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Universal screening as a recommendation for thyroid tests in pregnant women

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Abstract

According to recent recommendations, thyroid tests in pregnancy should be performed only in women in risk groups. However, detailed studies indicate that such an approach results in missing hypothyroidism in 30% and hyperthyroidism in 69% of pregnant women. The aim of this study was to compare the effectiveness of diagnosing hypothyroidism in pregnant women by applying universal screening tests, and assessing risk factors. The study was carried out on 270 non-selected women in single pregnancy who underwent screening for hypothyroidism (diagnostic criteria: TSH >2.5 mIU/L) during their first prenatal visit between the 6th - 10th week of gestation. After excluding the patients with pre-gestational hypothyroidism, risk factors for this disorder were assessed in the remaining subjects. A group of 28 patients (10.4% of all subjects) with hypothyroidism was selected for further thyroid tests, while the remaining 242 pregnant women (TSH <2.5mIU/L) aged 26.3+/-3.59 formed the control group. Twenty subjects (71.4%) were thyroid antibodies-positive, while 8 patients were thyroid antibodies-negative. When analyzing hypothyroidism risk factors, one was found in 10 subjects (35.7%), 2 in 5 subjects (17.8%), whereas, in 13 subjects (46.4%) none were present. Symptoms suggesting thyroid dysfunction were discovered in 8 patients (53.3%), goitre in 5 patients (33.3%), another 5 patients (33.3%) had a positive gynaecological history, and only 2 patients had a positive family history of autoimmune thyroid diseases. During the analysis, it was found that TSH positively correlated with the age of the subjects. In the whole study group, a significant correlation was found between log TSH and hypothyroidism risk factors. Hypothyroidism (TSH >2.5 mIU/L) was diagnosed in 10.4% of the patients. The primary cause of this pathology was thyroiditis which was diagnosed in 71.4% of the subjects. Hypothyroidism risk factors were present in 53.6% of the patients, while in 46.4% there were none, which indicates the necessity of carrying out screening tests in all pregnant women as a method of choice, regardless of the presence of thyroid disease risk factors. A positive correlation between the frequency of thyroid diseases risk factors, TSH, and the age of the patients in the presented study serves as an additional argument for the necessity of universal screening.

Key words

hypothyroidism, iodine deficiency, pregnancy, risk factors, universal screening

INTRODUCTION

The current Endocrine Society Clinical Practice Guideline recommends that targeted screening should be performed at the first prenatal visit, or at the diagnosis of pregnancy, on only those pregnant women who are in risk groups [1]. However, Vaidya *et al.* [2] showed that this approach results in missing as many as 30% of cases of both overt and subclinical hypothyroidism. Moreover, Horacek *et al.* [3] confirmed that screening detects twice as many thyroid disorders in early pregnancy than targeted high-risk case-finding. Despite the above cited findings, thyroid recommendations for pregnant women remain the same, which is a controversial issue. Even though universal screening, compared with targeted case-finding, does not decrease the rate of adverse pregnancy outcomes, early initiation of the treatment does decrease the risk of adverse obstetric outcomes [4]. It is a well established fact that maternal thyroid dysfunction and iodine deficiency in pregnant women negatively affect not only the development of the foetus but also they complicate the pregnancy and induce maternal post-partum adverse outcomes [5-7]. During pregnancy, in countries where iodine sources are sufficient, the thyroid gland may enlarge by 10%, and to a greater extent by 20% in iodine-poor countries, while the production of thyroid hormones and iodine requirement each increase by approximately 50% during pregnancy. Evidence reviewed by the Taskforce included findings from clinical trials showing harmful effects of subclinical thyroid disease, as well as overt hypothyroidism and hyperthyroidism on pregnancy and on maternal and foetal health.

This is a grave problem in terms of the Polish population, as epidemiologic studies conducted in 1992-1993 showed that Poland is a country with moderate iodine deficiency, with the exception of the coastal areas. Therefore, in compliance with the regulations of the Polish Ministry of Health, since 1996 an iodine deficiency prevention scheme has been implemented in Poland in the form of iodized salt and infant formulas. In compliance with the WHO recommendations, pregnant and nursing women should receive an additional dose of 100-150 ug of iodine daily, so that the daily dosage is 250 ug.

Iodine deficiency may result in grave consequences for the whole population as iodine is the main component of thyroid hormones [8]. This is why iodine deficiency in pregnancy may lead to goitre and hypothyroidism in women and, in consequence, to irreversible brain damage of the foetus. An

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extremely dangerous adverse outcome of thyroid hormonal deficiency is a decrease in higher functions of the brain e.g. ability to learn, remember and associate, which results in a decrease of the score of these functions i.e. IQ. Recent evidence suggests that even mild reductions in maternal thyroid hormone levels in early pregnancy are associated with reduced IQ in offspring [9,10]. The foetal thyroid gland reaches maturity close to the end of the first trimester i.e. by the 11^{th} - 12^{th} week, but begins to secrete thyroid hormones around the 16^{th} week. During this period, an adequate supply of maternal thyroid hormones must be sustained to ensure normal neurological development of the foetus [11]. Therefore, maternal hypothyroidism should be avoided. Even subclinical hypothyroidism (serum TSH concentration above the upper limit of the reference range with a normal free T_4) has been shown to be associated with an adverse outcome for both the mother and her offspring [1].

Current studies have shown that only around 50% of pregnant women receive an additional dose of multivitamin preparations, which calls for the close attention of physicians, especially obstetricians and endocrinologists [12]. Therefore, an early diagnosis of hypothyroidism in pregnancy, often accompanied by a correct iodine supplementation and risk factors evaluation, would help eliminate iodine deficiency which is one of the strategic problems of the Public Health in Poland.

The aim of the presented study was to compare the effectiveness of diagnosing hypothyroidism by screening or case finding methods.

MATERIALS AND METHODS

The study was carried out on 270 non-selected outpatients in single pregnancy from August 2009 - September 2010 during their first prenatal visit between the 6th - 10th week of pregnancy. All patients gave informed consent to participate in the study. At the same time, patients with pre-gestational hypothyroidism were excluded from the study. All blood samples were analyzed in the same laboratory, where TSH concentration, thyroid antibodies, thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) were assayed. TSH values (TSH3 ULTRA, norm=0.55-4.5 mIU/L) were measured by 2-site sandwich immunoassay using direct chemiluminescence technology on an ADVIA Centaur analyzer (Siemens, Germany), while the antibodies (norm<60.0 U/mL) were measured by immunoassay using direct chemiluminescence technology on an ADVIA Centaur analyzer (Siemens, Germany).

Nowadays, the upper cut-off value for TSH screening is controversial, not only in pregnant women [13]. For the purpose of this study, it was decided to lower the upper cut-off value for TSH and set it as a criterion for thyroid dysfunction for pregnant women in their first trimester at >2.5 mIU/L, which is in line with indirect conclusions drawn from the recommendations of the Endocrine Society Clinical Practice Guideline for the first trimester [1]. Conclusions shown by Negro *et al.* [14] served as an additional argument for lowering the upper cut-off value for TSH. After excluding the patients with pre-gestational hypothyroidism, the remaining subjects underwent a detailed assessment of hypothyroidism risk factors, as defined by the consensus guidelines [1]. The endocrine consultation included taking personal and family history, as well as performing physical examination with explicit attention to symptoms of thyroid diseases.

Statistical analysis. Statistical analysis of the acquired data was performed. Since there was no symmetry in the TSH distribution, we transformed this parameter by the natural logarithm to obtain the values approximately normally distributed. Comparative analysis of both groups was performed with Student's t-test for independent variables. In order to study the correlation between the pairs of measurable parameters (continuous and dichotomous), the significance test for Pearson's correlation coefficient was used. The adopted significance level was 5% ($p<0.05$), which allowed for revealing the presence of significant differences and correlations. Statistical analyses were performed with STATISTICA v.7 (StatSoft, Poland).

RESULTS

Patients' characteristics. A group of 28 patients 28+/-4.89 years of age (10.4% of all subjects) with primary thyroid dysfunction (TSH >2.5 mlU/L) was selected and subject to further thyroid tests. The remaining 242 patients (TSH<2.5 mlU/L) aged 26.3+/-3.59 ($p=0.02$) formed the control group.

TSH distribution in the study group

TSH of the studied patients is shown in log TSH because there was no symmetry in the TSH distribution (Figure 1). An argument for such a transformation is the fact that the values obtained were approximately normally distributed, which allowed for revealing significant correlations. During the analysis, it was found that TSH positively correlated with the age of the subjects ($p=0.012$).

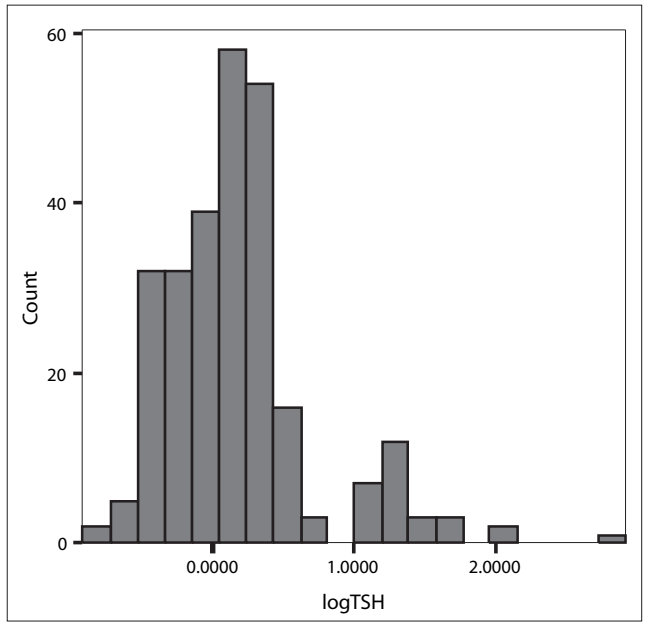

Figure 1. TSH distribution (log TSH) in the study group

Thyroid antibodies test with TSH concentration

Positive thyroid antibodies were detected in 20 of the pregnant women (71.4%), while in 8, none were found. A detailed analysis of the presence of antibodies with TSH levels is shown in Table 1. All patients with TSH >4.5

Table 1. Presence of thyroid antibodies (TPOAb) in patients with thyroid dysfunction (TSH >2.5 mIU/L) with TSH interval references and risk factors

Parameter	Thyroid antibodies (TPOAb)	
Group TSH (mIU/L)	Study group ± risk factors (N=28)	Subgroup with no risk factors (N=13)
2.5-3.5	5/10	2/3
3.5-4.5	6/9	3/6
>4.5	9/9	4/4

mIU/L, regardless of the presence of risk factors, were thyroid antibodies-positive, while patients with a lower TSH concentration were both thyroid antibodies-positive and negative.

Analysis of hypothyroidism risk factors. In the whole study group, a significant correlation between log TSH and hypothyroidism risk factors was found in terms of clinical symptoms, goitre, positive family and obstetric history ($p<0.05$) (Tab. 2). It should be noted that the above risk factors in patients with TSH <2.5 mIU/L were not common. When analyzing hypothyroidism risk factors in the subgroup of patients with TSH >2.5 mIU/L, only one in 10 subjects (35.7%) and 2 two in 5 subjects (17.9%) were found. No patient manifested 3 risk factors at a time, whereas in 13 subjects (46.4%) none were present (Figure 2).

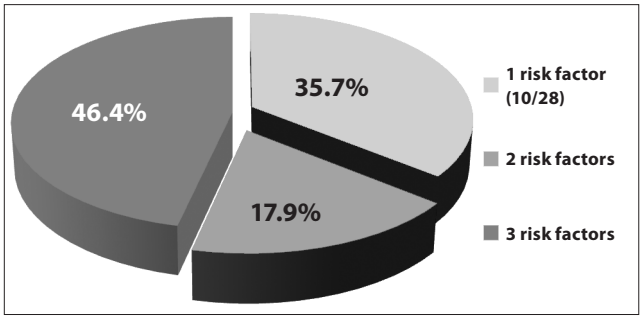

Figure 2. Hypothyroidism risk factors in pregnant women.

Among risk factors, the most frequent were those implying thyroid dysfunction and were found in 8 patients, goitre in 5 patients, 5 patients had a positive obstetric history, and only 2 patients had a positive family history of autoimmune thyroid diseases.

Levothyroxine ($L\text{-}T_4$) treatment was initiated in all 28 patients with primary hypothyroidism with dosages altered so that the TSH level could be <2.5 mIU/L.

DISCUSSION

In the presented study as many as 46.4% (~ 50%) of the patients with thyroid dysfunction with TSH limit for detection >2.5 mIU/L in early pregnancy showed no hypothyroidism risk factors. This would have resulted in missing almost half of the patients at diagnosis if only targeted case-finding had been taken into consideration. These findings clearly illustrate the necessity for carrying out screening tests in all pregnant women as a method of choice, regardless of the presence of thyroid disease risk factors. Horacek *et al.* [3] arrived at a similar conclusion and claimed that over half (55%) of gestational women in their study would have been missed if only those with high-risk criteria were examined. Even though they used a different study design with an upper cut-off value for TSH at >3.5 mIU/L, their conclusions were in line with the findings presented in this study, and is yet another debatable issue concerning screening. Being aware of different TSH values in consecutive trimesters, compared to non-pregnant women, researchers do not agree upon clear-cut trimester-specified ranges [15]. Australian studies carried out on 2,155 pregnant women between the 9th - 13th week of gestation clearly showed that the reference interval for TSH during the first trimester of pregnancy differs substantially from that for non-pregnant women, and applying the general laboratory reference range to pregnant women would result in misclassification of thyroid status for over 20% of the cases. As a consequence of this, the upper cut-off for TSH value was lowered from 4.0 mIU/L to 2.15 mIU/L, however, without specific recommendation due to time limits of the study [16].

This was also an issue in the presented study; however, we were only interested in the upper cut-off value as we studied hypothyroidism. We were aware of the necessity to lower the upper cut-off value for TSH in the first trimester of gestation on the basis of the findings of many already cited studies and on own experience. However, it was decided to refer, at least non-directly, to clear recommendations of the Endocrine Society Clinical Practice Guideline regarding the substitute therapy i.e. lowering the TSH value to a level below 2.5 mIU/L in the first trimester of gestation, regardless

Table 2. Pearson's correlations (N=270)

	log TSH	TSH group	present risk factors	Age	present clinical symptoms of hypothyroidism	goitre	positive obstetric history	positive family history
log TSH	1	0.793**	0.345**	0.152*	0.343**	0.237**	0.154*	0.126*
TSH group	0.793**	1	0.449**	0.141*	0.448**	0.275**	0.221**	0.133*
present risk factors	0.345**	0.449**	1	0.099	0.545**	0.516**	0.599**	0.381**
age	0.152*	0.141*	0.099	1	0.013	0.088	-0.008	0.146*
present clinical symptoms of hypothyroidism	0.343**	0.448**	0.545**	0.013	1	0.291**	0.148*	-0.027
goitre	0.237**	0.275**	0.516**	0.088	0.291**	1	-0.040	0.128*
positive obstetric history	0.154*	0.221**	0.599**	-0.008	0.148*	-0.040	1	0.104
positive family history	0.126*	0.133*	0.381**	0.146*	-0.027	0.128*	0.104	1

** Correlation significant at 0.01 (bilaterally).
* Correlation significant at 0.05 (bilaterally).

of whether hypothyroidism was diagnosed before or during pregnancy [1]. The fact that this choice was the right one was confirmed by the study performed by Negro *et al.* [14], who clearly showed that TPOAb-negative pregnant women whose TSH was within the range of 2.5-5.0 mIU/L had an increased risk of miscarriage. They suggested that in the first trimester the upper limit for TSH should be 2.5 mIU/L, which indicates the need of redefining the TSH upper limit in the first trimester to this value.

Another argument we present in favour of lowering the upper limit of TSH in the first trimester of pregnancy, as well as in favour of universal screening over targeted case-finding, is the results of the thyroid antibodies test. These showed that some patients whose TSH value was within the range regarded as normal, i.e. 2.5 mlU/L-4.5 mlU/L, suffered from completely asymptomatic thyroiditis with high TPOAb. This is an indication for the initiation of L-T_4 treatment and improve the final outcome of pregnancy, as it has been shown that there is a positive correlation between thyroid antibodies in the course of chronic thyroiditis and the frequency of miscarriage rate and premature deliveries [17,18]. It is worth noting that patients with no overt thyroid dysfunction risk factors were thyroid antibodies-positive. All these patients were diagnosed and treated only thanks to screening tests. Therefore, they had the chance of a positive pregnancy outcome.

At the same time, we are aware of the weaknesses of the presented study, as the small number of patients lowers its power. However, focusing on the integrity of race, age, as well as the comparability of laboratory tests, we completed enrolment after one year. Another limitation of the study was the lack of assayed free T_4 (fT_4) values, as not all pregnant women gave their consent for participation in expanded tests, and some of them had been treated earlier with L-T_4. Therefore, we could have missed pregnant women with isolated low serum fT_4 concentration and normal serum TSH. Such cases were found in 7.8% of the entire cohort reported by Vaidya *et al.* [2], with equal frequency in the low- and high-risk groups.

Moreover, the lack of both assessment of the course of pregnancy and its outcomes limits the conclusions. However, the fact must be emphasised that at the core of our interest was the comparison of 2 methods of diagnosing thyroid dysfunction with the advantage of screening tests over targeted case-finding.

The presented study is timely because there is now a growing debate about the merits of screening for thyroid dysfunction during pregnancy. Many professional associations of endocrinologists have taken varying views, with evidence-based review panels concluding that there is insufficient evidence to recommend universal screening, while other expert panels advocate screening [1,19]. The recommendations of the Guidelines Committee of the National Academy of Clinical Biochemistry should be emphasized here as they favour screening tests in women for TSH, TPOAb, both before pregnancy and in the first trimester, to detect mild thyroid insufficiency and assess their risk for post-partum thyroiditis. The American Association of Clinical Endocrinologists shares a similar view [20,21].

Universal screening tests for TSH carried out in all pregnant women or during the preconceptual stage entails costs, and it therefore remains controversial. However, applying this screening in one's practice together with carrying out well-documented, randomized studies, including high numbers of patients, would entail acting in the best interest of the patient and her offspring.

CONCLUSIONS

In summing-up, it must be emphasized that hypothyroidism (TSH >2.5 mlU/L) was diagnosed in 10.4% of pregnant women in the first trimester. The primary cause of this pathology was thyroiditis, diagnosed in 71.4% of the subjects. Thyroid dysfunction risk factors were found in 53.6% of the patients, while in 46.4% (~50%) no risk factors were noted, which indicates the necessity of carrying out screening tests in all pregnant women as a method of choice, regardless of the presence thyroid disease risk factors. Finding a positive correlation between TSH concentration and the patient's age, and the frequency of thyroid disease risk factors is yet another argument for universal screening tests.

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