

Over half (55%) of the pregnant women with clear abnormalities suggestive of autoimmune thyroiditis with or without thyroid insufficiency would be missed if only the high-risk criteria are examined.

Horacek J, Spitalnikova S, Dlabalova B, Malirova E, Vizda J, Sviliias I, Cepkova J, Mc Grath C, Maly J. Universal screening detects two-times more thyroid disorders in early pregnancy than targeted high-risk case finding. *Eur J Endocrinol* 2010;163:645-50. EJE-10-0516 [pii];10.1530/EJE-10-0516 [doi]

**SUMMARY**

**BACKGROUND**

Chronic autoimmune thyroiditis is often manifested by thyroid peroxidase antibodies (TPOAb) with or without thyroglobulin antibodies (TgAb), which is associated with a twofold to fourfold increase in the miscarriage rate and premature deliveries. Moreover, there is a 30 to 50% chance of postpartum thyroiditis (PPTD) developing in a pregnant woman with positive TPOAb. Even in regions of sufficient iodine intake, chronic autoimmune thyroiditis is still the most common cause of hypothyroidism, which often is at subclinical levels, and may further aggravate the increased requirement for thyroid hormones during pregnancy. The lack of thyroid hormone is associated not only with an increased risk for obstetrical complications, but also with impaired neuropsychological development early in the development of the child.

As levothyroxine replacement therapy can easily reduce the risk for obstetrical complications, even in euthyroid women with positive TPOAb levels, active screening for thyroid disease in pregnancy seems reasonable and cost-effective; yet screening pregnant women or those of childbearing age remains controversial. The Endocrine Society Clinical Practice Guideline recommends targeted case finding by measuring serum thyrotropin (TSH) in women with a specified high risk for thyroid disease. Studies that directly compared the outcome of universal screening with that of case findings based on a similar set of risk factors found that this approach would miss about a third of pregnant women with hypothyroidism. In addition, they focused on hypothyroidism, but also found women with positive TPOAb in 8% of their population, which is a similar fraction as that found in other studies, with most of them (73%) being euthyroid. As positive TPOAb confers risks of obstetric complications and PPTD independent of hypothyroidism, this variable seems worth including in the screening panel.

The yield and cost-effectiveness of screening are dependent not only on the range of the screened population, but also on the variables used and on assay cutoffs. Moreover, the reference range provided by the manufacturer is not suitable for women in early pregnancy, and the cutoffs should be adjusted. This is a pilot study of screening non-selected pregnant women for autoimmune thyroiditis with or without hypothyroidism using TSH, TPOAb, and free thyroxine (FT<sub>4</sub>), demonstrating that fewer than half of the women screened would have been identified if only those fulfilling the recommended criteria for targeted case finding were examined.

**SUBJECTS AND METHODS**

This is a study from University in Hradec Kralove, Charles University in Prague, Sokolska, Hradec Kralove, Czech Republic.

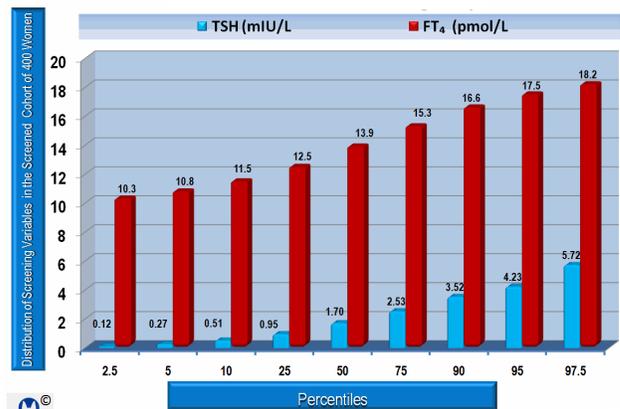
**Study Physicians**

Regional gynecologists were offered the addition of three thyroid-related variables into the prenatal screening panel in the 9th to 11th week of pregnancy that is offered to all pregnant women in this study. They explained the reasons for thyroid testing to the pregnant women and the possible participation of an endocrinologist in the follow-up and received written informed consent from the pregnant women. Funding was sufficient to recruit 400 women.

**Laboratory Studies**

Serum samples were sent to the same laboratory responsible for the standard prenatal screening and were assayed for TSH, FT<sub>4</sub>, and TPOAb. The TSH reference range of 0.15 to 5.0 mIU/L was measured by immunoradiometric assay, the FT<sub>4</sub> reference range of 11 to 23 pmol/L, and the TPOAb reference range of <12 IU/ml were all performed by national laboratories such as Immunotech, Beckman Coulter. The interassay coefficient of variation was 5.5% for TSH, 8.4% for FT<sub>4</sub>, and 7.5% for TPOAb. The recommended cutoff values for screening in pregnancy have

Distribution of the Screening Variables in the Screened Sample of 400 Women in the 9th to 11th Week of Pregnancy



**Figure 1.** This figure shows the distribution of screening variables in the screened sample of 400 women in the 9th to 11th week of pregnancy. FT<sub>4</sub> = free thyroxine; TPOAb = thyroid peroxidase antibodies. The data for this figure are derived from Table 1 of Horacek et al.

been a matter of controversy, but it is generally accepted that TSH levels in the first trimester are lower. A recent study from the Czech Republic suggested TSH 3.67 mIU/L as the upper limit of normal in this population, and patients with a TSH >3.5 mIU/L were invited to visit the Endocrine Clinic. In women with TSH below the reference range of 0.15 mIU/L, only those with increased FT<sub>4</sub> or clinical symptoms of hyperthyroidism were considered for endocrine consultation, but no women were found to have this problem. Women with FT<sub>4</sub> values <10 pmol/L were invited for consultation. The authors suggest that the selected value for positivity of TPOAb is method-dependent, and the manufacturer's cutoff values may not have been appropriate; the authors accordingly decided on the basis of their previous experience with the laboratory method to invite women with TPOAb >50 IU/ml.

**Endocrine Consultation**

The endocrine consultation included taking a detailed personal and family history and performing a physical examination with attention to the risk factors defined by the consensus guidelines of the Endocrine Society. In addition, patients had thyroid ultrasonography with power Doppler imaging, which estimated the thyroid-gland volume, and the gland was assessed for homogeneity, echogenicity, and vascularity, especially in women in whom chronic autoimmune thyroiditis was suspected, and were stratified on a modified semiquantitative scale: 1 = normal, 2 = borderline, 3 = suspect and 4 = typical thyroiditis. In the case of borderline screening values, the tests were repeated with further assays. Levothyroxine treatment (50 µg/day) was initiated in all women with a clearly positive TPOAb (>50 IU/ml) and suspect or typical sonographic pattern together strongly suggested chronic autoimmune thyroiditis. Treatment was targeted in women with TSH levels < 2.5 mIU/L, and if necessary the dose of levothyroxine was adjusted on a subsequent visit 4 weeks later. In addition, treatment was initiated in women

without a clear indication of chronic autoimmune thyroiditis but with a TSH that was consistently >2.5 mIU/L.

**RESULTS**

**The Distribution of Screening Variables (Figure 1)**

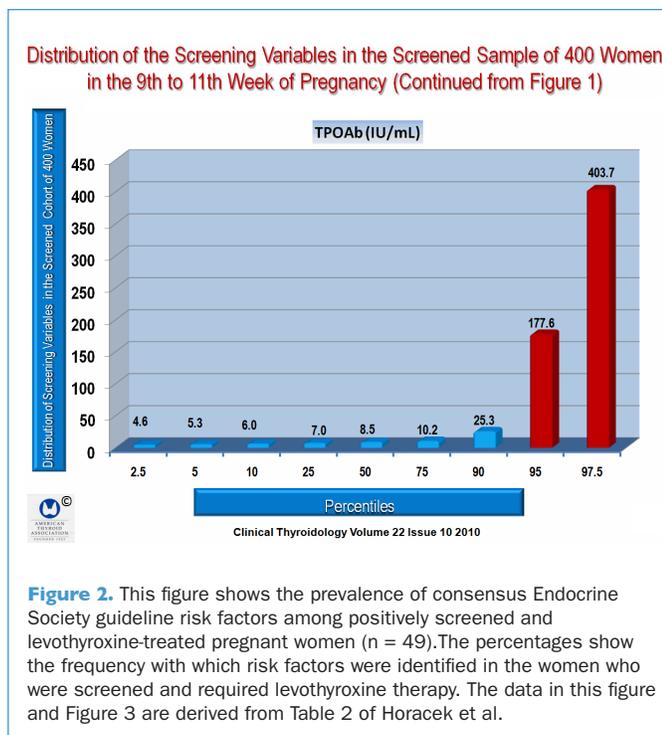
The distribution of the three screening variables is shown in Figure 1. Among the 400 pregnant women, TSH >3.5 mIU/L was found in 41 (10.3%), FT<sub>4</sub> <10 pmol/L in 8 (2%), and TPOAb >50 IU/ml in 33 (8.3%). A total of 65 women (16.3%) had at least one abnormality. Excluded from the analysis were 5 women already being treated who were receiving follow-up by their endocrinologist for autoimmune thyroiditis. The remaining women were offered endocrine consultation (Figure 1).

**Levothyroxine Therapy for Autoimmune Thyroiditis (Figure 2)**

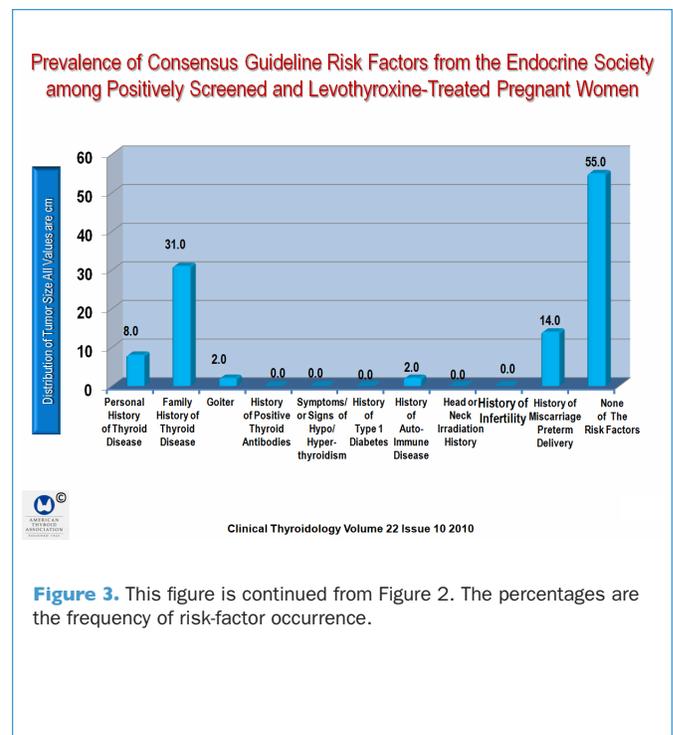
Fifty-one women were examined and had follow-up in the authors' clinic, 42 of whom (82%) had chronic autoimmune thyroiditis confirmed by ultrasonography and measurement of antibodies. Of this group, 27 (64%) also had TSH levels >2.5 mIU/L, suggesting thyroid insufficiency. Seven other women had consistently higher serum TSH levels without a typical pattern of autoimmune thyroiditis. Levothyroxine therapy was initiated in all of the 49 women (96%) with consistent abnormalities. A dose of 50 µg/day of levothyroxine was enough to maintain the TSH levels in 41 (84%) of the women at <2.4 mIU/L without an overdose of TSH to <0.15 mIU/L during follow-up. The women were also evaluated according to 10 accepted high-risk criteria, as shown in Figure 2.

**Risk Factors in Women in Women Treated with Levothyroxine (Figure 3)**

Of the 49 women who screened positively for levothyroxine therapy, there were no risk factors in 27 (55%; 95% confidence interval [CI], 40 to 69). Moreover, in a well-defined subgroup of



**Figure 2.** This figure shows the prevalence of consensus Endocrine Society guideline risk factors among positively screened and levothyroxine-treated pregnant women (n = 49). The percentages show the frequency with which risk factors were identified in the women who were screened and required levothyroxine therapy. The data in this figure and Figure 3 are derived from Table 2 of Horacek et al.



**Figure 3.** This figure is continued from Figure 2. The percentages are the frequency of risk-factor occurrence.

42 women with autoimmune thyroiditis, 21 (50%; 95% CI, 34 to 66) had no risk factors. A clustering of risk factors was even less common, as only 6 women had two risk factors and none had three or more risk factors.

The most accurate risk factors were a positive family history of miscarriage (present in 31%) or preterm delivery (14%) and a positive personal history (8%). A history of other autoimmune disorders and a history or presence of goiter was not diagnostically helpful. Overall, the presence of goiter was rare, as the largest sonographically measured thyroid volume was 21 ml. None of the

other risk factors was observed in this group. Of the other items of personal history that were not included in the consensus guideline criteria were a history of allergy that seemed to show some positive prognostic value, being positive in 14 of 49 women (29%), a proportion similar to the best of the consensus risk factors.

**CONCLUSION**

Over half (55%) of the pregnant women with clear abnormalities suggestive of autoimmune thyroiditis with or without thyroid insufficiency would have been missed if only the high-risk criteria were examined.

**COMMENTARY**

This is an important study, the main finding of which is that over half the patients with autoimmune thyroiditis would have been missed if only the current high-risk criteria were examined. The proportion of missed diagnoses was even higher in a study by Vaidya et al. (1), who noted that recent consensus guidelines do not advocate universal thyroid-function screening during pregnancy but instead recommend testing high-risk pregnant women with a personal history of thyroid or other autoimmune disorders or with a family history of thyroid disorders.

The objective of the study by Vaidya et al. was to evaluate the efficacy of a targeted high-risk case-finding approach to identify women with thyroid dysfunction during early pregnancy. This was a single-center cohort study in which the authors prospectively analyzed TSH, FT<sub>4</sub>, and free triiodothyronine in 1560 consecutive pregnant women during their first antenatal visit (median gestation, 9 weeks). TPOAb were tested in 1327 women (85%), and 413 (26.5%) who had a personal history of thyroid or other autoimmune disorders or a family history of thyroid were classified as a high-risk group. The study examined whether testing only such a high-risk group would pick up most pregnant women with thyroid dysfunction. The study found that 40 women (2.6%) had an elevated serum TSH (>4.2 mIU/L). The prevalence of which was greater in the high-risk group (6.8%, vs. 1.0% in the low-risk group); the relative risk (RR) was 6.5 (95% CI, 3.3 to 12.6; P<0.0001). The authors found that a personal history of thyroid disease (RR, 12.2; 95% CI, 6.8 to 22;

P<0.0001) or other autoimmune disorders (RR, 4.8; 95% CI, 1.3 to 18.2; P = 0.016), TPOAb (RR, 8.4; 95% CI, 4.6 to 15.3; P<0.0001), and family history of thyroid disorders (RR, 3.4; 95% CI, 1.8 to 6.2; P<0.0001) all significantly increased the risk of an elevated serum TSH. However, 12 of 40 women with raised serum TSH levels (30%) were in the low-risk group based on the current guidelines. The authors concluded that targeted thyroid-function testing of only the high-risk group would miss about one third of pregnant women with overt or subclinical hypothyroidism.

The Horacek study was focused on early detection of autoimmune thyroiditis, because of a higher risk for obstetrical complications as well as PPTD and hypothyroidism and the fact that these complications can be treated with levothyroxine (2-4). Ultrasonography played an important role in identifying women with thyroid disease in the Horacek study, and is gaining more use for this problem (5).

This is a complex and controversial issue that will require further study. Still, the fact that thyroid testing in early pregnancy misses a significant number of pregnant women with thyroid disease raises serious questions about the current approach to this problem, and the notion that more extensive screening will identify a significantly larger number of patients must be taken under consideration.

— Ernest L. Mazzaferri, MD, MACP

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