Screening pregnant women for autoimmune thyroid disease: a cost-effectiveness analysis

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Abstract

Objective: Untreated maternal hypothyroidism during pregnancy can have adverse consequences on maternal health and child intelligence quotient (IQ). Our objective was to examine the cost-effectiveness of screening pregnant women for autoimmune thyroid disease.

Design: We developed a state-transition Markov model and performed a cost-effectiveness analysis of screening pregnant US women, aged 15–45 years, with no known history of thyroid disease, in the first trimester.

Methods: Three strategies were compared: 1) no screening, 2) one-time screening using anti-thyroid peroxidase (anti-TPO) antibodies, and 3) one-time screening using TSH. Screening tests were added to the laboratory tests of the first prenatal visit. Abnormal screening tests were followed by further testing and subsequent thyroxine treatment of hypothyroid women.

Results: Screening pregnant women in the first trimester using TSH was cost-saving compared with no screening. Screening using anti-TPO antibodies was cost-effective compared with TSH screening with an incremental cost-effectiveness ratio of $15 182 per quality-adjusted life year. Screening using TSH remained cost-saving across a wide range of ages at screening, costs of treatment, and probabilities of adverse outcomes. The cost-effectiveness of anti-TPO screening compared with TSH screening was mostly influenced by the probability of diagnosing hypothyroidism in unscreened subjects or subjects with a normal screening test. Screening remained highly cost-effective in scenarios where we assumed no improvement of child IQ outcomes by levothyroxine treatment.

Conclusion: Screening all pregnant women for autoimmune thyroid disease in the first trimester is cost-effective compared with not screening.

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Introduction

About 11% of women aged 15–45 years have thyroid autoimmunity (1), while 2.2% of pregnant women have elevated thyroid stimulating hormone (TSH) at 15–18 weeks of gestation, and 0.3% are overtly hypothyroid (2, 3).

In the mother, untreated hypothyroidism during pregnancy increases the risk of gestational hypertension and complications at delivery (4–6). Women with elevated anti-thyroid peroxidase (TPO) antibody titers are at increased risk of developing postpartum thyroiditis (PPT) (7, 8). In women with unrecognized high TSH during pregnancy, the median interval to clinical diagnosis of hypothyroidism is 5 years (9); therefore, many mothers have undiagnosed hypothyroidism in the first years of their child’s life.

In the fetus, untreated maternal hypothyroidism is associated with adverse perinatal outcomes such as low birth weight and intrauterine growth retardation (4–6) as well as with decreased intelligence quotient (IQ) in childhood (9–13). The drop in IQ is more pronounced in children of mothers with the highest TSH levels (ten-point drop); however, even milder maternal thyroid dysfunction is associated with a five-point drop in IQ compared with controls (14). Given that 2.2% of pregnant women have an elevated TSH, out of about 4 000 000 pregnancies that occur annually in the US (15) as many as 88 000 infants are at risk for low IQ. Untreated maternal hypothyroidism in those cases would result in 12 320 more infants per year with IQ ≤85.

Though data from randomized trials are still lacking, observational studies have concluded that treatment of maternal hypothyroidism with thyroid hormone reduces the incidence of gestational hypertension in the mother (6) and improves IQ in the child (9, 10). Additionally, diagnosing and treating women with undiagnosed hypothyroidism could improve quality of life in both patients and their children.
These data make it imperative to consider screening pregnant women. There have been two cost-effectiveness analyses of screening the general population for thyroid disease, in adults over 35 (16) and 60 years old (17); both found screening to be cost-effective. The US Preventive Services Task Force recently concluded that population-wide screening for subclinical thyroid dysfunction in adults is unwarranted, but excluded pregnant women from their analysis (18). An expert panel on subclinical thyroid disease also recommended against population-wide screening, but found the evidence insufficient to recommend for or against routine screening in pregnant women, and instead recommended aggressive case finding (19). The American College of Obstetrics and Gynecology has a similar position (20). On the other hand, both the American Association of Clinical Endocrinologists (AACE) independently and a consensus panel with representatives from the American Thyroid Association, AACE, and the Endocrine Society have endorsed routine thyroid screening before or during pregnancy (21, 22). Finally, the recent Endocrine Society clinical practice guidelines for the management of thyroid dysfunction during pregnancy support targeted thyroid disease case-screening instead (23). Despite the lack of consensus among professional organizations, a recent study examining current practice in Maine has found that routine TSH testing is performed in 48% of all prenatal care practices and 76% of urban obstetric practices (24).

Our analysis was undertaken to determine whether it would be cost-effective to perform universal screening for autoimmune thyroid disease in pregnant women using either anti-TPO antibodies or TSH.

Methods

Decision model

A Markov model (25, 26) was developed using the TreeAge Pro 2004 Suite program (Williamstown, MA, USA) to investigate the difference in costs and health benefits between two strategies of screening pregnant women for autoimmune thyroid disease and not screening (Fig. 1). We used a modified societal perspective and ran a lifetime analysis using a discount rate of 3%. We adhered to the recommendations of the Panel on Cost-Effectiveness in Health and Medicine (27). Only women with no known history of thyroid disease were included in the model. Three strategies were evaluated: 1) no screening, 2) screening with anti-TPO antibody, and 3) screening with TSH. Screening occurred once in the woman’s lifetime, during the first trimester of pregnancy, at the age of 25 (mean age of mothers in their first pregnancy in the US) (15).

The screening test was added to the laboratory tests obtained at the first prenatal visit (6–12 weeks of gestation). The subjects who screened positive underwent further testing, follow-up, and treatment. Regardless of screening status, women with autoimmune thyroid disease and hypothyroidism were at risk for gestational hypertension, PPT, and low IQ in their children. Women with identified disease had these complications ameliorated if treated appropriately.

After the first postpartum year, all women entered a Markov cycle, in which they underwent annual transitions between five health states (Fig. 2). The likelihood of developing overt hypothyroidism differed according to the subject’s underlying anti-TPO antibody status and TSH level at screening (28).

Testing and treatment strategies

In screened patients, serum was saved at the initial blood draw for further testing. In the first screening strategy, if the anti-TPO antibody screen was positive, serum was tested for TSH. If TSH was high, serum was tested for free thyroxine (FT₄); a diagnosis of subclinical (normal FT₄) or overt (low FT₄) hypothyroidism was reached, the patient was referred to an endocrinologist, and treatment with levothyroxine was initiated. If the TSH was not high, patients were followed with a 6-month postpartum visit and thyroid function tests (TFTs: TSH and FT₄), and thereafter with annual clinic visits and TFTs.

In the second screening strategy, if the TSH was elevated, serum was tested for FT₄, a diagnosis of overt or subclinical hypothyroidism was reached, the patient was referred to an endocrinologist, and treatment with levothyroxine was initiated. If the TSH level was normal/low (under 95% percentile, corresponding to a TSH ≤ 3 mU/ml (29, 30)), no further testing was performed. If the TSH level was midrange (95–97.5th percentile, i.e. 3–5 mU/ml (29, 30)), serum was tested for anti-TPO antibodies. The subjects with positive anti-TPO antibodies were followed with a 6-month postpartum visit and TFTs, and thereafter with annual clinic visits and TFTs.

Once patients were diagnosed with overt hypothyroidism, patients had three follow-up visits with TFTs during the remainder of pregnancy, followed by three more visits with TFTs at 3, 6, and 12 months postpartum. Thereafter, they were followed with annual visits and TFTs. Subclinically hypothyroid patients were treated the same way as overtly hypothyroid patients until the end of the first postpartum year. Thereafter, thyroxine treatment was discontinued. They entered the Markov model as patients with no overt disease, and were followed with annual visits and TFTs. The patients who were antibody positive with a normal TSH during pregnancy had a follow-up visit with TFTs at 6 months postpartum in order to assess for development of PPT and were subsequently followed with annual visits and TFTs.
Subjects who screened negative or were not screened received no further testing. Disease was diagnosed and treated only in symptomatic patients, with a delay, after undergoing a medical workup for their symptoms.

Subjects diagnosed with overt hypothyroidism after pregnancy were treated with levothyroxine, had three follow-up visits with TFTs during the first year, and annual visits with TFTs thereafter. Throughout the model, women could be compliant or not with their recommended treatment. Non-compliant patients remained in the untreated overtly hypothyroid group until they became compliant (mean of 2.5 years).

**Probabilities**

We derived the probabilities for the decision tree and the Markov state transitions from epidemiology and prevalence studies in peer-reviewed journals, after extensive review of the literature (Table 1). The prevalence of anti-TPO antibodies and high TSH were varied as a function of maternal age (Table 2). Of the remaining pregnant women, we assumed that 95% would have normal/low TSH, and that the rest would have TSH in the midrange. The probabilities of abnormal TFTs in the various anti-TPO antibody and TSH subgroups were calculated from studies of prevalence of hypothyroidism in pregnant women (2, 3).

When probabilities were not available, they were estimated using expert clinical judgment. We estimated compliance with levothyroxine treatment to be 80 and 90% in non-pregnant and pregnant women respectively. We estimated that unscreened patients with overt or symptomatic subclinical hypothyroidism during pregnancy would take on average 2.5 years to diagnose.
This was based on clinical experience and was more conservative than the median interval to diagnosis of hypothyroidism in women with elevated TSH during pregnancy (5 years) (9).

We varied all assumptions and parameter values extensively in sensitivity analyses.

**Costs**

The costs for laboratory tests were obtained from the 2004 Medicare Clinical Laboratory Fee Schedule (31). The costs for clinic visits were obtained from the 2004 Medicare payment amounts for services provided in a facility (32) (Table 1). The cost of levothyroxine treatment was obtained from the 2004 Redbook (33). Screening cost consisted of an anti-TPO antibody titer (CPT 86 376) or TSH test (CPT 84 443). The cost of the initial visit to the endocrinologist was assumed to be that of a 30-min outpatient consultation (CPT 99 242).

Hypothyroidism treatment costs were calculated for the different scenarios described above using the costs of a 10-min follow-up outpatient visit (CPT 99 212), TSH test (CPT 84 443), FT₄ test (CPT 84 439), and annual cost of levothyroxine treatment. The costs of gestational hypertension were calculated as incremental costs compared with a pregnancy with no gestational hypertension (34). Costs for PPT and workup of unscreened women with hypothyroidism were obtained from the literature (16, 35). All costs were adjusted to $2004 using the Gross Domestic Product Deflator Inflation Calculator (http://www1.jsc.nasa.gov/bu2/inflateGDP.html).

We estimated the cost of low IQ using data on the relationship between cognitive ability and earning potential (36). A one-point difference in IQ is associated with about a 2% difference in earnings (range 1.76–2.37%) (36). Based on estimates published elsewhere (36), we assumed the discounted future earnings of a 2 year old to be $775 667 (adjusted to $2004). This assumption would mean a loss of $15 513 in future earnings per IQ point. Based on the follow-up to the Haddow study (14), we assumed that children of untreated overtly and subclinically hypothyroid mothers have on average a 9.2- and 4.2-point decrement in IQ respectively (after adjusting by 0.8 points for differences in socioeconomic status compared with controls).

In the Markov tree, we only included lifetime costs attributable to the diagnosis and treatment of hypothyroidism; we did not include future medical costs due to other illnesses.

**Patient preferences**

Patient preferences for the different health states were incorporated into the analysis using utilities, which ranged from 0 to 1 (Table 1). A utility of 1 was assigned to the ideal health state and 0 to the dead state. Asymptomatic subclinical hypothyroidism and asymptomatic PPT were assigned a utility of 1. Utilities for overt hypothyroidism and PPT were obtained from the literature (35, 37, 38). Symptomatic untreated subclinical hypothyroidism was estimated to have a utility of 0.9, which increased to 1 if treated. To derive the utility of treated gestational hypertension, we surveyed three obstetricians with experience in high-risk pregnancies, and we averaged the given values. Similarly, to obtain the utility of having a child with IQ ≤85, we averaged the values given by five pediatricians that we surveyed. We only assigned a utility decrement to the mother of the child with IQ ≤85, for her lifetime. We also obtained utility estimates for the child with low IQ and his/her second parent (0.66 and 0.75 respectively); however, we did not include those utilities in our base-case analyses.

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Base-case estimate</th>
<th>Range</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test characteristics (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity of anti-TPO Ab</td>
<td>90</td>
<td>80–100</td>
<td>(50–52)</td>
</tr>
<tr>
<td>Specificity of anti-TPO Ab</td>
<td>95</td>
<td>90–100</td>
<td>(50–52)</td>
</tr>
<tr>
<td>Anti-TPO Ab positivity in pregnant women</td>
<td>10.4</td>
<td>7–15</td>
<td>(1–3)</td>
</tr>
<tr>
<td>High TSH in anti-TPO Ab positive women</td>
<td>12</td>
<td>8–16</td>
<td>(2, 3)</td>
</tr>
<tr>
<td>High TSH in anti-TPO Ab negative women</td>
<td>1</td>
<td>Not varied</td>
<td>(2, 3)</td>
</tr>
<tr>
<td>Probability TSH high</td>
<td>2.2</td>
<td>1.3–2.6</td>
<td>(2, 3)</td>
</tr>
<tr>
<td>Probability TSH normal (for pregnancy)</td>
<td>95</td>
<td>93–97</td>
<td>Definition</td>
</tr>
<tr>
<td>FT₄ low in anti-TPO Ab positive women with high TSH</td>
<td>23</td>
<td>10–30</td>
<td>(2, 3)</td>
</tr>
<tr>
<td>FT₄ low in anti-TPO Ab negative women with high TSH</td>
<td>8</td>
<td>5–11</td>
<td>(2, 3)</td>
</tr>
<tr>
<td>Treatment variables (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment compliance in pregnant women</td>
<td>90</td>
<td>80–100</td>
<td>Estimate</td>
</tr>
<tr>
<td>Treatment compliance in non-pregnant women</td>
<td>80</td>
<td>60–100</td>
<td>Estimate</td>
</tr>
<tr>
<td>Annual new compliance among non-compliant patients</td>
<td>25</td>
<td>10–80</td>
<td>Estimate</td>
</tr>
<tr>
<td>Adverse outcome variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms in SH (%)</td>
<td>28</td>
<td>10–50</td>
<td>(16)</td>
</tr>
<tr>
<td>GHTN in inadequately treated women with OH (%)</td>
<td>7.9</td>
<td>5–10</td>
<td>(6)</td>
</tr>
<tr>
<td>GHTN in inadequately treated women with SH (%)</td>
<td>7.9</td>
<td>5–10</td>
<td>(6)</td>
</tr>
<tr>
<td>GHTN in inadequately treated women with OH (%)</td>
<td>36</td>
<td>20–50</td>
<td>(6)</td>
</tr>
<tr>
<td>GHTN in inadequately treated women with SH (%)</td>
<td>25</td>
<td>7.6–40</td>
<td>(6)</td>
</tr>
<tr>
<td>GHTN in women with normal TSH (%)</td>
<td>7.6</td>
<td>5–10</td>
<td>(6)</td>
</tr>
<tr>
<td>PPT in anti-TPO Ab-positive women (%)</td>
<td>50</td>
<td>30–70</td>
<td>(7, 8)</td>
</tr>
<tr>
<td>PPT in anti-TPO Ab-negative women (%)</td>
<td>0.5</td>
<td>0.3–2.5</td>
<td>(7, 8)</td>
</tr>
<tr>
<td>Symptoms given PPT (%)</td>
<td>68</td>
<td>33–88</td>
<td>(35)</td>
</tr>
<tr>
<td>Diagnosing PPT in unscreened or anti-TPO Ab-negative women (%)</td>
<td>25</td>
<td>10–75</td>
<td>(35)</td>
</tr>
<tr>
<td>Infant IQ ≤ 85 in adequately treated maternal OH or SH (%)</td>
<td>5</td>
<td>2–8</td>
<td>(9)</td>
</tr>
<tr>
<td>Infant IQ ≤ 85 in inadequately treated maternal OH (%)</td>
<td>19</td>
<td>10–30</td>
<td>(9)</td>
</tr>
<tr>
<td>Infant IQ ≤ 85 in inadequately treated maternal SH (%)</td>
<td>9.5</td>
<td>5–19</td>
<td>Estimate</td>
</tr>
<tr>
<td>Infant IQ ≤ 85 if maternal TSH not high (%)</td>
<td>5</td>
<td>2–8</td>
<td>(9)</td>
</tr>
<tr>
<td>Average IQ point loss in children of women with untreated maternal OH</td>
<td>9.2</td>
<td>0–15</td>
<td>(14)</td>
</tr>
<tr>
<td>Average IQ point loss in children of women with untreated maternal SH</td>
<td>4.2</td>
<td>0–10</td>
<td>(14)</td>
</tr>
<tr>
<td>Natural history variables (annual) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Development of OH in anti-TPO Ab-positive women with high TSH</td>
<td>4.3</td>
<td>3–5</td>
<td>(28)</td>
</tr>
<tr>
<td>Development of OH in anti-TPO Ab-positive women with not high TSH</td>
<td>2.1</td>
<td>1–3</td>
<td>(28)</td>
</tr>
<tr>
<td>Development of OH in anti-TPO Ab-negative women with high TSH</td>
<td>2.6</td>
<td>1.6–3.6</td>
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</tr>
<tr>
<td>Development of OH in anti-TPO Ab-negative women with not high TSH</td>
<td>0.3</td>
<td>0.1–0.5</td>
<td>(28)</td>
</tr>
<tr>
<td>Rate of diagnosis of OH in unscreened women with OH or symptomatic SH</td>
<td>25</td>
<td>10–80</td>
<td>Estimate</td>
</tr>
<tr>
<td>Costs ($ 2004)</td>
<td></td>
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<tr>
<td>Thyroid peroxidase Ab test</td>
<td>20.33</td>
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</tr>
<tr>
<td>Thyroid stimulating hormone test</td>
<td>23.47</td>
<td>10–50</td>
<td>(31)</td>
</tr>
<tr>
<td>Free thyroxine test</td>
<td>12.6</td>
<td>5–30</td>
<td>(31)</td>
</tr>
<tr>
<td>Levothyroxine sodium 1 year supply</td>
<td>130.67</td>
<td>100–200</td>
<td>(33)</td>
</tr>
<tr>
<td>Outpatient visit, new, 30 min</td>
<td>69.45</td>
<td>50–100</td>
<td>(32)</td>
</tr>
<tr>
<td>Outpatient visit, established, 10 min</td>
<td>23.52</td>
<td>20–50</td>
<td>(32)</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>3890</td>
<td>1860–5920</td>
<td>(34)</td>
</tr>
<tr>
<td>PPT</td>
<td>536.10</td>
<td>220–660</td>
<td>(35)</td>
</tr>
<tr>
<td>Workup of unscreened women with OH, symptomatic SH, or symptomatic PPT</td>
<td>309</td>
<td>165–490</td>
<td>(16)</td>
</tr>
<tr>
<td>Cost per one IQ point loss</td>
<td>15 513</td>
<td>13 652–18 383</td>
<td>(36)</td>
</tr>
<tr>
<td>Utilities</td>
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</tr>
<tr>
<td>Euthyroid</td>
<td>1</td>
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<td>Subclinical hypothyroidism, asymptomatic</td>
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<td>Subclinical hypothyroidism, symptomatic, untreated</td>
<td>0.90</td>
<td>0.70–0.95</td>
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<td>Subclinical hypothyroidism, symptomatic, treated</td>
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<td>Overt hypothyroidism, untreated, first year</td>
<td>0.7085</td>
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</tr>
<tr>
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<td>(37, 38)</td>
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<td>(37, 38)</td>
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<td>Estimate</td>
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<td>PPT, symptomatic, undiagnosed</td>
<td>0.81</td>
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<td>PPT, symptomatic, correctly diagnosed</td>
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<td>0.82–1</td>
<td>(35)</td>
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<td>Gestational hypertension, treated</td>
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<td>0.85–0.95</td>
<td>Expert</td>
</tr>
<tr>
<td>Having a child with IQ ≤ 85</td>
<td>0.75</td>
<td>0.60–0.90</td>
<td>Expert</td>
</tr>
<tr>
<td>Other variables</td>
<td></td>
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<tr>
<td>Discount rate, annual (%)</td>
<td>3</td>
<td>0–5</td>
<td>(27)</td>
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</table>

Anti-TPO Ab, anti-thyroid peroxidase antibody; TSH, thyroid stimulating hormone; PPT, postpartum thyroiditis; GHTN, gestational hypertension; OH, overt hypothyroidism; SH, subclinical hypothyroidism; IQ, intelligence quotient.

*aThe base-case estimate represents the best estimate for each value. Costs are expressed in 2004 US dollars.

*bVariable is a function of other variables.

*cAdjusted for difference in socioeconomic status between hypothyroid subjects and controls (based on data in (9)).
Assumptions of the model
The following additional assumptions were made:

1) Hyperthyroidism is diagnosed much more readily than hypothyroidism through symptoms, while subclinical hyperthyroidism has no adverse impact on pregnancy outcomes (39). We therefore did not include hyperthyroid patients in the model.

2) Free T4 is assessed in assays that have pregnancy-specific reference ranges and only defined as low when lower than the manufacturer-specific and trimester-specific reference ranges.

3) Women diagnosed with subclinical hypothyroidism during pregnancy get treated until 12 months postpartum. We made this assumption based on the detrimental effects of high TSH, even in the absence of overt hypothyroidism, on pregnancy complications and fetal IQ (6, 9) and the current consensus recommendations of treating such pregnant women (19). Treatment was continued in the first postpartum year, given the high incidence of PPT during that period in susceptible women. Since treatment of subclinical hypothyroidism in non-pregnant patients has questionable benefits (19), we did not continue treatment after 12 months postpartum.

4) Women with overt hypothyroidism are all symptomatic. Once they get diagnosed, they require lifelong therapy and follow-up.

5) Among the unscreened patients and those who screen negative, patients with symptomatic subclinical disease during pregnancy, have a 25% probability of diagnosis and treatment by 12 months postpartum. Asymptomatic patients are not diagnosed. The patients who develop symptomatic subclinical disease after the first postpartum year do not get diagnosed until they become overtly hypothyroid.

6) All compliant patients are successfully treated and therefore assumed to no longer have high TSH.

7) The diagnosis of PPT is correctly made in all symptomatic patients (68% of PPT patients) (35) in the screened, anti-TPO antibody-positive group. Symptomatic patients with PPT who screen anti-TPO antibody-negative or are not screened, have only a 25% chance of correct diagnosis; the remaining 75% incur additional cost of workup of their symptoms ($309) (35).

8) The probability of child IQ ≤ 85 in untreated subclinically hypothyroid mothers is half of the probability corresponding to overtly hypothyroid mothers (0.095 vs 0.19). This was based on the fact that the follow-up to the Haddow study (14) showed that children born to mothers with the highest TSH (mean TSH of 32 mU/l) had a ten-point IQ difference compared with controls, whereas children born to mothers with slighter TSH elevations (mean TSH of 9 mU/l) had a five-point IQ difference compared with controls (before adjusting for socioeconomic status). Since the IQ deficit was halved in mothers with milder TSH elevations, we assumed that the percentage of children born to mothers with subclinical hypothyroidism would be half that of children born to mothers with overt disease.

Results
Base-case analysis
Under base-case assumptions, screening pregnant women with TSH in the first trimester was cost-saving (saved $102) and increased quality-adjusted life expectancy by 5.84 days relative to no screening. Screening with anti-TPO antibodies increased quality-adjusted life expectancy by 5.11 days at a cost of $212 relative to TSH screening, for an incremental cost-effectiveness ratio (ICER) of $15 182 per QALY (Table 3).

Sensitivity analyses
Screening with TSH or anti-TPO antibodies remained cost-effective across a wide range of parameters tested. In one-way sensitivity analysis, TSH screening continued to dominate no screening across all parameters varied over a clinically valid range. The analysis was most sensitive to the annual probability of diagnosing overt hypothyroidism in women who are unscreened or those with
negative screening tests. This probability was varied across a very wide range (0.1–0.8), because the estimation of the base-case value was based on clinical experience. Screening using TSH became cost-saving compared with anti-TPO screening when that probability was 0.78 or larger (data not shown).

Screening using TSH remained cost-saving at all ages (Table 4), whereas screening using anti-TPO antibodies became more cost-effective compared with TSH screening as maternal age increased (Table 4), reflecting the higher prevalence of autoimmune thyroid disease in older women. When we doubled the costs associated with the screening and diagnostic tests, TSH screening continued to dominate no screening, while the cost-effectiveness of anti-TPO antibody screening compared with TSH screening decreased (ICER: $21 550/QALY, Table 4). Recognizing that the occurrence of hypothyroidism can differ among various populations of women, we varied the probability of high TSH across a wide range (1.3–2.6%) and found no significant changes in the cost-effectiveness of the screening strategies compared with the base-case scenario (data not shown).

### Cost-effectiveness at different scenarios of low IQ variables

We explored the effects of low IQ in the children of untreated mothers with hypothyroidism by varying simultaneously a number of parameters associated with low IQ. When we assumed that untreated hypothyroidism (both overt and subclinical) during pregnancy had no adverse effect on child IQ, TSH screening was cost-effective compared with no screening (ICER: $4956/QALY), and anti-TPO antibody screening remained cost-effective compared with TSH screening (ICER: $9133/QALY; Table 4). When we assumed no treatment benefit with levothyroxine regarding low child IQ, we obtained similar results (Table 4).

### Table 3 Health and economic outcomes.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost ($)</th>
<th>Incremental cost ($)</th>
<th>QALY (years)</th>
<th>Incremental QALYs (days)</th>
<th>Incremental C-E ratio ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No screen</td>
<td>970</td>
<td></td>
<td>26.854</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screen with TSH</td>
<td>868K</td>
<td>-102</td>
<td>26.870</td>
<td>5.84</td>
<td>Dominates</td>
</tr>
<tr>
<td>Screen with anti-TPO Ab</td>
<td>1080</td>
<td>212</td>
<td>26.894</td>
<td>5.11</td>
<td>15 182</td>
</tr>
</tbody>
</table>

Dominates, the ‘screen with TSH’ strategy is less costly and more effective than the ‘no screen’ strategy and is therefore said to ‘dominate’ the no-screening strategy; QALY, quality-adjusted life year; C-E, cost-effectiveness; TSH, thyroid stimulating hormone; anti-TPO Ab, anti-thyroid peroxidase antibody.

### Table 4 Sensitivity analysis results for other select variables.

<table>
<thead>
<tr>
<th>Sensitivity analysis scenario</th>
<th>TSH versus no screening</th>
<th>Anti-TPO Ab screening versus no screening</th>
<th>Anti-TPO Ab screening versus TSH screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base-case analysis</td>
<td>TSH dominates</td>
<td>3637</td>
<td>15 182</td>
</tr>
<tr>
<td>No adverse effect of untreated maternal SH or OH on child IQ</td>
<td></td>
<td>4956</td>
<td>7769</td>
</tr>
<tr>
<td>No improvement of child IQ with levothyroxine treatment of OH and SH mothers during pregnancy</td>
<td>TSH dominates</td>
<td>5029</td>
<td>7566</td>
</tr>
<tr>
<td>Screening and diagnostic test costs doubled</td>
<td>TSH dominates</td>
<td>8185</td>
<td>21 550</td>
</tr>
<tr>
<td>Anti-TPO Ab ($40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH ($50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FT4 ($25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age (base case: 25 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 years</td>
<td>TSH dominates</td>
<td>5242</td>
<td>23 999</td>
</tr>
<tr>
<td>25 years</td>
<td>TSH dominates</td>
<td>3642</td>
<td>15 182</td>
</tr>
<tr>
<td>35 years</td>
<td>TSH dominates</td>
<td>2995</td>
<td>13 186</td>
</tr>
<tr>
<td>45 years</td>
<td>TSH dominates</td>
<td>2270</td>
<td>11 613</td>
</tr>
<tr>
<td>Annual probability of diagnosing hypothyroidism in unscreened or those with a negative screen (base case: 25%)</td>
<td>TSH dominates</td>
<td>1759</td>
<td>6102</td>
</tr>
<tr>
<td>10%</td>
<td>TSH dominates</td>
<td>9983</td>
<td>53 922</td>
</tr>
<tr>
<td>50%</td>
<td>TSH dominates</td>
<td>9983</td>
<td>53 922</td>
</tr>
<tr>
<td>80%</td>
<td>TSH dominates</td>
<td>27 234</td>
<td>TSH dominates</td>
</tr>
</tbody>
</table>

Dominates, the ‘screen with TSH’ strategy is less costly and more effective than the ‘no screen’ strategy and is therefore said to ‘dominate’ the no-screening strategy; TSH, thyroid stimulating hormone; anti-TPO Ab, anti-thyroid peroxidase antibody; QALY, quality-adjusted life year; SH, subclinical hypothyroidism; OH, overt hypothyroidism; IQ, intelligence quotient; FT4, free thyroxine.

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We further explored the effects of various low IQ variables on the cost-effectiveness of screening by focusing on subclinically hypothyroid women, who constitute >85% of the subjects with elevated TSH. Screening using anti-TPO antibody remained cost-effective compared with TSH screening as the probability of child IQ %85 in untreated women increased, the number of IQ points lost increased, or the cost per unit IQ increased (Table 5), although the cost-effectiveness decreased as the number of IQ points lost increases (Table 5). Screening with anti-TPO antibody became cost-saving compared with no screening if we assumed a probability of IQ %85 of 0.19 (base case: 0.095) and an IQ loss of 6.93 points or greater (base case: 4.2) in children of untreated mothers (data not shown).

Discussion

Screening pregnant women in the first trimester with TSH is cost-saving compared with no screening, while screening with anti-TPO antibodies is cost-effective compared with TSH screening, at $15 182/QALY. This compares favorably with the cost-effectiveness of other well accepted screening practices (Table 6). The increase in quality-adjusted life expectancy by screening in our study (5.84 days) is similar to that estimated in other studies for screening the general population for HIV (4.70 days)(40), 40-year-old asymptomatic women for hypertension (4 days) (41), and adult women over 35 years for TSH (6 days) (16). Screening using TSH continued to dominate the no-screening strategy and anti-TPO antibody screening continued to be the most favorable screening strategy economically in sensitivity analyses. Importantly, because of its other benefits, screening remained highly cost-effective even in scenarios where we assumed no adverse effects of maternal hypothyroidism on child IQ or no efficacy of levothyroxine in improving IQ outcomes.

This is the first cost-effectiveness analysis of screening pregnant women for autoimmune thyroid disease. The increased benefits derived from improving gestational

Table 5 Multi-way sensitivity analysis of different low IQ variables: effects of varying the probability of low IQ and IQ point loss in children of women with untreated SH, and the cost of low IQ on the incremental cost-effectiveness of anti-TPO Ab versus TSH screening.

<table>
<thead>
<tr>
<th>Incremental cost-effectiveness ratio ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQ point loss in children of women with SH</td>
</tr>
<tr>
<td>Prob IQ %85 in children of women with untreated SH: 0.05</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>0.2</td>
</tr>
<tr>
<td>0.5</td>
</tr>
<tr>
<td>Prob IQ %85 in children of women with untreated SH: 0.095</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>0.2</td>
</tr>
<tr>
<td>0.5</td>
</tr>
<tr>
<td>Prob IQ %85 in children of women with untreated SH: 0.19</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>0.2</td>
</tr>
<tr>
<td>0.5</td>
</tr>
</tbody>
</table>

Base-case conditions are denoted in bold. *Anti-TPO Ab screening dominates no screening under these conditions (i.e. is less costly and more effective). Anti-TPO Ab, anti-thyroid peroxidase antibody; TSH, thyroid stimulating hormone; IQ, intelligence quotient; QALY, quality-adjusted life year; Prob, probability; SH, subclinical hypothyroidism.

Table 6 Cost-effectiveness of other well established screening practices compared with screening for thyroid disease, adjusted to 2004 US dollars.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Incremental cost-effectiveness ratio $/QALY</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening practice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension screening in asymptomatic 40-year-old women</td>
<td>33 015</td>
<td>(41)</td>
</tr>
<tr>
<td>Hypertension screening in asymptomatic 40-year-old men</td>
<td>23 152</td>
<td>(41)</td>
</tr>
<tr>
<td>Mammography every 2 years in 45- to 69-year-old women</td>
<td>18 170</td>
<td>(53)</td>
</tr>
<tr>
<td>Fecal occult blood screening in 50-year-old women</td>
<td>25 520</td>
<td>(54)</td>
</tr>
<tr>
<td>Fecal occult blood screening in 50-year-old men</td>
<td>37 62</td>
<td>(54)</td>
</tr>
<tr>
<td>Screening for thyroid disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH screening every 5 years in 35- to 75-year-old women</td>
<td>10 956</td>
<td>(16)</td>
</tr>
<tr>
<td>TSH screening every 5 years in 35- to 75-year-old men</td>
<td>26 841</td>
<td>(16)</td>
</tr>
<tr>
<td>Anti-TPO antibody screening compared with TSH screening in first trimester of pregnancy in women of 15–45 years old</td>
<td>15 182</td>
<td>Current analysis</td>
</tr>
</tbody>
</table>

QALY, quality-adjusted life year; TSH, thyroid stimulating hormone; TPO, thyroid peroxidase.
hypertension, correctly diagnosing PPT, improving intellectual ability of children of affected mothers, and more promptly diagnosing overt thyroid disease when it develops, make screening in pregnant women economically favorable. Screening using TSH results in both reduced costs and improved quality of life compared with no screening, making the case for TSH screening very strong. Further research regarding the potential benefits of treatment of the anti-TPO antibody-positive women, regardless of TSH level, would be very valuable in more accurately assessing the cost-effectiveness of the anti-TPO antibody screening strategy.

Our study has several important strengths. The testing and treatment strategy is comprehensive, including all appropriate physician and laboratory follow-up. We take into account subject compliance and transition to compliance in non-compliant subjects. Finally, the base-case analysis is based on very conservative estimation of parameters, potentially resulting in underestimation of cost-effectiveness. We have also not included some other potential benefits of screening and treatment. The risk of developing permanent overt hypothyroidism has been shown to be even higher in the subset of anti-TPO antibody-positive women who experience PPT, compared with women who do not experience PPT (42). Furthermore, a recent study of euthyroid pregnant women with autoimmune thyroid disease demonstrated that levothyroxine treatment significantly reduced miscarriage rates (43). Such additional benefits of screening would make screening for autoimmune thyroid disease even more cost-effective than demonstrated in the current calculation.

A limitation of our analysis is that the probabilities of low IQ in children of treated or untreated mothers are based on retrospective studies, which can be flawed if one fails to control for important potential confounders. The Haddow study has been criticized for the fact that the parental IQ was not directly measured. However, we believe that every effort was made to control for parental IQ in that study both by matching subjects to controls according to number of years of education in the design phase, and by taking into account small differences that were noted in the socioeconomic status of the different study groups, in the analysis phase of the study (9). We also took this into account in our analysis using the socioeconomic status-adjusted difference in IQ, rather than the total IQ difference noted. Unfortunately, there are no prospective studies yet regarding the effects of treated versus untreated maternal hypothyroidism on child IQ. Two randomized controlled trials are underway to address the effect of treatment of hypothyroid women on the IQ of their children: one in the United Kingdom (44) and one in the United States (45). We await those results with much anticipation; however, the studies are still in the early enrollment phase and data on child IQ at 5 years of age are not going to be available in the near future. In the meantime, recent basic science discoveries strongly support a role of thyroid hormone in fetal neurodevelopment (46–48). In addition, even though randomized controlled trials on the effect of levothyroxine in reversing neurodevelopmental abnormalities are not yet available, this has been clearly demonstrated in a recent animal study (46) and is further supported by three observational clinical studies, where treatment of hypothyroid mothers with levothyroxine (9, 10) or spontaneous increase of FT4 in mothers with hypothyroxinaemia in early pregnancy (12) resulted in normal child IQ.

Even though there is no agreement in current position statements from the various medical societies regarding universal screening of pregnant women for autoimmune thyroid disease, all societies support aggressive case-finding. Screening only high-risk women, however, would fail to diagnose one-third of women with high TSH (49). The current study demonstrates that screening all pregnant women for autoimmune thyroid disease is a good use of our healthcare dollars.

In conclusion, screening pregnant women with TSH in the first trimester of pregnancy is cost-saving compared with no screening, while screening using anti-TPO antibodies is an economically favorable screening strategy. The medical community should strongly consider screening pregnant women for autoimmune thyroid disease using either anti-TPO antibodies or TSH at the first prenatal visit.

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