

Treating thyroid hormone abnormalities during pregnancy decreases adverse outcomes, but neither case finding nor universal thyroid screening decrease adverse outcomes in pregnancy.

Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. *J Clin Endocrinol Metab* 2010. doi:10.1210/jc.2009-2009

SUMMARY

BACKGROUND

Multiple adverse outcomes are associated with thyroid disease during pregnancy. The object of this study was to determine whether treatment of thyroid disease during pregnancy decreases the incidence of adverse outcomes and whether universal screening or case finding is better for detecting thyroid dysfunction in this setting.

METHODS

Women were recruited from the Division of Obstetrics and Gynecology in the Vito Fazzi Hospital and in the Casa Di Cura Salus in Italy. Women were recruited from March 2005 through February 2008, and the study was completed in December 2008. The study subjects were spontaneously pregnant women with a singleton pregnancy in the first 11 weeks of gestation without a history of thyroid disease. A total of 4562 white women in their first trimester of pregnancy were recruited into the study (Figure 1). On the first obstetrical visit, all had blood samples tested and were randomly assigned to either the case-finding group (n = 2282, 50%) or the universal-screening group (n = 2280, 50%). Women were considered to be at high risk if they had any of the following risk factors: family history of

autoimmune thyroid disease, goiter, signs and symptoms of thyroid disease, thyroid dysfunction, history of type 1 diabetes mellitus or other autoimmune disease, prior neck irradiation, or previous miscarriages or preterm deliveries. The obstetricians were not informed about which group the woman had been assigned to. The Endocrine Society guidelines for screening women at high risk were used in the universal screening group and in high-risk women in the case-finding group. Serums were immediately tested for thyrotropin (TSH), free thyroxine (FT₄) and thyroid peroxidase antibody (TPOAb). Frozen serums were stored at -70°C in the low-risk women and assayed post partum.

Women were classified as hypothyroid based on a serum TSH >2.5 mIU/L and TPOAb-positivity, as hyperthyroid on the basis of an undetectable serum TSH and an elevated FT₄, and as euthyroid if they were TPOAb-negative and were not further tested. During the second and third trimester, women who were TPOAb-positive with a TSH >2.5 mIU/L were treated with levothyroxine titrated to keep the TSH <3.0 mIU/L and antithyroid drug treatment of hyperthyroidism, based on the endocrinologist's clinical judgment. Thyroid function was tested in the second and third trimesters in euthyroid, TPOAb-positive women.

After randomization, 46 women did not perform all the tests or had delivery in other hospitals and were lost to follow-up. These women were evenly divided between the two arms of the study and did not differ significantly in the proportion of high- and low-risk individuals as compared with women not lost to follow-up. Ten of them (5 in each group) were at high-risk and the remaining women were at low-risk, 20 in the case-finding group and 16 in the universal screening group.

The statistical analysis tested the hypotheses that universal screening would be associated with a lower rate of adverse outcome events, 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. Analysis was conducted on an intention-to treat basis.

RESULTS

Thyroid Status (Figure 2)

In the case-finding high-risk group, 454 (19.9%) met the criteria for high risk, whereas 1828 (80.1%) were low risk (Figure 2). In the universal screening group, 482 (21.1%) would have been classified as high risk and 1798 (78.9%) as low risk, which was not a statistically significant difference (P = 0.31). In the case-finding high-risk group, 432 (95.2%) were euthyroid, 20 (4.4%) were hypothyroid and two (0.4%) were hyperthyroid. In the case-finding low-risk group, 1789 (97.9%) were euthyroid, 34 (1.9%) were hypothyroid, and 5 (0.2%) were hyperthyroid. Low-risk women in the case-finding group were more likely to

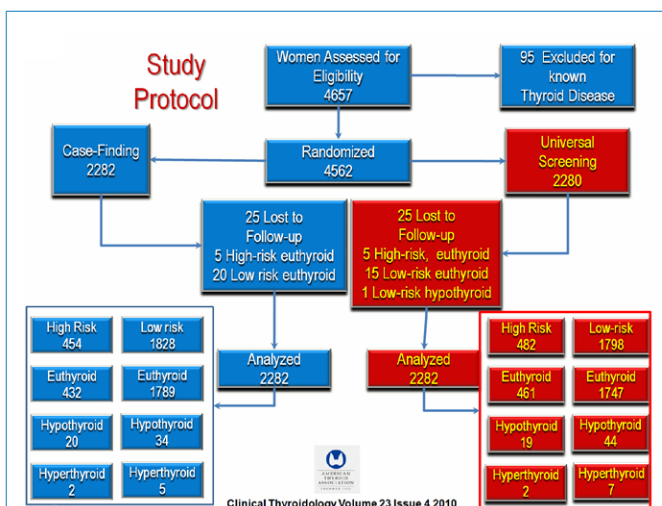


Figure 1. This figure shows the study protocol and number of patients assigned to each group in this study and the thyroid status of women in each group. The thyroid status of women deemed to be at low risk for an adverse outcome of pregnancy is based on frozen serum analyzed post partum. This figure is adapted from Figure 1 of Negro et al. Approximately 5% of euthyroid women in the universal-screening and the case-finding groups were TPOAb-positive, which is lower than in an earlier study by Negro et al. that defined euthyroidism as a TSH <4.2 mIU/L, whereas the current study defined euthyroidism as a serum TSH <2.5 mIU/L.

be euthyroid than high-risk women in this group (P = 0.005). In the case-finding low-risk group, 39 women were hypothyroid or hyperthyroid, and were thus not diagnosed or treated.

In the universal screening group, 2208 (96.8%) were euthyroid, 63 (2.8%) were hypothyroid, and 9 (0.4%) were hyperthyroid. Because all women in this group had been screened, those with hypothyroidism or hyperthyroidism were treated. There was no difference in thyroid function by study-group assignment (P = 0.83). Figure 2 shows that approximately 5% of euthyroid women in the universal screening and case-finding groups were TPOAb-positive, which is lower than in an earlier study by Negro et al. that defined euthyroidism as a TSH <4.2 mIU/L, whereas the current study defined euthyroidism as a serum TSH <2.5 mIU/L. None of the TPOAb-negative women had a TSH level >5.0 mIU/L. The number of TPOAb-positive women who had a TSH >2.5 mIU/L were as follows: in the case-finding high-risk group, 68 of 427 (15.9%); in the case-finding low risk group, 282 of 1769 (15.9%); in the universal-screening high-risk group 50 of 456 (11%); and in the universal-screening low-risk group, 242 of 1732 (14%). Euthyroid women who were TPOAb-positive in the first trimester and subsequently requiring treatment are as follows: case-finding high-risk group, 3 of 25 (12%); universal-screening high-risk group, 3 of 27 (11.1%); and universal-screening low-risk group, 10 of 105 (9.5%).

Among hypothyroid patients treated with levothyroxine, the number who had a TSH <3.0 mIU/L in the second trimester was: in the case-finding high risk group, 18 of 20 (90%); in the universal-screening high-risk group, 18 of 20 (90%); in the universal-screening high-risk group, 14 of 19 (73.4%), and in the universal-screening low-risk group, 43 of 44 (97.7%). The number of women who had a TSH <3.0 mIU/L in the third trimester was: in the case-finding high-risk group, 19 of 20 (95%); in the universal-screening high-risk group, 18 of 19 (94.7%); and in the

universal-screening low-risk group, 44 of 44 (100%). None of the women with hypothyroidism treated with thyroxine had TSH values >5.0 mIU/L during the second or third trimester. Sixteen patients had hyperthyroidism, 11 of whom were investigated (2 in the case-finding high-risk group, 2 in the universal-screening high-risk group, and 7 in the universal-screening low-risk group). Of the 11 patients, one woman had an autonomously functioning nodule, 3 had gestational thyrotoxicosis, and 7 had Graves' disease, 4 of whom were treated with antithyroid drugs.

Relationship between Risk Classification and Thyroid Status (Figures 2 to 4)

Risk status was associated with thyroid status. There were

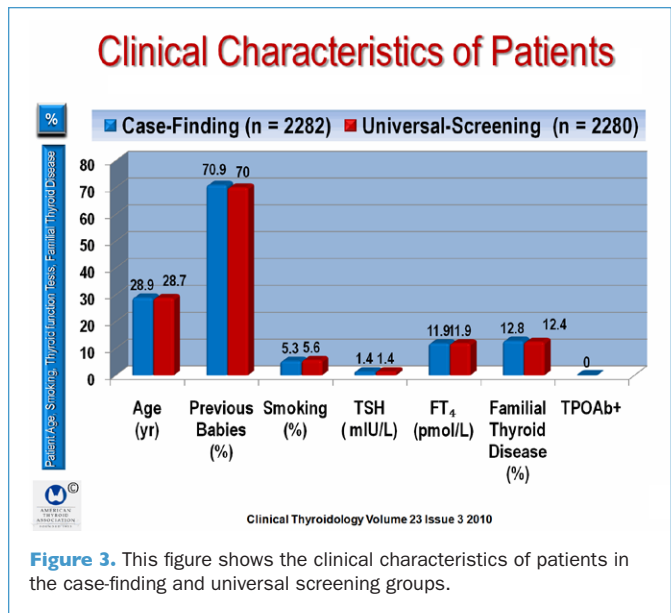


Figure 3. This figure shows the clinical characteristics of patients in the case-finding and universal screening groups.

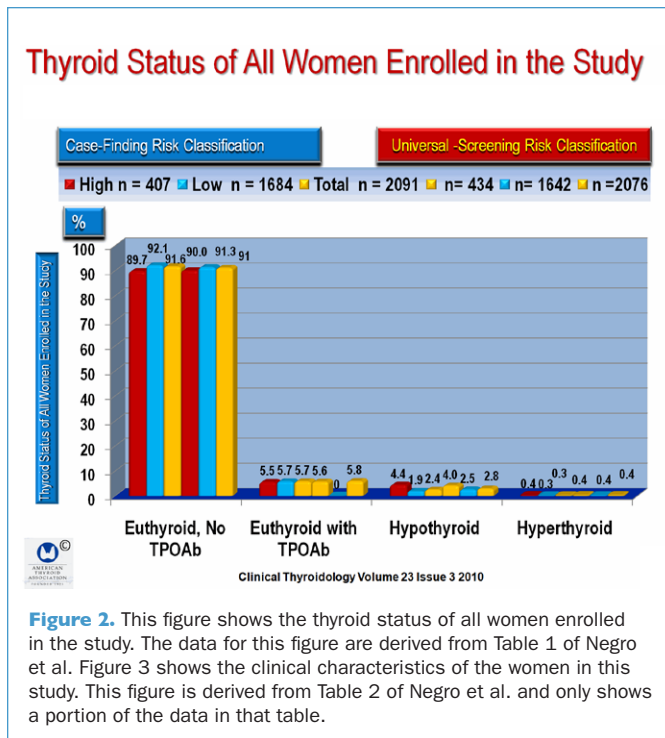


Figure 2. This figure shows the thyroid status of all women enrolled in the study. The data for this figure are derived from Table 1 of Negro et al. Figure 3 shows the clinical characteristics of the women in this study. This figure is derived from Table 2 of Negro et al. and only shows a portion of the data in that table.

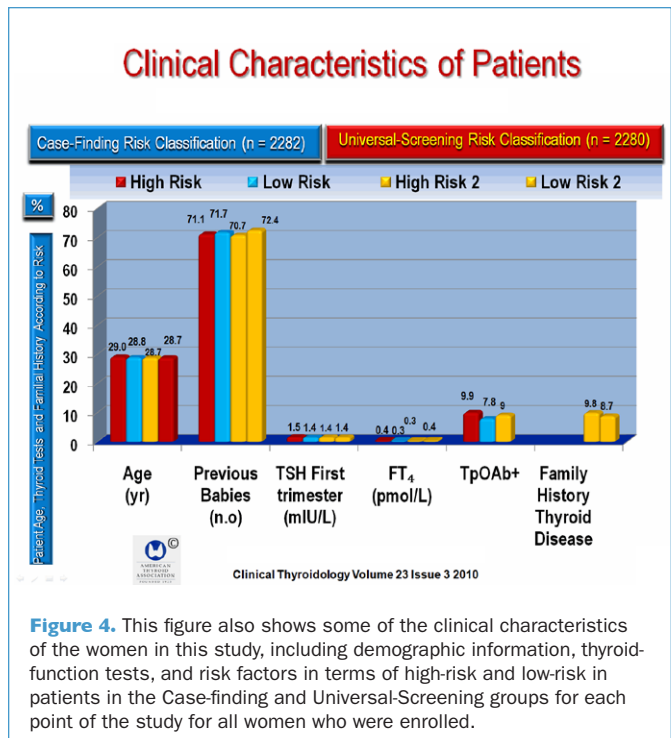


Figure 4. This figure also shows some of the clinical characteristics of the women in this study, including demographic information, thyroid-function tests, and risk factors in terms of high-risk and low-risk in patients in the Case-finding and Universal-Screening groups for each point of the study for all women who were enrolled.

fewer women with hypothyroidism and more euthyroid women without antibodies who would be classified as low risk than among women who would be classified as high risk (P = 0.005) (Figure 2). The relationship between risk classification and hypothyroidism was also significant in the case-finding group, in which 1.9% of low-risk and 4.5% of high-risk women had hypothyroidism (P= 0.01); however, this did not reach significance in the universal screening group, among whom 2.4% of low-risk women and 4.0% of high-risk women had hypothyroidism (P = 0.062). Figures 3 and 4 show the demographic data and thyroid status of the women enrolled in the study, randomly assigned to two groups, and also by the four analyzed cohorts (high-risk and low-risk). In the two randomized groups, there were no significant demographic differences. The probability of abnormal thyroid function, hyperthyroidism, or hypothyroidism in a 29-year-old woman was 2.8%. However advancing age was mildly associated with an increasing probability of abnormal thyroid function (odds ratio [OR] for each additional year of age, 1.05; 95% confidence interval [CI], 1.02 to 1.09).

Adverse Outcomes (Figures 5 and 6)

The adverse outcomes among the women in this study ranged from none to eight, and across the groups, 59.5% had no adverse outcomes, 25.6% had one, 6.6% had two, and 3.5% had four or more. At least 1 of the 930 women in the case-finding group and 900 in the universal-screening group experienced an adverse outcome (Figures 5 and 6). There were no significant differences between the total number of adverse outcomes in the case-finding group of 1545 women and the universal-screening group of 1559 women (P = 0.69).

The mixed logistic-regression model found that women in the screening group did not have fewer overall adverse outcomes, but there was a significant interaction between the trial arm and thyroid status (P = 0.014). The mixed logistic-regression

model also found relationships between adverse outcomes and other characteristics of low-risk women. The OR for age was 1.09 (95% CI, 1.08 to 1.10). The OR for the number of previous births was 1.51 (95% CI, 1.35 to 1.69). The OR for smoking was 1.71 (95% CI, 1.35 to 1.69). All were associated with an increased risk of adverse outcomes. These are general risk factors for adverse outcomes in pregnancy, independent of thyroid function. In women at high risk for adverse outcomes of pregnancy, there was no difference between the case-finding and universal-screening arms of the study. An adverse event was not significantly different for the women in the high-risk as compared with the low-risk universal-screening group, but it was higher for the low-risk case-finding group, as a consequence of the events associated with undetected and untreated hypothyroidism and hyperthyroidism (Figure 6).

Benefit of Treating Women with Low-Risk Hypothyroidism or Hyperthyroidism

To describe the benefit of treating low-risk hypothyroid or hyperthyroid women, the authors compared the likelihood of at least one adverse outcome for hyperthyroid women in the case-finding (untreated) group with that in the low-risk hypothyroid or hyperthyroid women in the universal screening (treated) group. 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 women for low-risk thyroid dysfunction

To further characterize the benefit of screening low-risk women, the authors compared the likelihood of at least one adverse outcome for all low-risk women in the case-finding group with that for the low-risk women in the universal screening group. Because many low-risk women with normal thyroid function had adverse outcomes in both groups, screening did not show a

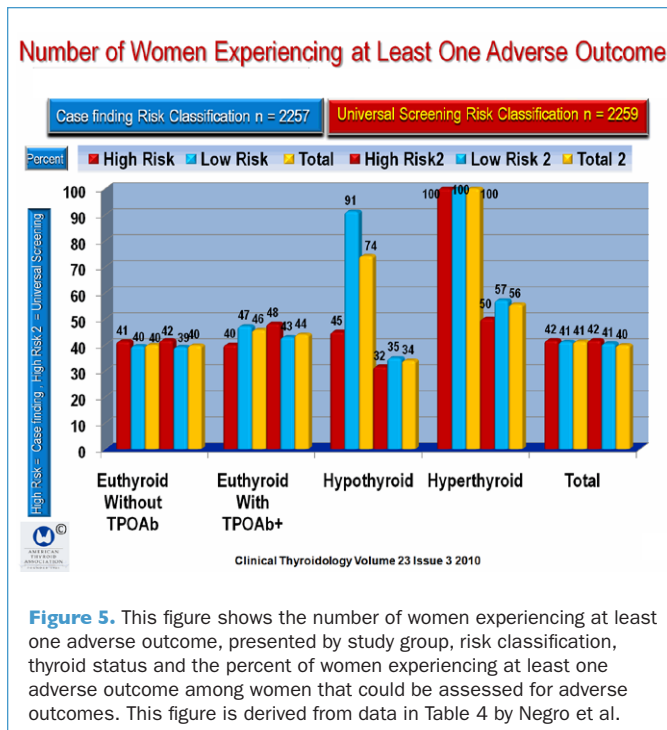


Figure 5. This figure shows the number of women experiencing at least one adverse outcome, presented by study group, risk classification, thyroid status and the percent of women experiencing at least one adverse outcome among women that could be assessed for adverse outcomes. This figure is derived from data in Table 4 by Negro et al.

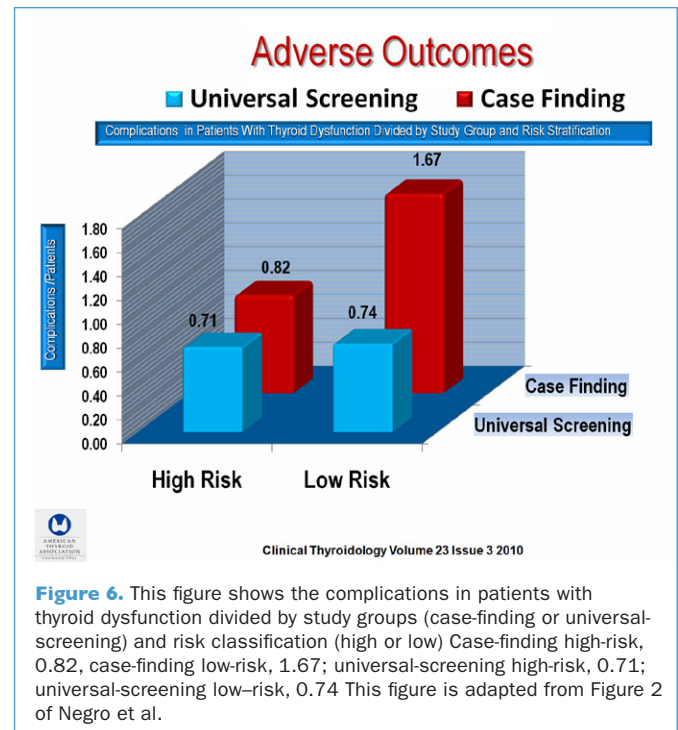


Figure 6. This figure shows the complications in patients with thyroid dysfunction divided by study groups (case-finding or universal-screening) and risk classification (high or low) Case-finding high-risk, 0.82, case-finding low-risk, 1.67; universal-screening high-risk, 0.71; universal-screening low-risk, 0.74 This figure is adapted from Figure 2 of Negro et al.

significant benefit. The number needed to screen to prevent one woman from having any adverse outcome was 60 (95%CI21.); However, the authors performed a mixed-model analysis that suggested this is likely an underestimate of the true benefit of screening because some women may be identified and treated, but still experience fewer adverse outcomes 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 years of age.

The Benefit of Screening for Low-Risk Women

Screening 1798 low-risk women identified 51 with abnormal thyroid function, who were then treated. The overall screening yield thus was 51 of 1798 (2.8%; 95% CI, 2.1 to 3.7), excluding the value of identifying euthyroid women with thyroid antibodies. The number needed to screen to detect one woman with hypothyroidism or hyperthyroidism was approximately 36 (95% CI, 27 to 48).

To further characterize the benefit of screening low-risk women, the likelihood of at least one adverse outcome for all low-risk

women in the case-finding group was compared with that for low-risk women in the universal-screening group. Because many low-risk women with normal thyroid function had adverse outcomes in both groups, screening did not show a significant benefit; however, the number needed to screen to prevent one woman from having any adverse outcome was 60 (95% CI, 21 to ∞). Still, the mixed-model results suggested that this is likely to be an underestimate of the true benefit of screening, as some women may be identified and treated but still have adverse outcomes, but fewer would have experienced an adverse outcome had they not been treated. On the basis of mixed-model results, screening low-risk women was associated with 2.48% fewer adverse events than would have been expected ($P = 0.012$), which corresponds to an inferred number needed to screen to prevent a single adverse outcome, but not all adverse outcomes, in a low-risk woman of approximately 40 years of age.

CONCLUSION

There were no significant differences in adverse outcomes between the case-finding and the universal-screening groups for thyroid dysfunction during pregnancy. Treatment of hyperthyroidism or hypothyroidism identified by screening a low-risk group was associated with a lower rate of adverse outcomes.

COMMENTARY

Thyroid disease has a number of deleterious effects on pregnancy, the developing fetus, and during the postpartum period. Complications include miscarriage, decreased intelligence quotient, visual-motor deficiencies in the children born to these women, preterm delivery, and postpartum thyroiditis (1-3). Screening for thyroid disease during pregnancy is controversial (4,5). The main issue of the debate concerns the impact of treating thyrotoxicosis in pregnant women (4,5).

This is the first prospective, randomized trial to compare case finding with universal screening for thyroid dysfunction during pregnancy. Universal screening as compared with case finding did not decrease the rate of adverse outcomes. Low-risk women in the universal-screening group had fewer adverse outcomes as compared with low-risk women in the case-finding group. However, low-risk women in the universal-screening group with

abnormal thyroid function who were treated avoided adverse outcomes more often than did low-risk women in the case-finding group with abnormal thyroid function that was not detected and thus not treated.

This study demonstrates that although universal screening did not result in a decrease in adverse outcomes, treatment of identified thyroid-hormone abnormalities during pregnancy resulted in a significant decrease in adverse outcomes. The study confirms that case finding fails to detect the majority of pregnant women with thyroid disease.

The authors of this important study suggest that a comprehensive cost-effectiveness analysis is required to resolve the debate of universal screening for thyroid disease in pregnancy.

— Ernest L. Mazzaferri, MD, MACP

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