CLINICAL STUDY

Universal screening detects two-times more thyroid disorders in early pregnancy than targeted high-risk case finding

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Abstract

Objective: Screening of thyroid disorders in pregnancy has been controversial. Recent recommendations favour targeted high-risk case finding, though this approach may miss a significant number of those affected. We aimed to assess the prevalence of accepted high-risk criteria in women with autoimmune thyroiditis and/or hypothyroidism detected from universal screening in an iodine-sufficient population.

Design: In 400 non-selected women in the 9–11th gestational week, thyroid-related tests were performed, and those with abnormalities were offered consultation.

Methods: TSH was determined by IRMA, and the upper cut-off value for screening was set at 3.5 mIU/l. For free thyroxine (FT₄) and thyroperoxidase antibodies (TPO-Ab), RIAs were used, with cut-offs of < 10 pmol/l and > 50 IU/ml respectively. Endocrinological consultation included Doppler ultrasonography and was aimed to confirm autoimmune thyroiditis and/or hypothyroidism. The prevalence of consensus high-risk criteria was assessed.

Results: Among the 400 women, 65 (16.3%) had ≥ 1 abnormality: higher TSH was found in 10.3%, lower FT₄ in 2% and positive TPO-Ab in 8.3%. Fifty-one women were examined and followed up. Levo-T₄ treatment was initiated in 49 women for autoimmune thyroiditis (in 42), hypothyroidism (in 34) or both (in 27). Only 22 (45%) of 49 treated women fulfilled ≥ 1 high-risk criterion: most commonly family history (31%), history of miscarriage or preterm delivery (14%) and personal history (8%).

Conclusions: Over half (55%) of pregnant women with abnormalities suggestive of autoimmune thyroiditis and/or hypothyroidism would be missed if only those with high-risk criteria were examined. A more extensive screening of thyroid autoimmunity and dysfunction seems warranted.

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Introduction

Chronic autoimmune thyroiditis, often manifested only by thyroid peroxidase (TPO-Ab) and/or thyroglobulin antibodies (Tg-Ab), is associated with a two- to four-fold increase in miscarriage rate and premature deliveries (1–3). Moreover, a pregnant woman with positive TPO-Ab has a 30–52% chance of developing *post-partum* thyroiditis (PPTD) (4, 5). In iodine-sufficient regions, chronic autoimmune thyroiditis is also the most common cause of hypothyroidism, often at subclinical levels, that may be further aggravated by the increased need for thyroid hormones in pregnancy (6). The lack of thyroid hormones, even subclinical, is associated not only with an increased risk of obstetrical complications but also with an impaired neuropsychological development of the child (7, 8).

As hypothyroidism is easily treated by levothyroxine (L-T₄) replacement and equally the same treatment may effectively reduce the risk of obstetrical complications also in euthyroid women with positive TPO-Ab (2), active screening for thyroid disease in pregnancy seems reasonable (9) and cost effective (10, 11). Nevertheless, the suggested range of screened population has remained controversial. The recent Endocrine Society Clinical Practice Guideline recommends targeted case finding by measurement of TSH in women with specified high risk for thyroid disease (12).

Vaidya *et al.* (13) directly compared the outcome of universal screening with that of case finding based on a similar set of risk factors (14), and reported that the latter approach would miss about a third of pregnant women with hypothyroidism. This finding may support the idea of a more general screening (15). Furthermore,

they focused on hypothyroidism, but they also found women with positive TPO-Ab in 8% of their population, a similar fraction as observed in other studies, with most of them (73%) being euthyroid (13). As positive TPO-Ab confer risks (of obstetric complications and PPTD) independent of hypothyroidism, this variable seems worth including in the screening panel (9, 10).

The yield and cost effectivity of screening are dependent not only on the range of the screened population but also on the variables used and on assay cut-offs. Often the reference range (RR) provided by the manufacturer is not suitable for women in early pregnancy, and the cut-offs should be adjusted (16, 17).

Here, we present a pilot study of screening for autoimmune thyroiditis and/or hypothyroidism in non-selected pregnant women using TSH, TPO-Ab and free T₄ (FT₄) demonstrating that less than half of those positively screened would have been identified if only those fulfilling the recommended criteria for targeted case finding were examined.

Subjects and methods

Regional gynaecologists were offered the addition of three thyroid-related variables into the prenatal screening panel in the 9–11th week of pregnancy offered to all pregnant women in our study population. 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. The project was approved by the appropriate ethics committee. Funding was sufficient for the recruitment of 400 women.

The serum samples were sent to the same laboratory responsible for the standard prenatal screening and were assayed for TSH, FT₄ and TPO-Ab. TSH (RR, 0.15–5.0 mIU/l) was measured by IRMA (Immunotech, Beckman Coulter, Prague, Czech Republic). FT₄ (RR, 11–23 pmol/l) and TPO-Ab (RR <12 IU/ml) were determined by RIA (Immunotech, Beckman Coulter). The inter-assay coefficient of variation (CV) was 5.5% for TSH, 8.4% for FT₄ and 7.5% for TPO-Ab.

The recommended cut-off values for screening in pregnancy have been a matter of controversy (16, 17). It is generally accepted that TSH levels in the first trimester are lower; indeed, a recent study from our country suggested 3.67 mIU/l as the upper limit of normal in this population (17). We invited those with

TSH > 3.5 mIU/l to visit our endocrine clinic. In women with TSH below the RR (0.15 mIU/l), only those with increased FT₄ or clinical symptoms of hyperthyroidism were considered for endocrine consultation, but no such case was found in our sample. As for low FT₄, women with values <10 pmol/l were invited for consultation. The selected value for positivity of TPO-Ab is probably the most complicated aspect, clearly method dependent, and the manufacturer's cut-off values may not be appropriate (17). Based on our previous experience with the method, we decided to invite those with TPO-Ab > 50 IU/ml.

The endocrine consultation included a detailed personal and family history and physical examination, with an explicit attention to the risk factors defined by the consensus guidelines (12). Moreover, thyroid ultrasonography (Toshiba Nemio, 9 MHz linear transducer, with power Doppler imaging) was performed. The thyroid gland volume was estimated, and the structure was assessed for homogeneity, echogenicity and vascularity, especially valuable in cases of suspicion of chronic autoimmune thyroiditis, on a modified semi-quantitative scale: 1 – normal, 2 – borderline, 3 – suspect and 4 – typical (18, 19). If necessary (due to borderline screening values), the tests for screening were repeated together with further assays: free triiodothyronine (RIA, Immunotech, Beckman Coulter, RR, 2.5–5.7 pmol/l, CV, 6.4%) and Tg-Ab (RIA, Immunotech, Beckman Coulter, RR, <100 IU/ml, CV, 10.4%).

L-T₄ treatment (50 µg/day) was initiated in all women with clearly positive TPO-Ab (> 50 IU/ml) and suspect or typical sonographic pattern together strongly suggestive of chronic autoimmune thyroiditis (2). As optimal TSH in pregnancy seems to be in low normal values (20), the treatment was targeted to TSH <2.5 mIU/l (16) and, if necessary, the dose was adjusted on a subsequent visit 4 weeks later. In addition, the treatment was initiated in those without a clear indication of chronic autoimmune thyroiditis but with TSH consistently > 2.5 mIU/l.

Results

The distribution of three screening variables in our sample is shown in Table 1. Among 400 pregnant women, TSH > 3.5 mIU/l was found in 41 (10.3%), FT₄ < 10 pmol/l in 8 (2%) and TPO-Ab > 50 IU/ml in 33 (8.3%) women; a total of 65 (16.3%) had at least one

Table 1 Distribution of the screening variables in the screened sample of women in the 9–11th week of pregnancy (n=400).

Percentile	2.5	5	10	25	50	75	90	95	97.5
TSH (mIU/l)	0.12	0.27	0.51	0.95	1.70	2.53	3.52	4.23	5.72
FT ₄ (pmol/l)	10.3	10.8	11.5	12.5	13.9	15.3	16.6	17.5	18.2
TPO-Ab (IU/ml)	4.6	5.3	6.0	7.0	8.4	10.2	25.3	177.6	403.7

FT₄, free thyroxine; TPO-Ab, thyroperoxidase antibodies.

abnormality. After exclusion of five women already treated for autoimmune thyroiditis (and followed by their endocrinologists), the remaining women were offered endocrine consultation.

Fifty-one positively screened women were examined in our clinic and followed up. In 42 (82%) women, chronic autoimmune thyroiditis was confirmed by ultrasonography and antibodies; of them 27 (64%) also had TSH > 2.5 mIU/l, suggestive of relative thyroid insufficiency. In addition, seven women had consistently higher TSH without the typical pattern of autoimmune thyroiditis. In all the 49 women with consistent abnormalities (96%), L-T₄ treatment was initiated. Typically (in 41, i.e. 84%) the dose of 50 µg/day was enough to maintain their TSH levels < 2.5 mIU/l, and no case of overdose (TSH < 0.15 mIU/l) was found on follow-up.

The women were also assessed according to ten accepted high-risk criteria (Table 2). Of the 49 positively screened women indicated for L-T₄ treatment, there were no risk factors in 27 (i.e. 55%, 95% confidence interval (CI), 40–69%) women. Moreover, in a well-defined subgroup of 42 women with autoimmune thyroiditis, 21 women (50%, CI 34–66%) had no risk factors.

Clustering of risk factors was even less common as only six women had two of them, and none had three or more risk factors.

The most promising risk factors included positive family history (present in 31%), history of miscarriage or preterm delivery (14%) and positive personal history (8%). Determining the history of other autoimmune disorders and a history or presence of goitre were not productive. In general, the presence of goitre was rare as the largest sonographically measured thyroid volume was 21 ml. None of the remaining five risk factors was observed in our sample.

Of other items of personal history, which were not included in the consensus guideline criteria, it was the 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.

Table 2 Prevalence of consensus guideline risk factors (ref. (23)) among positively screened and levothyroxine-treated pregnant women (n=49).

Consensus guideline risk factor	Occurrence (%)
Personal history of a thyroid disorder	4 (8%)
Family history of a thyroid disorder	15 (31%)
Goitre	1 (2%)
History of positive thyroid antibodies	0 (0%)
Symptoms/signs of thyroid hypo/hyperfunction	0 (0%)
History of type 1 diabetes mellitus	0 (0%)
History of other autoimmune disorders	1 (2%)
Infertility	0 (0%)
History of head/neck irradiation	0 (0%)
History of miscarriage or preterm delivery	7 (14%)
None of them	27 (55%)

Discussion

In our sample of pregnant women with clear abnormalities suggestive of autoimmune thyroiditis and/or thyroid insufficiency, and indicated for treatment, over half (55%) would be missed if only those with high-risk criteria were examined.

This proportion was even higher than that reported by Vaidya *et al.* (13), who arrived at similar conclusions, though they used a different design, namely, they concentrated on hypothyroid women (defined as TSH > 4.2 mIU/l), and they did not consider TPO-Ab positivity. Moreover, they compared their yield with previous (slightly different) consensus criteria (14). They observed that 'only' one-third of hypothyroid women would be missed when just consensus criteria were used.

In our approach, we focused on early detection of autoimmune thyroiditis because of higher risk of various obstetrical complications as well as of PPTD and hypothyroidism (1–5). Therefore, ultrasonography was also used to confirm the diagnosis. Ultrasonography was performed by an experienced endocrinologist. There is the possibility of bias in this operation since ultrasound was performed after the laboratory results were available and the women were invited for consultation. However, this was the same for all the women invited for consultation, and by eliminating operator dependency, we maintained consistency over sonographic interpretation within the group.

The value of ultrasonography in this area is increasing. For example, Premawardhana *et al.* (19) showed useful predictive value of the combination of thyroid status, TPO-Ab and ultrasonography (the same triad as used in our study) in autoimmune PPTD. They showed that the hypothyroid form of PPTD, high TPO-Ab levels and a hypoechogenic ultrasound pattern lead to a high risk (relative risk, 32) of long-term thyroid dysfunction. Thus, early screening may again help in identifying those women for follow-up.

Therefore, we consider a more extensive, and probably universal, screening of thyroid autoimmunity and thyroid dysfunction in pregnancy to be the desired end point. In addition, it may also enable earlier identification of potentially serious problems in women without clear-cut risk factors, and since the treatment is relatively cheap and easy, this approach may be cost effective (10, 11). Indeed, as the awareness of these problems is spreading among gynaecologists (21), there is increasing tendency for more extensive screening (22). The recent large randomised study by Negro *et al.* (23) brought rather controversial results. While in the overall sample, universal screening compared with case finding did not result in a decrease in adverse obstetrical and neonatal outcomes, in the low-risk group, there was a clear improvement in the early detected and treated women. The editorial published in the same issue (24) comments on this apparent discrepancy and

points out that treating the detected cases in high-risk groups in both arms of the study became 'dilutive' to the ultimate analysis. As there is no doubt that the high-risk group should be investigated anyway, the finding that the low-risk group would also benefit from testing and treatment is clearly supportive of universal screening.

The disadvantages of the screening include the cost and some maternal anxiety. The two available cost-effective analyses (10, 11) took only the potential decrease in IQ of the children into consideration and still regarded the screening as cost effective. Our own experience with maternal anxiety was rather reassuring; in many pregnant women, there was no real anxiety (just interest), and a humane and professional approach, with adequate explanation, printed information and a hot line for further consultation, relieved any anxiety in the rest of the group.

While universal screening is gaining increasing support (24), the methods of screening, i.e. the variables measured and their cut-off values, are more controversial (16). In addition, the yield of screening may be influenced by regional differences, namely, by iodine sufficiency (25).

As for the variables, TPO-Ab seems to be particularly useful because it may allow for early detection of autoimmune thyroiditis, enabling appropriate treatment (2) and long-term follow up. In our sample, all 30 women with TPO-Abs > 50 IU/ml in screening and observed in our endocrine clinic also had sonographic patterns suggestive of autoimmune thyroiditis. The cut-off value for screening may be a problem; using the manufacturer's upper limit (usually not specific for pregnant women) may inadequately increase the number of positively screened and decrease the specificity. Springer *et al.* (17) using a different assay found 143 kU/l as a more adequate decision value for endocrine consultation than the manufacturer's cut-off value of 60 kU/l. We also used an even stricter value of 50 IU/ml instead of the manufacturer's cut-off of 12 IU/ml, and sonography confirmed that positively screened women indeed had autoimmune thyroiditis. However, looking at the distribution (Table 1), 25 IU/ml might have been more appropriate, thus indicating seven (2%) more women for endocrine consultation. Clearly, the cut-off value for screening must be method dependent and population dependent, and should reflect the trade-off between sensitivity and specificity.

Similar considerations apply to the upper limit of TSH. It is generally agreed that TSH levels are lower in early pregnancy (6), and it appears that lower values are also more desirable for the pregnancy outcome (16, 20), but there is no generally accepted decision value for screening. Again, it should be method specific and population specific, and the cut-off values previously reported for hypothyroidism range from 5.2 to 2.0 mIU/l (2, 8, 13, 14, 17, 26–29). Based on our previous experience (unpublished) that a value of 2.5 mIU/l brings too many false positives that are

subsequently excluded from intervention when a combination of clinical history, (repeat) laboratory findings and ultrasonography is used, we selected 3.5 mIU/l as the screening cut-off value for TSH. In our sample of 400 pregnant women, this value is close to the 90th percentile (Table 1), bringing about 10% of the cohort into further consideration. Among the 339 women with negative TPO-Ab (≤ 12 IU/ml, i.e. within the manufacturer's RR), this value lies between the 92nd and 93rd percentiles. We believe that the use of a screening target of 3.5 mIU/l and a treatment target of 2.5 mIU/l in women identified as having autoimmune thyroiditis provides a satisfactory return.

We also used FT₄ as one of the screening variables in this study. Unlike TSH, it is not generally recommended for screening (12). In accordance with this, FT₄ was much less effective in selecting women from our sample for endocrine consultation. Isolated FT₄ abnormality (with TSH and TPO-Ab normal) was only found in 4 of 65 (6%) positively screened women, and none of them was actually seen in our clinic, so they did not influence our conclusions. However, as isolated hypothyroxinaemia (with normal TSH in the range 0.15–2.0 mIU/l) was associated with delayed mental and motor functions (8–10 points on the mental and motor scales at the age of 1 and 2 years, ref. (8)), this has made many researchers start to include FT₄ into the testing battery. Interestingly, the preliminary data from the Controlled Antenatal Thyroid Screening Study, so-called CATS study (9), showed that 'utilising both parameters (i.e. TSH and FT₄) results in two abnormal pregnant populations – namely, about half with a low T₄ and an equal number with a high TSH, with very few having both a low T₄ and a high TSH'. The authors suggest that the former pattern may be related to iodine deficiency, while the latter to autoimmune thyroiditis (being also associated with TPO-Ab). Although iodine sufficiency was not specifically tested in our sample, we assume a generally satisfactory iodine status, as was recently demonstrated in our country in a population study using urinary iodine concentration and sonographically measured thyroid volume (30). Moreover, the thyroid volume in our sample (median 11 ml, interquartile range 9–13 ml) was not significantly different from that in the respective age and gender population subgroup (31). So iodine sufficiency may also explain the lower proportion of isolated hypothyroxinaemia in our cohort. On the other hand, removing FT₄ from the screening panel may be inappropriate in those countries where iodine deficiency continues to be a problem. As with the other variables, the cut-off value selected may also prove to be controversial.

In summary, limitation of thyroid testing in early pregnancy only to women with generally accepted high-risk factors would miss a significant proportion (in our sample over half) of those indicated for endocrine care. More comprehensive screening of thyroid autoimmunity and dysfunction seems warranted. TPO-Ab

and TSH (and possibly FT₄) are best suited for this purpose, but their screening cut-off values should be a matter of further research, in terms of sensitivity and specificity.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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