were sent to her primary care physician. Women with positive TAb but normal TSH values during pregnancy and postpartum were advised to have repeat tests within 1 year.

Table 1. Kronus Reference Ranges in Adult Serum

Thyroid Antibody Reading	
TPOAb	
Normal:	< 1 U/mL
Intermediate:	1 – 2 U/mL
Positive:	> 2 U mL
Sensitivity:	0.68 U/mL
TGAb	
Normal:	< 2 U/mL
Intermediate:	2 - 3 U/mL
Positive:	> 3 U/mL
Sensitivity:	1.4

Source: Hofman, 2004.

Results

Data during pregnancy

Of the 494 women tested during pregnancy, 91 (18.4%) had abnormal TSH values (>4.0 mU/L), positive thyroid antibodies (+TPOAb>2 U/mL;+TGAb>3 U/mL), or both. (Table 2) After this study was concluded, other studies reported upper normal TSH reference values in women during pregnancy as low as 2.5 mU/L in North American populations and higher (3.0 and 3.7 mU/L)[18,35] in some European populations, while other studies report trimester-specific ranges.[4,35–37] Therefore, we analyzed our data by selecting groups with positive TAb and TSH values >2.5,>3.0 and <3.0 mU/L (Table 2). As expected, when the upper cutoff value for TSH is lower and thyroid antibodies are positive, a greater number and percentage of the total population of women have abnormal screening test results. We found that 140 pregnant women (28.3%) had TSH values >2.5 mU/L and that 13% of the population of women with TSH values less than 3.0 mU/L had positive thyroid antibodies.

Table 2. TSH and Thyroid Antibodies (TAb)* in Pregnant Women

Pregnant women	n	*% of Total*
Total population:	494	100.0
TSH>4.0 mU/L and/or positive TPOAb - TGAb:	91	18.4
TSH>3.0 mU/L:	110	22.3
TSH>2.5 mU/L:	140	28.3
TSH<3.0, TAb positive:	64	13.0

TSH Values with Positive and Negative Thyroid Antibodies (TAb)*

Pregnant women	n	*% of Total*
Patient population:	494	100.0
TSH>2.5 &+TAb:	16	3.2
TSH>2.5 & - TAb:	14	2.8
TSH>3.0 &+TAb:	13	2.6
TSH>3.0 & - TAb:	6	1.2
TSH>4.0 &+TAb:	9	1.8
TSH>4.0 & - TAb:	0	0

*TAb=Thyroid Peroxidase antibodies (TPOAb) and/or Thyroglobulin Antibodies (TGAb).

Evaluation during the postpartum

Of the 494 women tested during pregnancy, 178 (36%) were available and volunteered for testing during the postpartum. A greater percentage of postpartum women (24.2%) had abnormal TSH values and/or positive thyroid antibody results compared to pregnant women (18.4%) (Table 3). This observation likely reflects, in part, an inherent bias since the greater number of women who tested positive during pregnancy had an incentive to return for postpartum testing. (We had informed them that there was a possibility that their tests would be abnormal during the postpartum period as a result of losing the immune-suppressive effects during pregnancy.) A larger percentage of postpartum women (22.5%) compared to pregnant women (13%) had positive thyroid antibodies when TSH values were <2.5 mU/L. also supportive of immune-suppression on the serologic expression of autoimmune thyroid disease in pregnancy. Among women with normal tests during pregnancy, TSH values became elevated in two of them; TPOAb values became positive in seven; and TGAb converted to positive in nine subjects during the postpartum. Six of nine women were TPOAb positive during pregnancy and the postpartum.

Evaluation of women with preexisting thyroid disease

Only 10 of 91 women (11%) with abnormal screening results were receiving levothyroxine therapy for previously diagnosed primary hypothyroidism (Table 4). Five of 10 women had TSH values >3mU/L. All 10 of them tested positive for one or both thyroid antibodies: TPOAb and TGAb were positive in four; only TPOAb was positive in five; and only TGAb was positive in one woman whose TSH value was 8 mU/L.

Discussion

Cumulative data over five decades indicate that early detection of hypothyroidism and adequate thyroid hormone therapy in pregnant women prevent adverse outcomes for mothers and their children.[3–4,10–13,19,23–28,33] These data in humans were preceded by comparable findings through well-designed studies in experimental animals.[34] The debate continues as to whether or not there should be universal screening for all women early in pregnancy or even prior to conception, or whether the current recommended policy should be continued for screening only select populations of pregnant women who have a high risk for hypothyroidism.[3–4,11,23–24,26–28]

Societies in North America do not recommend universal screening at this time[33,35] or screening for autoimmune thyroiditis,[22,35] whereas other countries have data in support of

Table 3. TSH and Thyroid Antibodies (TAb)* in Postpartum Women

Postpartum women	n	*% of Total*
Patient population:	178	36.0
Abnormal TSH &/or+TAb:	43	24.2
TSH>2.5 mU/L:	3	1.7
TSH<2.5 mU/L:	40	22.5

*TAb=Thyroid peroxidase antibodies (TPOAb) and/or Thyroglobulin antibodies (TGAb).

Table 4. Thyroid Screening of Pregnant Women Receiving L-Thyroxine Therapy

1. 10 of 91 women with TSH > 4.0 mU/L and positive thyroid antibodies (TPOAb and/or TGAb) during pregnancy were receiving daily levothyroxine.		
2. Screening results:		
TPOAb and TGAb positive:	4	
TPOAb only positive:	5	
TGAb only positive:	1	The TSH value was 8 mU/L.
3. TSH values > 3 mU/L:	5	
5. TSH values < 3 mU/L:	5	All were positive for TPOAb.

Recommendation[35,37]: Women on levothyroxine prior to pregnancy should increase their dose by 30% or more as soon as pregnancy is confirmed and arrange for a TSH test to assure adequacy of the dose during pregnancy.

recommendations for universal screening.[5,18,19,23] Our study supports previous data that testing for TGAb in addition to TPOAb is not beneficial, and only TPOAb testing is necessary to detect autoimmune thyroiditis during pregnancy.

The cost-effectiveness of screening for hypothyroidism during pregnancy and the postpartum has been extensively studied, with generally favorable results.[26–28,33] Furthermore, the use of the neonatal screening concept has been suggested [11] and now confirmed in this study to further advance the cost-effective concept of population screening for women. The overall cost-effectiveness of screening in pregnancy for subclinical hypothyroidism is calculated to be in excess of $8 million for every 100,000 pregnant women screened.[28] Current information from commercial laboratories indicate that the cost of serum TSH with or without serum TPOAb are at least twice the cost of testing the same analytes using filter paper specimens.

Maternal screening for hypothyroidism is beneficial to mother and her unborn child[14,36–37] as well-established programs have shown it to be in newborn screening using the same inexpensive collection techniques.[25] Women with primary hypothyroidism who receive thyroxine replacement therapy prior to conception, but whose thyroxine dose during early pregnancy is inadequate,[22,33–34] also are identified when the neonatal screening method for TSH is used to detect primary hypothyroidism.[25] However, maternal screening can be individualized by patient–physician decisions using the least expensive and most reliable tests.

The reviews of several scientific studies were considered to provide insufficient support for population-based screening for subclinical hypothyroidism in pregnant women.[14] Specific guidelines for diagnosis and management were described, and the issue of the normal TSH range for women throughout pregnancy was raised.[14,31–32] Subsequent reports supported a narrower TSH reference range.[32] Ninety-five percent of normal pregnant women have TSH levels below 2.5 mU/L in the United States and 3.0 to 3.7 in Europe.[31–32] Values above these levels were likely to have underlying thyroid disease, most often autoimmune (Hashimoto) thyroiditis.[4,32,36] Our data confirm the need for accurate normative data of thyroid function throughout pregnancy when levels of chorionic gonadotropin with its inherent TSH-biologic activity are increased. Appropriate cutoff values throughout pregnancy and the postpartum need to be determined for each method adapted for screening.

Very recent studies support maternal screening for thyroid dysfunction either before conception or early during pregnancy and in the postpartum.[5,23] There is very compelling evidence that the early detection of autoimmune thyroid disease will reduce the percentage of women with obstetrical complications (notably, increased risks of miscarriage and premature deliveries).[4,37–38] Women early in pregnancy with + TPOAb who were not receiving thyroxine therapy had risks of miscarriages (13.8%) and premature deliveries (22.4%) that were significantly greater than women with + TPOAb who were treated with levothyroxine (L-T4) (3.5%, 7%) and women with negative TPOAb (–TPOAb) and not treated (2.4%, 8.2%), respectively.[37–38,40–41] Recent prospective studies report lower rates of miscarriage in levothyroxine-treated, antibody-positive pregnant women compared to controls.[37] An increase in pregnancy loss rate was found in thyroid antibody-negative pregnant women during the first trimester when TSH levels were between 2.5 and 5.0 mU/L.[36] Recent studies as well as our own study confirm that a significant number of pregnant women with hypothyroidism will be missed if screening is selective or targeted for high-risk women only.[18–21,23] Until now, none have studied and validated the use of DBS filter paper specimens as a cost-effective, convenient, and validated method of screening.

Several reports on the effects of thyroid testing for hypothyroidism and thyroiditis on maternal outcome.[18–20,23,35–40] support thyroid testing of pregnant women, and none reported a lack of benefit. However, the effects of maternal thyroid testing[44–46] on the outcome of infants did not show defined benefit,[45] although detection of maternal hypothyroidism and treatment before the third trimester was associated with normal cognitive outcome in offspring.[46] Severe maternal hypothyroidism clearly is associated with devastating neurodevelopmental outcomes and death.[15,17] Another study found higher maternal TSH levels at delivery to be associated with significantly lower scores on the general cognitive index at age 5.5 years among infants born at ≤ 34 weeks to mothers with mild maternal thyroid dysfunction.[44] Currently, a multicenter randomized placebo-controlled clinical trial organized by the Maternal Fetal Medicine Unit at the National Institutes of Health is in progress to determine the IQ outcome of the child at age 5 years.[23] Also, screening before or during early pregnancy for autoimmune thyroid diseases also alerts physicians to the increased risk for postpartum autoimmune thyroid diseases.[8] These diseases can be treated whenever postpartum TSH levels are elevated and thyroid antibodies are positive prior to the development of clinical symptoms and progression to deleterious side effects.[8,37,42]

DBS filter paper screening is now validated for screening pregnant and postpartum women. It also provides a very convenient, low-cost specimen for molecular and biochemical screening to detect other treatable diseases,[25] including genomic analysis to screen the general population,[47] as is evident by the number of diseases recommended for first-trimester maternal screening. DBS specimens to screen for TSH and TPOAb can be implemented at much lower costs than serum testing, and results are available within 24 hours of receipt in the laboratory. The filter paper collection technique and the simplified laboratory analytical methods are

ideal for use in those countries where TSH and thyroid antibody testing is difficult to obtain, yet where prompt specimen transport to a centralized laboratory is available.

Conclusion

Maternal screening for autoimmune thyroiditis and primary hypothyroidism during early pregnancy, and again early during the postpartum, will identify women who have an increased risk for primary hypothyroidism. The most cost-effective testing method to screen is the analysis of thyroid analytes in eluates from DBS filter paper specimens using automated analytical equipment to test for TSH and TPOAb. Early screening for hypothyroidism will identify affected women and through the prompt initiation of adequate L-thyroxine therapy should eliminate the development of adverse effects from maternal, fetal, and postpartum hypothyroidism. The maternal screening strategies described in this study can be implemented for routine testing early in pregnancy.

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Author Disclosure Statement

At the time of the study, the four authors were affiliated with Neo Gen Screening, Inc. which no longer exists. Edwin W. Naylor, PhD. was a paid Principal Investigator of the supporting grants and President and Laboratory Director of Neo Gen Screening, Inc. Judith C. Henry, RN, was a paid Research Nurse Coordinator and Investigator who was an employee of Neo Gen Screening, Inc. at the time the study was conducted. Thomas P. Foley Jr. and Lindsay F. Hofman, PhD, were paid research coordinator and research investigators, respectively. Thomas P. Foley Jr., MD, as Professor of Pediatrics and Epidemiology at the time of the study and as Professor Emeritus during manuscript drafting and revisions, discloses that he had been paid as a Physician Research Consultant for Neo Gen Screening, Inc. and for the subsequent businesses that purchased the laboratory. There are no other potential conflicts of interest, specific financial interests, or affiliations relevant to the manuscript. This article has not been published previously in any publication, nor is it under review for publication elsewhere.

This study was conducted in Allegheny County and the City of Pittsburgh, Pennsylvania.

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