Comparison of universal screening with targeted high-risk case finding for diagnosis of thyroid disorders

Sima Nazarpour, Fahimeh Ramezani Tehrani¹, Masoumeh Simbar, Maryam Tohidi²,
Hamid AlaviMajd³ and Fereidoun Azizi⁴

Department of Reproductive Health and Midwifery, Faculty of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences and Health Services, Tehran, Iran, ¹Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran, ²Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran, ³Department of Biostatistics, Faculty of Paramedicine, Shahid Beheshti University of Medical Sciences and Health Services, Tehran, Iran and ⁴Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Correspondence
should be addressed
to F Ramezani Tehrani
Email
fah.tehrani@gmail.com

Abstract

Objective: Debate about the need for universal screening of thyroid dysfunction in pregnancy is ongoing. The present study aimed to compare universal screening with targeted high-risk case findings for early diagnosis of thyroid disorders in Iranian pregnant women.

Study design: This cross-sectional prospective study was carried out on 1600 pregnant women in their first trimester. A checklist, including all related risk factors recommended by The American Thyroid Association, was completed for all participants. Serum concentrations of thyroxine (T₄), T-uptake, TSH and thyroid peroxidase antibody (TPOAb) were measured and thyroid status was documented, based on hormonal measurements and clinical examinations.

Results: There were 656 women (44.3%) that had at least one risk factor for thyroid diseases and were eligible for the targeted high-risk case finding (high-risk group) approach, while 55.7% had no risk factors (low-risk group). Using the universal screening approach, there were 974 women (65.8%) with normal thyroid status and 506 participants (34.2%) with thyroid disturbances, including overt hyperthyroidism (0.7%), overt hypothyroidism (1.1%), subclinical hypothyroidism (30.1%; positive TPOAb (5.5%) and negative TPOAb (24.6%); and euthyroid and positive TPOAb (2.3%). Of women with thyroid dysfunction, 64.4% were in the high-risk group and 35.6% were in the low-risk group ($P < 0.0001$).

Conclusions: The targeted high-risk case finding approach overlooks about one-third of pregnant women with thyroid dysfunction. If ongoing prospective trials provide evidence on the efficacy of treating subclinical hypothyroidism in pregnancy, in populations with a low prevalence of presumed risk factors, the targeted high-risk case finding approach will be proven inefficient.

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Introduction

Thyroid dysfunction is the second most common endocrine disturbance in women of reproductive age (1, 2), with a high prevalence in pregnant women. About 2–3% of pregnant women are diagnosed with hypothyroidism (0.3–0.5% with overt hypothyroidism and 2–2.5% with

subclinical hypothyroidism), whereas hyperthyroidism has been reported in 0.1–0.4% of pregnant women. Furthermore, about 10–20% of all euthyroid pregnant women are positive for thyroid antibodies (3). While complications of hypothyroidism or overt

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hyperthyroidism in pregnancy outcomes as well as neonatal and childhood development are well known (4, 5, 6, 7, 8), there is still no consensus on the association of subclinical thyroid disorders or increasing thyroid antibodies with complications of pregnancy and childhood. Some studies have shown that subclinical hypothyroidism and thyroid autoimmunity are associated with adverse maternal and fetal outcomes (8, 9, 10, 11, 12, 13).

The possible adverse outcomes of thyroid disorders in pregnancy are causing an increase in the tendency for universal screening (14, 15). However, the American Association of Clinical Endocrinologists (AACE), American Thyroid Association (ATA) and American College of Obstetrics and Gynecology (ACOG) do not recommend universal thyroid assessment for every pregnant woman, and suggest the targeted high-risk case finding approach (4, 16, 17), an approach which needs to be evaluated for its effectiveness in routine clinical practice (18).

Several studies comparing various screening approaches, reported that not using the universal approach resulted in overlooking a significant number of pregnant women with thyroid dysfunction (19, 20). It has been shown that 30–90% of women with thyroid disturbances may be omitted using the targeted high-risk case finding approach (20, 21, 22, 23, 24, 25). With current increases in potential risk factors, the efficiency of the screening method has also increased. As Potlukova *et al.* (26) reported, by including age ≥ 30 years as a risk factor, the sensitivity of high-risk case finding strategy increased from 55.3–85.6%.

Given the differences in prevalence of potential risk factors in various societies, it is reasonable to identify the majority of pregnant women with thyroid dysfunction overlooked by using the targeted high-risk case finding approach in certain races and societies with different risk factors and iodine status. In this study, we aimed to compare the universal screening with targeted high-risk case finding approaches for early diagnosis of thyroid disorders in pregnant Iranian women.

Subjects and methods

This is a prospective study carried out in Tehran from September 2013 to September 2014. In this study, 1600 pregnant women in their first trimester were selected, using a cluster sampling method from among those receiving prenatal care in centers under coverage of Shahid Beheshti University of Medical Sciences, which provides health services to over two-thirds of Tehran's population. A written informed consent form was

obtained from all participants and the study was approved by the Ethical committee of the Research Institute of Endocrine Sciences. A comprehensive questionnaire including demographic, reproductive, medical and prenatal history was filled out during face-to-face interviews. A checklist including all potential risk factors, as recommended by the American Thyroid Association (27), was completed for all participants and physical exams including thyroid, weight, height, systolic and diastolic pressure. Overnight blood samples were collected, following centrifugation they were sent to the Research Institute of Endocrine Sciences of Shahid Beheshti University of Medical Sciences for thyroid hormonal assessment including thyroxine (T_4), T-uptake, thyrotropin (TSH) and thyroid peroxidase antibody (TPOAb). Since free T_4 (FT_4) immunoassays may be influenced by pregnancy-related changes of serum thyroxine binding globulin and albumin, in a method-specific manner, FT_4 index (FT_4I) was used to assess FT_4 status (28).

Pregnant women, aged < 18 years ($n=52$), those with twin pregnancies ($n=24$) and those diagnosed with thyroid diseases ($n=44$) were excluded from this study. Gestational age was calculated according to the first day of their last menstrual cycle (LMP) (for women with regular cycles), and/or ultrasonography for those with irregular cycles or those who could not remember their LMP.

Using RIA and immunoradiometric assay (IRMA), T_4 and TSH were measured by commercial kits (Izotop Kit, Budapest co., Hungary) and the Gama-counter (Dream Gamma-10, Goyang-si, Gyeonggi-do, South Korea). T-uptake and TPOAb were measured by the enzyme immunoassay (EIA) (Diaplus Kit, San Francisco, CA, USA) and immunoenzymometric assay (IEMA) (Monobind Kit, Costa Mesa, CA, USA), using a calibrated ELISA reader (Sunrise, Tecan Co., Salzburg, Austria). Inter and intra assay coefficients of variation for T_4 , T-uptake, TSH and TPO-Ab were 1.1 and 3.9%, 2.2 and 4.3%, 1.9 and 4.7%, and 1.0 and 1.6% respectively.

Participants were categorized into two groups, according to their risk factors, as the low-risk (without any risk factors) and the high-risk (with one or more risk factors) groups.

Based on results of laboratory examinations, patients with TSH level < 2.5 $\mu\text{IU/ml}$, FTI: 1–4.5 and TPO antibodies < 50 IU/ml (negative), were considered normal. Patients with TSH levels > 10 $\mu\text{IU/ml}$, or 5–10 $\mu\text{IU/ml}$ and FTI < 1 , were diagnosed as overt hypothyroidism and those with TSH levels < 0.02 $\mu\text{IU/ml}$ and FTI > 4.5 as overt hyperthyroidism. Those with TSH levels between 2.5 and 10 $\mu\text{IU/ml}$, and FTI between 1 and

4.5, as sub-clinically hypothyroid, regardless of TPOAb status, whether positive or negative. Women with TSH levels <2.5 $\mu\text{IU/ml}$, FTI <1 and TPO antibodies <50 IU/ml (negative), were considered as isolated hypothyroxinemia and those with TSH levels <2.5 $\mu\text{IU/ml}$, FTI between 1 and 4.5 and TPO antibodies >50 IU/ml (positive), were considered as positive TPOAb euthyroid.

Statistical analysis

Continuous variables were checked for normality using the one-sample Kolmogorov-Smirnoff test. Categorical variables are expressed as percentages and were compared using Pearson's χ^2 test. Distributions of variables between the two groups were compared using t test and expressed as mean $\pm$ s.d. Logistic regression was used to identify the association between each risk factor and thyroid dysfunction. Statistical analysis was performed by using SPSS software version 18.

Results

Demographic and reproductive characteristics of study participants are presented in Table 1. Mean $\pm$ s.d.s of age, BMI and gestational age of the women were 27.4 ± 4.9 years, 25.2 ± 4.7 kg/m^2 and 11.4 ± 4.2 weeks respectively. Past history of thyroid disorders was given by 57 (3.9%) women (31 women with hypothyroidism, 18 with hyperthyroidism), but 8 women were unaware of the type of their disorder). Family history of thyroid disorders was reported by 168 (11.4%) women.

Table 1 Characteristics of study population ($n=1480$).

Characteristics	
Maternal age (year)*	27.4 (± 4.9)
Maternal BMI (kg/m^2)	25.2 (± 4.7)
Gestational age (weeks)*	11.4 (± 4.2)
Gestational age, n (%)	
< 14 weeks	1108 (74.9)
14–20 weeks	372 (25.1)
History of infertility n (%)	66 (4.5)
Current pregnancy using infertility medication, n (%)	12 (0.8)
Reproductive history	
Primigravida	504 (34.1)
Multigravida	976 (56.9)
Abortion, n (%)	244 (16.5)
Stillbirth, n (%)	6 (0.4)
Previous history of thyroid disease, n (%)	57 (3.9)
Family history of thyroid disease, n (%)	168 (11.4)

*Mean ($\pm$ s.d.).

Using the predefined classification, 65.8% ($n=974$) had normal thyroid function and 34.2% ($n=506$) had thyroid disorders, including overt hyperthyroidism (0.7%, $n=10$), overt hypothyroidism (1.1%, $n=17$), subclinical hypothyroidism (30.1%, $n=445$), including positive TPOAb (5.5%) and TPOAb negative (24.6%). Overall, 31.2% ($n=462$) had hypothyroidism (1.1% with overt hypothyroidism and 30.1% subclinical). Finally, 8.9% ($n=132$) had positive TPOAb, 2.3% ($n=34$) being euthyroid, with positive TPOAb.

Table 2 presents the prevalence of each risk factor in women with and without thyroid dysfunction. The three most prevalent risk factors were age ≥ 30 years (30.7%), history of abortion (16.5%) and family history of thyroid disorders (11.4%).

In the low-risk group, mean BMI and gestational age of those women with thyroid disorders were significantly higher than those without disorders. In the high-risk group, mean age of women without thyroid disorders was significantly higher than those with the disorders. Thyroid disorders were identified in 39.6 and 27.4% of women in the high- and low-risk groups respectively ($P<0.0001$). Prevalence of abnormal thyroid tests was 64.4 and 35.6% in the high- and low-risk groups respectively.

Eight cases with hyperthyroidism were in the high-risk group and two were in the low-risk group; 88.2% ($n=15$) of cases with overt hypothyroidism were in the high-risk group and 11.8% ($n=2$) were in the low-risk one. Of cases with subclinical hypothyroidism, 60.9% ($n=271$) were in the high-risk group and 39.1% ($n=174$) were in the low-risk group.

Logistic regression analysis demonstrated 15 risk factors, previous history (Odds: 4.44, 95% CI: 2.51–7.84, $P<0.001$) or family history of thyroid disorders (Odds: 1.44, 95% CI: 1.04–1.99, $P=0.031$) was associated with thyroid dysfunction (Table 3).

Discussion

Using the targeted high-risk case finding approach for thyroid dysfunction overlooks about one out of every three pregnant women suffering from these disorders. Of all the risk factors considered for this approach, only past history (Odds: 4.44, 95% CI: 2.51–7.84) or family history of thyroid disorders (Odds: 1.44, 95% CI: 1.04–1.99) were associated with thyroid dysfunction.

Debate about the need for universal screening of thyroid dysfunction in pregnancy is ongoing. Despite lack of sufficient evidence that identification and treatment of pregnant women with subclinical hypothyroidism

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Table 2 The prevalence of risk factors in women with and without thyroid dysfunction. Data are presented as *n*(%).

Risk factor	With thyroid dysfunction	Without thyroid dysfunction	Total
Women with previous history of thyroid dysfunction	39 (7.7)	18 (1.8)	57 (3.9)
Women currently receiving L-thyroxine replacement	5 (1.0)	2 (0.2)	7 (0.5)
Women treated with radioactive iodine	0	2 (0.2)	2 (0.1)
Women with prior therapeutic head or neck irradiation or prior thyroid surgery**	2 (0.4)	0	2 (0.1)
Women with a family history or autoimmune thyroid disease or hypothyroidism	70 (13.8)	98 (10.1)	168 (11.4)
Women with goiter	6 (1.2)	18 (1.8)	24 (1.6)
Women with thyroid antibodies, primarily thyroid peroxidase antibodies	134 (26.5)	0	132 (8.9)
Women with type 1 DM or other autoimmune disorders**	0	8 (0.8)	4 (0.3)
Women with a prior history of miscarriage or preterm delivery	80 (15.8)	164 (16.8)	244 (16.5)
Women with a prior history of preterm delivery	8 (3.0)	18 (3.3)	26 (1.8)
Women with infertility	22 (4.3)	44 (4.5)	66 (4.5)
Women with morbid obesity (BMI ≥ 40)	2 (0.4)	6 (0.7)	8 (0.5)
Women aged ≥ 30 years	150 (29.6)	304 (31.2)	454 (30.7)

**There was no pregnant woman with previous history of other autoimmune disorders or history of head/neck irradiation.

improves maternal or neonatal outcomes, the low cost treatment and widespread availability of screening test is causing the universal screening approach to have fast-gaining popularity (29, 30).

In this study, we found that when potential risk factors for thyroid disease are used, case finding misses 20.0% of those with hyperthyroidism, 11.8% of those with overt hypothyroidism or 39.1% of those with subclinical hypothyroidism. In agreement with our results, Vaidya *et al.* (20) reported that about 30% of women with hypothyroidism and 69% of women with hyperthyroidism were overlooked using the targeted high-risk case finding approach. Wang *et al.* (24) reported that a case identification screening strategy failed to diagnose 81.6%

of pregnant women with hypothyroidism and 80.4% of pregnant women with hyperthyroidism. In a retrospective cohort study, Chang *et al.* (22) also reported that 80% of women with high TSH levels could not be diagnosed using the high-risk case finding approach. The Yang *et al.* (25) study showed that using the high-risk case finding strategy, all the women with overt hypothyroidism and 66.7% of women with overt hyperthyroidism were identified in the first trimester, indicating that this method is inefficient for identification of patients with overt thyroid disorders. The Ohashi *et al.* (23) study also showed that targeted high-risk case finding for diagnosis of thyroid disorders in pregnant women identified only 10% of women with thyroid dysfunction, i.e. 90% of

Table 3 The odds ratio and 95%CI of various risk factors for prediction of thyroid disturbances.

Risk factors	Exp (B)	95% CI Exp (B)	P
Previous history of a thyroid disorder	4.44	2.51–7.84	<0.001
Family history of a thyroid disorder	1.44	1.03–1.99	0.031
History of thyroid drug use	4.85	0.94–25.09	0.060
History of radioactive iodine therapy	0.00	0.00	0.999
Goiter	0.64	0.25–1.62	0.343
History of type 1 diabetes mellitus	0.00	0.00	0.999
History of miscarriage	0.93	0.69–1.24	0.613
History of preterm delivery	0.92	0.40–2.14	0.847
History of other autoimmune disorders	–	–	–
Infertility	0.96	0.57–1.62	0.881
History of head/neck irradiation	–	–	–
Morbid obesity (BMI ≥ 40)	0.64	0.13–3.18	0.585
Women aged ≥ 30	0.93	0.74–1.17	0.535

women with thyroid dysfunction were not identified. Ahmed *et al.* (21) also reported that considering the case finding approach introduced by The Endocrine Association, 34.5% of pregnant women with clinical or subclinical hypothyroidism were overlooked. These variations in results could be partly explained by using various thresholds for TSH, FTI and TPOAb, while we defined normal thyroid status as TSH <2.5 µIU/ml, FTI: 1–4.5 and TPO antibodies <50 IU/ml. Yang *et al.* (25) used cut-off values of 3.47 mU/l in the first trimester and 3.81 mU/l in the second trimester for TSH. Various prevalence of assumed risk factors for thyroid disorders (e.g. age and BMI) in different populations could partly explain these variations in results. In the current study, the average age was 27.4 ± 4.9 years, which differed to that (30.8 ± 4.7 years) of the Ohashi *et al.* study (23). In addition, these variations may be due to the differences in the iodine sufficiency status of regions, because in areas with severe iodine deficiency resulting in a higher prevalence of goiter, more women have the risk factor required for being eligible for the case targeted high-risk case finding approach.

There is no consensus on the risk factors that need to be included in a case finding approach. While American Thyroid Association and European societies guidelines considered age ≥ 30 years as a risk factor and suggested screening all women over the age of 30 years, there is insufficient evidence on the association between age and abnormal thyroid function (31). It has been shown that the addition of women age ≥ 30 years increased the proportion of women identified in a case finding approach from 55.3 to 85.6% (26). It seems that due to wide differences in the prevalence of these risk factors in various communities (32, 33), thyroid screening policies need to be evidence-based for each society (27).

The current study showed that considering the relatively low prevalence of risk factors among Iranian pregnant women, over one-third of women with thyroid disorders (35.6%) are missed by not using universal screening. However, those overlooked women mostly had subclinical thyroid disorders (34.4%, $n=174$) but current data on the impact of treating these women are limited and conflicting. While some studies demonstrate subclinical hypothyroidism results in adverse outcomes of pregnancy (3, 13, 34, 35, 36, 37, 38) and intervention with L-thyroxine (L-T₄) may prevent these complications (39, 40). However, this has not been reported by others (41, 42).

The present study showed that among the risk factors for thyroid dysfunction, past and family histories of

thyroid disorders are significant prognostic factors for prediction of thyroid dysfunction. Pregnant women with a history of thyroid disorders had 4.5 (95% CI) times more chance of having thyroid dysfunction, than those without this history, and a person with a family history of thyroid disorders has a 1.5 times higher chance of having thyroid dysfunction (95% CI) compared to women without this history. In agreement with our results, Dehghani Zahedani *et al.* (2011) and Feki *et al.* (2008) reported predictive ability of past history of thyroid diseases for thyroid disorders in pregnant women, but they demonstrated no significant relationship between a positive family history of thyroid dysfunction and thyroid disorders in pregnancy (41, 42), which was reported by Vaidya *et al.* (20) and Bulmus *et al.* (43). Data also shows that comprehensive assessment of medical and family history of pregnant women could identify 6.7% of thyroid diseases among the pregnant women (43).

The main strength of this study is its methodology, because it is a study conducted mainly on pregnant Iranian women in their first trimester. Comprehensive thyroid assessment including history, physical exam and thyroid function tests were done for all study participants, while in some other studies these have not been measured for all participants (20, 23, 44). However, the results of our study cannot be generalized to other areas with different statuses of iodine sufficiency or other underlying risk factors.

In conclusion, targeted high-risk case finding approach overlooks about one-third of Iranian pregnant women suffering from some type of thyroid dysfunction. While universal screening for thyroid diseases in pregnancy seems to be reasonable considering the low cost treatment and widespread availability of screening test, as current data on the impact of treating subclinical hypothyroidism are limited and conflicting, it cannot yet be recommended. If ongoing prospective trials provide evidence on the efficacy of treating subclinical hypothyroidism in pregnancy, the targeted high-risk case finding approach will be proven inefficient, especially in populations with a low prevalence of presumed risk factors.

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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