Universal Screening *Versus* Case Finding for Detection and Treatment of Thyroid Hormonal Dysfunction During Pregnancy

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Context: Thyroid disease during pregnancy has been associated with multiple adverse outcomes. Whether all women should be screened for thyroid disease during pregnancy is controversial.

Objective: The objective of the study was to determine whether treatment of thyroid disease during pregnancy decreases the incidence of adverse outcomes and compare the ability of universal screening *vs.* case finding in detecting thyroid dysfunction.

Design: Women in the first trimester were randomly assigned to the universal screening group or case-finding group. Women in both groups were stratified as high risk or low risk based on risk factors for thyroid disease. All women in the universal screening group, and high-risk women in the case-finding group, were immediately tested for free T_4, TSH, and thyroid peroxidase antibody. Low-risk women in the case-finding group had their sera tested postpartum.

Setting: The study was conducted at two ambulatory clinics of community hospitals in southern Italy.

Patients: A total of 4562 women were randomly assigned to the universal screening or case-finding group.

Intervention: Intervention included levothyroxine in women with a TSH above 2.5 mIU/liter in TPO antibody-positive women and antithyroid medication in women with a undetectable TSH and elevated free T_4.

Main Outcome Measure: Total number of adverse obstetrical and neonatal outcomes was measured.

Results: No significant differences were seen in adverse outcomes between the case-finding and universal screening groups. Adverse outcomes were less likely to occur among low-risk women in the screening group than those in the case-finding group.

Conclusions: Universal screening compared with case finding did not result in a decrease in adverse outcomes. Treatment of hypothyroidism or hyperthyroidism identified by screening a low-risk group was associated with a lower rate of adverse outcomes. **(*J Clin Endocrinol Metab* 95: 1699–1707, 2010)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2009-2009 Received September 21, 2009. Accepted January 12, 2010.
First Published Online February 3, 2010

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Abbreviations: CI, Confidence interval; fT4, free T_4; OR, odds ratio; TPO-Ab, thyroid peroxidase antibody.

Thyroid disease has multiple deleterious impacts on pregnancy, the postpartum, and the developing fetus. Complications include miscarriage (1–5), decreased intelligence quotient (6, 7), visual-motor deficiencies in the offspring (8), preterm delivery (9, 10), and postpartum thyroiditis (11–13). Screening for thyroid disease during pregnancy is controversial with strong proponents on both sides (14–16). Central to the debate is the impact of treating pregnant women with thyroid abnormalities in regard to decreasing maternal and fetal complications. Negro *et al.* (17) demonstrated a significant decrease in both miscarriage and preterm delivery in euthyroid antibody positive women treated with levothyroxine.

In 2007 The Endocrine Society Clinical Practice Guideline on the Management of Thyroid Dysfunction during Pregnancy and Postpartum was published. The guideline recommended case finding among pregnant women identified as high risk for thyroid disease (18). Shortly after publication, Vaidya *et al.* (19) demonstrated that screening only high-risk pregnant women failed to detect 30% of hypothyroid and 69% of hyperthyroid women. The present study was designed to assess the impact of treating thyroid dysfunction during pregnancy on the incidence of maternal and neonatal complications under two conditions: universal screening and case finding.

Subjects and Methods

Women were recruited from the Division of Obstetrics and Gynecology, Vito Fazzi Hospital (Lecce, Italy) and the Division of Obstetrics and Gynecology, Casa di Cura Salus (Brindisi, Italy) from March 2005 through February 2008. The study was completed in December 2008. Eligibility criteria included spontaneously pregnant women with singletons within the first 11 wk of gestation and no history of thyroid disease. Four thousand six hundred fifty-seven Caucasian women in their first trimester of pregnancy participated (Fig. 1), with 95 women excluded due to a history of thyroid disease. Accordingly 4562 women were randomized. The study was approved by the ethical committees of both institutions and written informed consent was obtained.

All women had a blood sample obtained at the first obstetrical visit. A computer program randomly assigned patients (stratified by center) to either the case-finding (n = 2282; 50%) or universal screening (n = 2280; 50%) group. Two computer-generated concealed randomization schedules, using permuted blocks of four, were created. When an eligible patient enrolled, the research assistant used sealed opaque envelopes to allocate the patient to the next sequential randomization number. The obstetrician obtained information regarding risk factors. Women were considered high risk if they had any one of the following risk factors: family history for autoimmune thyroid disease, presence of goiter, signs and symptoms suggestive for thyroid dysfunction, personal history for type 1 diabetes or other autoimmune disease, history of neck irradiation, previous miscarriages, or preterm deliveries. The obstetricians were not aware to which group (case finding or universal screening) the patients belonged. These

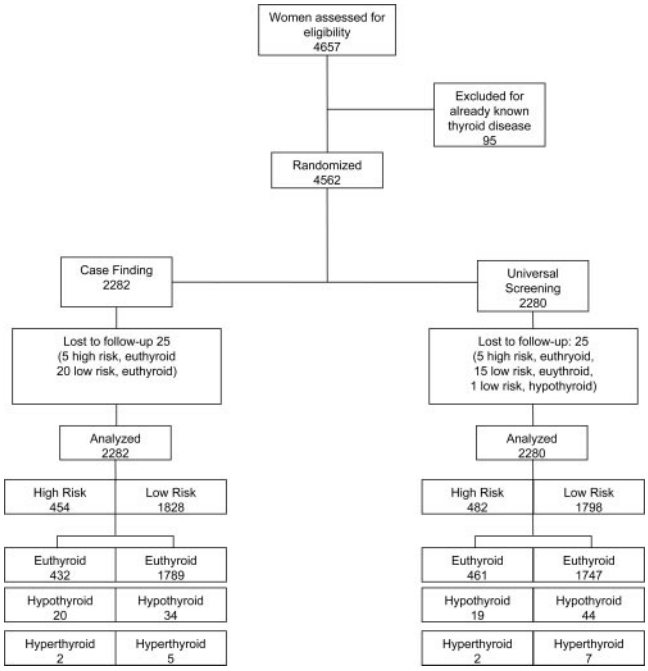

FIG. 1. Flow diagram of the study protocol, number of patients assigned to each group, and thyroid status of the women in each group. Thyroid status of low-risk women in the case-finding group is assessed based on frozen sera analyzed postpartum.

risk factors were all included in The Endocrine Society's guidelines for screening high-risk women (18). All women in the universal screening group, and high-risk women in the case-finding group, had their sera immediately tested for TSH, free T_4 (fT4), and thyroid peroxidase antibody (TPO-Ab). Low-risk women in the case-finding group had their sera frozen at −70 C and assayed postpartum.

Women were classified as hypothyroid, hyperthyroid, or euthyroid based on the following: hypothyroid-TSH greater than 2.5 mIU/liter in TPO-Ab+ women; hyperthyroid-undetectable TSH concentration and elevated fT4. Women classified as hypothyroid or hyperthyroid were referred to the endocrinologist (R.N.), by the 12th gestational week. The endocrinologist was blinded to group assignment. Euthyroid patients, without antibodies, had no further thyroid function testing performed. In euthyroid TPO-Ab-positive women, thyroid function was tested in both the second and third trimesters.

In women identified as hypothyroid at initial screening, levothyroxine was initiated and titrated during the first trimester to maintain the TSH level less than 2.5 mIU/liter. During the second and third trimesters, levothyroxine was titrated to keep the TSH less than 3.0 mIU/liter. Treatment of hyperthyroid women was based on the endocrinologist's clinical judgment. In hyperthyroid patients, methimazole or propylthiouracil was administered, when necessary, to keep fT4 concentrations around the upper limit of normal and avoid undetectable TSH values. All patients with thyroid dysfunction had thyroid function tests performed at least once during the second and third trimesters.

After randomization, 46 women did not perform all the tests or delivered in other hospitals and therefore were lost to follow-up. The 46 women were evenly divided between the two arms of the study and did not differ significantly in the proportion of high *vs.* low risk compared with the subjects not lost to follow-up; 10 of them (five in each group) were high risk, whereas the remain-

der (20 in the case finding group and 16 in the universal screening group) were low risk.

Obstetrical and neonatal complications (see below) had been established before the initiation of the study and were collected by the obstetricians and neonatologists, who were not aware of which group the patient belonged to.

Assays

Serum TSH and fT4 were measured using a third-generation electrochemiluminescence immunoassay (Roche, Basel, Switzerland). The reference values were 0.27–4.2 mIU/liter for TSH and 9.3–18.0 ng/liter (12–33.5 pmol/liter) for fT4. Intraassay and interassay coefficients of variation were 2.5 and 9.3% for TSH and 4.5 and 7.1%, respectively, for fT4. TPO-Ab titers were determined using a RIA kit (Brahms Diagnostica, Berlin, Germany). The reference range was 0–100 kIU/liter (positive >100 kIU/liter).

Statistical analyses

The primary outcome for the study was obstetrical and neonatal complications obtained from a review of medical records. Because there were no extant prospective trials, it was concluded that all adverse potential outcomes should be evaluated. Each adverse outcome evaluated had been associated with thyroid disease during pregnancy. Adverse outcomes were prospectively defined as miscarriage (4, 5, 20), hypertension (21), preeclampsia (22, 23), gestational diabetes (22, 24), placental abruption (9), thyroid storm, caesarean delivery (22), congestive heart failure (25), preterm labor (4, 9, 22, 25, 26), respiratory distress (9), neonatal intensive care unit admission (9), low birth weight (≤2500 g) (23), high birth weight (>4000 g) (26), preterm (34–37 wk) or very preterm (<34 wk) delivery (4, 9, 22–25), Apgar score 3 or less at 5 min (24), perinatal/neonatal death (4, 20, 25), or other (intraventricular hemorrhage, umbilical artery blood pH <7.0, necrotizing enterocolitis, or major malformations). Detection and adverse outcome rates for hypothyroid, hyperthyroid, and euthyroid TPO-Ab+ women were tabulated for the women in the case-finding and universal screening groups, with confidence intervals constructed based on a Poisson distribution. Because high-risk women are treated identically across groups, we also conducted specific planned comparisons of the two low-risk cohorts (case finding and universal screening) for which management differed.

Rather than conduct analyses on each adverse outcome separately (which would have required a correction for multiple comparisons and presented concerns related to clustering of outcomes and limited power to compare rare outcomes), we treated the various adverse outcomes as if each were an occurrence of an interchangeable adverse outcome event, and we conducted both per-woman and clustered outcome analyses. On a per-woman basis, we compared the number of women in each group who suffered at least one adverse outcome event to test the hypothesis that universal screening would result in more women with no adverse outcomes. On a clustered outcome basis, a mixed-effects (random intercept) logistic regression model was fitted to characterize the strength of association between predictor variables (including screening *vs.* case finding group, risk classification, thyroid function, the interactions between group, risk classification, and thyroid function, age, previous babies, and smoking status) and (any) adverse outcomes, controlling for the clustering of outcomes within women using an unstructured covariance matrix. When interactions were present, tests of simple effects (*i.e.* the effect of one predictor at a fixed level of the other predictor in the interaction) were also conducted.

This analysis approach tested the hypothesis that universal screening would be associated with a lower rate of adverse outcome events within women (controlling for correlations between outcomes likely to co-occur in women), that abnormal thyroid function would be associated with a higher rate of adverse outcome events, and that the impact of universal screening would depend on risk classification and abnormal thyroid function (*e.g.* that universal screening would be beneficial only when low-risk women were found to by hypo- or hyperthyroid and subsequently treated). Analysis was conducted on an intention-to-treat basis; women lost to follow-up were assumed to have no adverse outcomes, regardless of group assignment in the main analysis. (This assumption was varied in two secondary analyses in which: 1) all women lost to follow-up were assumed to have had an adverse outcome, and 2) women lost to follow-up in the case-finding group were assumed to have no adverse outcomes, whereas women lost to follow-up in the universal screening group were assumed to have adverse outcomes imputed at the same rate as women of comparable age, smoking status, number of previous births, and thyroid status in the overall study. Because neither of these analyses yielded substantially different results, we limit ourselves to the analysis described in the text.) Data analysis was performed using SPSS 15 (SPSS, Chicago, IL) and SAS 9.1 PROC GLIMMIX (SAS Institute, Cary, NC). Significance level for all analyses was less than 0.05 and all testing was two sided.

Results

In the case-finding group, 454 (19.9%) met the criteria for high risk, whereas 1828 (80.1%) were low risk. In the universal screening group, 482 (21.1%) would have been classified as high risk and 1798 (78.9%) as low risk. This difference was not significant [χ^2 (1) = 1.03, P = 0.31].

Thyroid status

Table 1 displays the thyroid status of women in the study, classified by study group (case finding or universal screening) and risk classification (high risk or low risk). In the case-finding high-risk group, 432 (95.2%) were euthyroid, 20 (4.4%) hypothyroid, and two (0.4%) hyperthyroid. In the case-finding low risk group, whose serum samples were assayed postpartum, 1789 (97.9%) were euthyroid, 34 (1.9%) hypothyroid, and five (0.2%) hyperthyroid; low-risk women in the case-finding group were more likely to be euthyroid than high-risk women in this group [χ^2 (2) = 10.5, P = 0.005]. The 39 hypothyroid and hyperthyroid women in the case-finding low-risk group were thus not diagnosed or treated. In the universal screening group, 2208 (96.8%) were euthyroid, 63 (2.8%) hypothyroid, and nine (0.4%) hyperthyroid. Because all women in this group were screened, all hypothyroid and hyperthyroid women were treated. There was no

TABLE 1. Thyroid status of all women enrolled in the study

	Case finding Risk classification			Universal screening Risk classification		
	High	Low	Total	High	Low	Total
Euthyroid without antibodies (%)	407 (89.7%)	1684 (92.1%)	2091 (91.6%)	434 (90%)	1642 (91.3%)	2076 (91%)
Euthyroid with antibodies (%)	25 (5.5%)	105 (5.7%)	130 (5.7%)	27 (5.6%)	105 (5.8%)	132 (5.8%)
Hypothyroid (%)	20 (4.4%)	34 (1.9%)	54 (2.4%)	19 (4%)	44 (2.5%)	63 (2.8%)
Hyperthyroid (%)	2 (0.4%)	5 (0.3%)	7 (0.3%)	2 (0.4%)	7 (0.4%)	9 (0.4%)
Total	454	1828	2282	482	1798	2280

Thyroid hormonal and antibody status of all women enrolled in the study is classified by study group and risk classification. Thyroid status of low-risk women in the case-finding group is assessed based on frozen sera analyzed postpartum. Percentages are presented.

difference in the distribution of thyroid function by study group assignment [χ^2 (3) = 0.87, P = 0.83]. Table 1 demonstrates that approximately 5% of euthyroid women in the universal screening and case-finding groups were thyroid antibody positive. A higher percentage of thyroid antibody positivity in euthyroid women was detected in the earlier Negro study because Negro defined euthyroidism in that study as a TSH less than 4.2, whereas the present study defined euthyroidism as a TSH less than 2.5 (17).

None of the antibody-negative women had a TSH level above 5.0. The number of antibody-negative women who had a TSH greater than 2.5 (but <5.0) were as follows: in case finding high risk, 68 of 427 (15.9%); case finding low risk, 282 of 1769 (15.9%); universal screening high risk, 50 of 456 (11%); and universal screening low risk, 242 of 1732 (14%). Women who were euthyroid antibody positive in the first trimester and subsequently developed an elevated TSH in the second or third trimester requiring treatment are as follows: case-finding high risk, three of 25 (12%); universal screening high risk, three of 27 (11.1%); and universal screening low risk, 10 of 105 (9.5%). Among hypothyroid patients treated with thyroxine, the number of those who achieved TSH less than 3.0 in the second trimester was: case-finding high risk, 18 of 20 (90%); universal screening high risk, 14 of 19 (73.7%); and universal screening low risk, 43 of 44 (97.7%). The number of those who achieved TSH less than 3.0 in the third trimester was: case finding high risk, 19 of 20 (95%); universal screening high risk, 18 of 19 (94.7%); and universal screening low risk, 44 of 44 (100%). None of the hypothyroid women treated with thyroxine displayed TSH values higher than 5.0 during the second or third trimester. Sixteen patients were diagnosed with hyperthyroidism, of which 11 were investigated (two case finding high risk, two universal screening high risk, seven universal screening low risk). Of the 11 patients, one woman had an autonomously functioning nodule, three women had gestational transient thyrotoxicosis, and seven women were diagnosed with Graves' disease. Four of the 11 patients were treated with antithyroid drugs.

Relationship between risk classification and thyroid status

Examining women across study groups, risk status was associated with thyroid status. Specifically there were relatively fewer hypothyroid women and relatively more euthyroid women without antibodies among women who would be classified as low risk than among women who would be classified as high risk [χ^2 (3) = 12.8, P = 0.005]. The relationship between risk classification and hypothyroidism was also significant in the case-finding group, in which 1.9% of low-risk women and 4.5% of high-risk women were hypothyroid [χ^2 (1) = 10.2, P = 0.001] but not did not reach significance in the universal screening group, in which 2.4% of low-risk women and 4.0% of high-risk women were hypothyroid [χ^2 (1) = 3.48, P = 0.062].

Tables 2 and 3 present demographic data and thyroid status of the women enrolled in the study, grouped by the two randomized groups, and then by the four analyzed cohorts. There were no significant demographic differences between the two randomized groups. The probability of abnormal thyroid function (hyperthyroid or hypothyroid) in a 29-year old woman was 2.8%. Increasing age was mildly associated with increasing probability of abnormal thyroid function [OR for each additional year of age 1.05, 95% CI (1.02, 1.09)].

Adverse outcomes

Individual women experienced from no to eight adverse outcomes; across groups, 59.5% of women experienced no adverse outcomes, 25.6% experienced one adverse outcome, 6.6% experienced two adverse outcomes, 4.8% experienced three adverse outcomes, and 3.5% experienced four or more adverse outcomes. Table 4 presents the number of women who experienced at least one adverse outcome in the case-finding group (930) and in the universal

TABLE 2. Clinical characteristics of patients

	Case finding (n = 2282)	Universal screening (n = 2280)
Age (yr)	28.9 ± 5	28.7 ± 5
Previous babies (%)	1619 (70.9%)	1595 (70%)
Smoking (%)	120 (5.3%)	128 (5.6%)
First gynecological visit (wk)	8.8 ± 1.6	8.8 ± 1.5
TSH first trimester (mIU/liter)	1.4 ± 1.3	1.4 ± 1.4
fT4 first trimester (pmol/liter)	11.9 ± 2.4	11.9 ± 2.5
TPO-Ab+ (%)	186 (8.2%)	198 (8.7%)
Family history of thyroid disease (%)	292 (12.8%)	283 (12.4%)
Goiter (%)	20 (0.9%)	23 (1%)
Symptoms of hypo- or hyperthyroidism (%)	167 (7.3%)	179 (7.8%)
Type 1 diabetes/autoimmune disease (%)	22 (0.9%)	25 (1%)
Irradiation (%)	2 (0.09%)	0
Previous miscarriage/preterm deliveries (%)	30 (1.3%)	36 (1.6%)

Included are demographic information, thyroid function tests, and risk factors at each point of the study for all women who were enrolled. Data are expressed as mean ± SD. Thyroid results of low-risk women in the case-finding group is based on frozen sera analyzed postpartum.

screening group (900).There was no significant difference between the total number of adverse outcomes in the case-finding group (1545) and the universal screening group (1559) (Table 5) [χ^2 (1) = 0.16, P = 0.69].

The mixed logistic regression model revealed that although women in the screening group did not have fewer adverse outcomes overall, there was a significant interaction between trial arm and thyroid status [F(2,77554) = 4.26, P = 0.014]. Considering only the cohorts of low-risk women (who are screened under universal screening but not under case finding), the mixed logistic model revealed that adverse outcomes were less likely to occur among women in the universal screening group than women in the case-finding group [odds ratio (OR) 0.43, 95% confidence interval (CI; 0.26, 0.70)]. For a nonsmoking, nulliparous, 29-yr-old woman in the low-risk universal screening group, the absolute probability of an adverse event was 0.044 (0.031, 0.063). For a nonsmoking, nulliparous, 29-yr-old woman in the low-risk case-finding group, the absolute probability of an adverse event was 0.098 (0.071, 0.133). This effect was driven primarily by adverse outcomes experienced by low-risk hypothyroid women [simple effect F(1,61641) = 8.06, P = 0.005] and low-risk hyperthyroid women [simple effect F(1,61641) = 6.24, P = 0.013] who received treatment in the universal screening group but not in the case-finding group; there was no difference in adverse outcomes experienced by low-risk euthyroid women between the universal screening and case-finding groups [simple effect F(1,61641) = 0.99, P = 0.32].

The mixed logistic regression model also found relationships between adverse outcomes and other characteristics of low-risk women. Age [in years; OR 1.09, 95% CI (1.08, 1.10)], number of previous births [OR 1.51, 95% CI (1.35,1.69)], and smoking [OR 1.71, 95% CI (1.44, 2.03)] were all positively associated with increased risk of adverse outcomes. These factors represent general risk factors for adverse outcomes in pregnancy, independent of thyroid function.

In the high-risk women, there was no difference in adverse outcomes between the case-finding and universal screening arms [OR 0.60, 95% CI (0.26, 1.39)]. Absolute probabilities of adverse events were 0.038 (0.020, 0.073) and 0.062 (0.037, 0.103), for universal screening and case-finding arms, respectively. That is, the probability of

TABLE 3. Clinical characteristics of patients

	Case finding (n = 2282)		Universal screening (n = 2280)	
	High risk (n = 454)	Low risk (n = 1808)	High risk (n = 482)	Low risk (n = 1732)
Age (yr)	29 ± 5	28.8 ± 4.9	28.7 ± 5.1	28.7 ± 4.9
Previous babies (n)	323 (71.1%)	1296 (71.7%)	341 (70.7%)	1254 (72.4%)
Smoking (%)	24 (5.3%)	96 (5.3%)	27 (5.6%)	101 (5.8%)
First gynecological visit (wk)	8.8 ± 1.7	8.8 ± 1.6	8.8 ± 1.5	8.8 ± 1.5
TSH first trimester (mIU/liter)	1.5 ± 1.5	1.4 ± 1.2	1.4 ± 1.5	1.4 ± 1.4
fT4 first trimester (pmol/liter)	11.8 ± 2.6	11.9 ± 2.4	11.8 ± 2.5	11.9 ± 2.5
TPO-Ab+ (%)	45 (9.9%)	141 (7.8%)	47 (9.8%)	151 (8.7%)
Family history of thyroid disease (%)	292 (64.3%)	0	283 (58.7%)	0
Goiter (%)	20 (4.4%)	0	23 (84.8%)	0
Symptoms of hypo- or hyperthyroidism (%)	167 (36.8%)	0	179 (37.1%)	0
Type 1 diabetes/autoimmune disease (%)	22 (4.9%)	0	25 (5.2%)	0
Irradiation (%)	2 (0.5%)	0	0	0
Previous miscarriage/preterm deliveries (%)	30 (6.6%)	0	36 (7.5%)	0

Included are demographic information, thyroid function tests, and risk factors at each point of the study for all women who were enrolled. Data are expressed as mean ± SD. Thyroid results of low-risk women in the case-finding group is based on frozen sera analyzed postpartum.

TABLE 4. Number of women experiencing at least one adverse outcome

	Case finding (total n = 2257)			Universal screening (total n = 2259)		
	High risk	Low risk	Total	High risk	Low risk	Total
Euthyroid without antibodies	166 (41.3%)	658 (39.5%)	824 (39.9%)	179 (41.7%)	637 (39.1%)	816 (39.7%)
Euthyroid with antibodies	10 (40%)	49 (47.1%)	59 (45.7%)	13 (48.1%)	45 (42.9%)	58 (43.9%)
Hypothyroid	9 (45%)	31 (91.2%)	40 (74.1%)	6 (31.6%)	15 (34.9%)	21 (33.9%)
Hyperthyroid	2 (100%)	5 (100%)	7 (100%)	1 (50%)	4 (57.1%)	5 (55.5%)
Total	187 (41.7%)	743 (41.1%)	930 (41.2%)	199 (41.7%)	701 (40.5%)	900 (39.8%)

Presented by study group, risk classification, thyroid status, and number and percentage of women experiencing at least one adverse outcome among women for whom adverse outcomes could be assessed (n = 2257 for case-finding group and n = 2259 for university screening group). Thyroid status of low-risk women in the case-finding group is assessed based on frozen sera analyzed postpartum.

an adverse event was not significantly different for the high-risk universal screening, high-risk case-finding, or low-risk universal screening groups but was higher for the low-risk case-finding group (due to events associated with undetected and untreated hypothyroidism and hyperthyroidism) (Fig. 2).

Benefit of treatment for low-risk hypo- and hyperthyroid women

To describe the benefit of treating low-risk hypo- or hyperthyroid women, we compared the likelihood of at least one adverse outcome for the low-risk women with hypo- or hyperthyroid in the case-finding (untreated) group (36 of 39 women had at least one adverse outcome) with that for the low-risk women with hypo- or hyperthyroid in the universal screening (treated) group (19 of 51 women had at least one adverse outcome). For these women, treatment was of significant benefit; the inferred number needed to treat to prevent one woman from experiencing any adverse outcome was 1.8 (95% CI 1.4, 2.5).

Benefit of screening for low-risk women

In this study, screening 1798 low-risk women identified 51 women with abnormal thyroid function who were then treated. Thus, the overall screening yield was 51 of 1798 [2.8%, 95% CI (2.1%, 3.7%)], excluding the value of identifying euthyroid women with thyroid antibodies. The number needed to screen to detect one hypothyroid or hyperthyroid woman among low-risk women was approximately 36 [95% CI (27, 48)].

To further characterize the benefit of screening low-risk women, we compared the likelihood of at least one adverse outcome for all low-risk women in the case-finding group (743 of 1828 low risk women had at least one adverse outcome) with that for the low-risk women in the universal screening group (701 of 1798 low risk women had at least one adverse outcome). Because many low-risk women with normal thyroid function had adverse outcomes in both groups, screening did not show a significant benefit; the number needed to screen to prevent one woman from having any adverse outcome was 60 (95% CI 21, ∞). However, the mixed-model results suggest that this is likely to be an underestimate of the true benefit of screening because some women may be identified, treated, and still experience some adverse outcomes but fewer than they would have experienced had they not been treated. Based on mixed-model results, screening low-risk women was associated with 2.48% fewer adverse events that would have been otherwise expected ($P = 0.012$), which corresponds to a inferred number needed to screen to prevent a single adverse outcome (but not all adverse outcomes) in a low-risk woman of approximately 40 yr.

Discussion

The present study is the first prospective randomized trial of case-finding *vs.* universal screening for thyroid dysfunction in pregnancy. Universal screening compared with case finding did not result in a decrease in adverse outcomes. Low-risk women in the universal screening group had fewer overall adverse outcomes than low-risk women in the case-finding group; moreover, more low-risk women in the universal screening group with abnormal thyroid function (who were treated) avoided any adverse outcome more often than low-risk women in the case-finding group with abnormal thyroid function (who were not detected and therefore not treated).

This study purposefully lacked a direct comparison of treatment and nontreatment among high-risk women. Nevertheless, the present study provides indirect evidence that treatment is also beneficial for high-risk women because these women are more likely to be hypothyroid, and treatment of (low risk) hypothyroid women was beneficial. Because no national organization recommends the screening of low-risk women for thyroid disease, we felt that screening low-risk women, and storing their sera until

TABLE 5. Adverse outcomes

	Case finding 2257 (50)						Universal screening 2259 (50)					
	High risk (n = 449) (19.9%)			Low risk (n = 1808) (80.1%)			High risk (n = 477) (21.1%)			Low risk (n = 1782) (78.9%)		
	Eu (n = 427) (95.1)	Hypo (n = 20) (4.4)	Hyper (n = 2) (0.4)	Eu (n = 1769) (97.8)	Hypo (n = 34) (1.9)	Hyper (n = 5) (0.3)	Eu (n = 456) (95.6)	Hypo (n = 19) (4.0)	Hyper (n = 2) (0.4)	Eu (n = 1732) (97.2)	Hypo (n = 43) (2.4)	Hyper (n = 7) (0.4)
Miscarriage	18 (4.2)	1 (5.0)	0 (0)	76 (4.3)	7 (20.6)	0 (0)	18 (3.9)	1 (5.3)	0 (0)	70 (4.0)	2 (4.7)	1 (14.3)
Gestational hypertension	24 (5.9)	1 (5.3)	1 (50)	91 (5.4)	3 (11.1)	2 (40)	24 (5.5)	1 (5.6)	0 (0)	97 (5.8)	1 (2.4)	1 (16.7)
Preeclampsia	10 (2.4)	1 (5.3)	0 (0)	70 (4.1)	2 (7.4)	1 (20)	17 (3.9)	0 (0)	0 (0)	54 (3.2)	2 (4.9)	0 (0)
Gestational diabetes	12 (2.9)	2 (10.5)	0 (0)	73 (4.3)	3 (11.1)	0 (0)	16 (3.7)	2 (11.1)	0 (0)	63 (3.8)	3 (7.3)	0 (0)
Placental abruption	2 (0.5)	0 (0)	0 (0)	5 (0.3)	1 (3.7)	1 (20)	1 (0.2)	0 (0)	0 (0)	6 (0.4)	0 (0)	0 (0)
Thyroid storm	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cesarean delivery	87 (21.3)	3 (15.8)	1 (50)	347 (20.5)	9 (33.3)	2 (40)	95 (21.7)	4 (22.2)	0 (0)	372 (22.4)	6 (14.6)	2 (33.3)
Congestive heart failure	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Preterm labor	27 (6.6)	1 (5.3)	0 (0)	85 (5.0)	4 (14.8)	1 (20)	27 (6.2)	1 (5.6)	0 (0)	107 (6.4)	3 (7.3)	1 (16.7)
Respiratory distress syndrome	7 (1.7)	1 (5.3)	1 (50)	22 (1.3)	1 (3.7)	2 (40)	5 (1.1)	0 (0)	1 (50)	20 (1.2)	1 (2.4)	0 (0)
Admission NICU	24 (5.9)	2 (10.5)	1 (50)	78 (4.6)	6 (22.2)	3 (60)	26 (5.9)	1 (5.6)	1 (50)	87 (5.2)	3 (7.3)	1 (16.7)
Birth weight 2500 g or greater	15 (3.7)	0 (0)	0 (0)	86 (5.1)	4 (14.8)	0 (0)	18 (4.1)	0 (0)	0 (0)	80 (4.8)	3 (7.3)	1 (16.7)
Birth weight greater than 4000 g	25 (6.1)	1 (5.3)	0 (0)	95 (5.6)	4 (14.8)	0 (0)	28 (6.4)	1 (5.6)	0 (0)	99 (6.0)	4 (9.8)	0 (0)
Very preterm (<34 wk)	7 (1.7)	0 (0)	0 (0)	32 (1.9)	3 (11.1)	1 (20)	8 (1.8)	0 (0)	0 (0)	31 (1.9)	2 (4.9)	1 (16.7)
Preterm delivery (34–37 wk)	23 (5.6)	1 (5.3)	0 (0)	78 (4.6)	2 (7.4)	1 (20)	18 (4.1)	1 (5.6)	0 (0)	85 (5.1)	1 (2.4)	0 (0)
Apgar score 5 min, 3 or less	2 (0.5)	0 (0)	0 (0)	11 (0.6)	1 (3.7)	1 (20)	2 (0.5)	0 (0)	0 (0)	8 (0.5)	0 (0)	0 (0)
Perinatal/neonatal death	3 (0.7)	0 (0)	0 (0)	10 (0.6)	0 (0)	0 (0)	3 (0.7)	0 (0)	0 (0)	9 (0.5)	0 (0)	0 (0)
Other complications	4 (1.0)	0 (0)	0 (0)	12 (0.7)	0 (0)	1 (20)	5 (1.1)	1 (5.6)	0 (0)	11 (0.7)	0 (0)	0 (0)
All complications (complications/patients)	1545 [0.68 (0.65, 0.71)]						1559 [0.69 (0.66, 0.73)]					
All complications (complications/patients)	308 [0.68 (0.61, 0.76)]			1237 [0.69 (0.65, 0.73)]			325 [0.68 (0.61, 0.76)]			1234 [0.69 (0.65, 0.73)]		
All complications (complications/patients)	290 (0.68)	14 (0.7)	4 (2)	1172 (0.66)	48 (1.4)	17 (3.4)	310 (0.68)	13 (0.68)	2 (1)	1197 (0.68)	30 (0.69)	7 (1)
All complications (complications/patients)	18 [0.82 (0.49, 1.30)]			65 [1.67 (1.29, 2.13)]			15 [0.71 (0.40, 1.17)]			37 [0.74 (0.52, 1.02)]		

Adverse outcomes are presented by study group, risk classification, and thyroid hormonal status among women for whom adverse outcomes could be assessed (n = 2257 for case finding group and n = 2259 for university screening group). Thyroid status of low-risk women in the case-finding group is assessed based on frozen sera analyzed postpartum. Confidence intervals for summaries of outcomes are based on a Poisson distribution. Numbers in parentheses represent percentage; in the last four rows, numbers in parentheses represent complications to patients ratio and 95% CI.

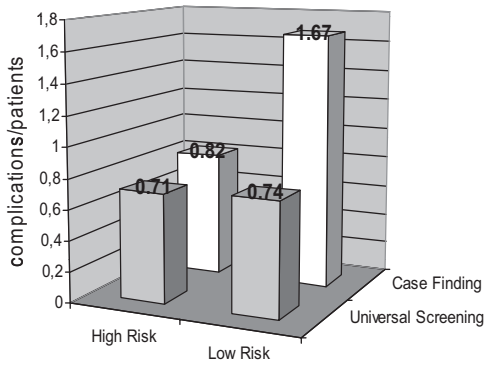

FIG. 2. Complications in patients with thyroid dysfunction, divided by study group (case finding or universal screening) and risk classification (high risk or low risk) (complications/patients: case finding high risk, 0.82; case finding low risk, 1.67; universal screening high risk, 0.71; universal screening low risk, 0.74).

after delivery, provided this group the accepted standard of care in the United States and therefore was ethically sound.

These results have direct bearing on the debate regarding whether all pregnant women should be screened. Thyroid, endocrine, and obstetric organizations have position statements on this issue (27–29). At present, no organization recommends universal screening. The recommendation of the international panel (18) for case finding was shown by Vaidya *et al.* (19), and presently confirmed, to fail to identify the majority of women with thyroid disorders. That universal screening was not beneficial in our study most probably reflects the fact that the majority of adverse effects were in the 95% of women who were euthyroid. Nevertheless, treating women identified with thyroid disorders (as identified in the low risk group) resulted in a significant decline in adverse outcomes. Due to the low frequency of thyroid hormonal abnormalities in the low-risk group, 36 women must be screened to identify one woman who requires therapy. Because the Number Needed to Treat is 1.8, this translates into screening 60 low-risk women to prevent one from experiencing any adverse outcome or screening 40 women to prevent a single adverse outcome.

The major limitation of this study is that all participants were Caucasian women from southern Italy, and as such, confirmatory studies would be beneficial. Another limitation was that a power analysis was not performed to determine sample size. Because women were not stratified by risk group before randomization, it is possible that risk classification could have been performed differently in each arm; thus, comparisons of low-risk women should be considered a cohort design rather than a randomized controlled trial. We believe this is a minor concern because risk classification was performed by the obstetricians without knowledge of study arm assignment. Finally, 46 of the 4562 women randomized (1%) were lost to follow-up.

In conclusion, the present manuscript demonstrates that whereas universal screening did not result in a decrease in adverse outcomes, treatment of identified thyroid hormonal abnormalities during pregnancy results in a significant decrease in adverse outcomes. Our study confirms that case finding fails to detect the majority of pregnant women with thyroid disease. A comprehensive cost-effectiveness analysis is required to resolve the debate of universal screening for thyroid disease in pregnancy.

Acknowledgments

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Disclosure Summary: A.S.-G. is a consultant for Abbott Pharmaceuticals. R.N., A.S., R.G., A.T., and T.M. have nothing to declare.

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