

SCREENING FOR THYROID DISORDERS IN THE FIRST TRIMESTER OF PREGNANCY

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Abstract

Screening for thyroid disorders during pregnancy is an essential method of detection and could prevent maternal and foetal complications to a considerable extent. The aim of this study was to establish the prevalence of hypothyroidism in pregnancy and to compare universal, targeted and no screening. A prospective-retrospective study was conducted at Neoclinic Medical Centre and University Obstetrics and Gynaecology Hospital “Maichin Dom” between 2018 and 2020 in 420 pregnant women. It was conducted in two parts, with the first part (133 subjects) involving universal screening in the first trimester of newly registered pregnant women during their first obstetrician-gynaecologist visit, and the second part (287 subjects) involving patients in the third trimester who had been screened for thyroid-stimulating hormone (TSH) during pregnancy, with the screening reasons being later on analyzed and, respectively, whether the patients were covered by screening and with what type of screening the patients with thyroid disorder would have been diagnosed. TSH was tested in all patients, and a value of 2.5 mIU/L was accepted as the upper limit of normal for the screening in the first trimester. We found hypothyroidism in 28.6% (38/133) of the patients using universal screening. At least one criterion for increased risk of developing thyroid disorder during pregnancy was present in 78.9% (30/38). Thus, a targeted screening would miss 21.1% (8/38) of the patients in risk. In the second part of the study, the disease was detected in 65.51% (188/287) by either prophylactic testing or universal screening during pregnancy; 31.36% (90/287) of the subjects were diagnosed due to clinical suspicion and 3.13% (9/287) due to family history. Eighty per

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cent (153/190) of the patients with hypothyroidism were high-risk with the most common criteria being: age above 30 – 63.2% (120/190), autoimmune co-morbidity – 35.8% (68/190) and personal history of miscarriage – 31.1% (59/190). Targeted screening would miss 19.5% (37/190) of them. Most of the patients with clinical hypothyroidism (49/64) would have been classified as high-risk had they been screened universally and therefore 23.4% (15/64) would have been missed in a targeted screening. About 21.1% (8/38) of the patients with hypothyroidism would have been missed with targeted screening and between 28.6% (38/133) and 65.51% (188/287) in the absence of any screening suggesting the need of universal screening establishment at the first visit to an obstetrician-gynaecologist.

Key words: hypothyroidism, pregnancy, screening

Introduction. Thyroid function disorders are relatively common in women of reproductive age. That is why we often encounter them during pregnancy, more so as a newly diagnosed condition. They often present no symptoms or if symptomatic they are difficult to distinguish from the typical complaints of pregnancy. Subclinical hypothyroidism occurs in an average of 2.5% of pregnant women, with a much higher incidence reported in China (4.0%), Belgium (6.8%) and Northern Spain (13.7%). Clinical hypothyroidism is less common (0.2–0.5%), and subclinical hypothyroidism is also reported in up to 2% of children [1].

Thyroid hormones have a determining role in foetal growth and neurological development and can affect both foetal and maternal condition. Hypothyroidism during pregnancy is associated with adverse outcomes for the foetus including increased incidence of low foetal birth weight, foetal distress, intrauterine death and post-partum neurological events, such as reduced intellectual abilities, mental retardation and cerebral palsy. Women with untreated hypothyroidism during pregnancy also have increased chances of miscarrying, developing anaemia, preeclampsia, hypertension, cardiac dysfunction, post-partum haemorrhage, and placental abruptions [2]. Even sub-clinical hypothyroidism has been associated with a number of adverse outcomes – miscarriage, gestational hypertension, preterm birth, neurologic deficit [3, 4].

Considering the above complications, systematic screening of pregnant women seems rational, even if it predominantly detects women with sub-clinical hypothyroidism.

National health programs in different countries offer two approaches – mass screening for thyroid disorders of pregnant women or only when risk factors are present (targeted). While universal screening is recommended in some countries (Spain, China, Poland), other countries use targeted screening to detect high-risk patients (UK, USA). In universal screening, all pregnant women are tested, while in targeted screening testing is performed only in the presence of risk factors for thyroid disorders during pregnancy. According to the European Thyroid Association (ETA), risk factors for inclusion in screening are: clinical symptoms of

thyroid disease, elevated thyroid antibodies or goiter, history of thyroid surgery, ongoing Levothyroxine therapy, age of 30 or more, family history of thyroid disease, type 1 diabetes, autoimmune disease, previous miscarriage or preterm birth, multiple pregnancy, morbid obesity, Amiodarone, Lithium, iodine-containing radiopaque agents in the last weeks before pregnancy, women from iodine-deficient regions [1,5]. The American Thyroid Association (ATA) adds 3 more risk factors: a history of thyroid dysfunction, x-ray exposure in the neck region, two or more prior pregnancies [6].

Screening may be performed in either the first or the second trimester; however, most authors highlight the benefits of conducting screening as early as possible in order to initiate treatment during early foetal neurodevelopment. Peripheral TSH and fT4 levels are variable across different stages of pregnancy, maternal iodine status, and measurement technique, and therefore the establishment of population-based and trimester-specific reference ranges is important [7].

Screening only high-risk patients would result in missing a large percentage of cases, and according to the economic model, universal screening is more cost-effective than targeted screening [8].

Materials and methods. A prospective-retrospective study was conducted between 2018 and 2020. A total of 420 pregnant women were included. In the first part of the study, universal screening was performed at the Neoclinic Medical Centre in all patients who were newly registered and an intrauterine singleton pregnancy was confirmed at the first visit – 133 patients; The second part was conducted at University Obstetrics and Gynaecology Hospital “Maichin Dom” and included 287 patients who were examined during pregnancy for their thyroid status.

Inclusion criteria for the first part of the study patients ($n = 133$): 1) women in the first trimester of pregnancy; 2) singleton pregnancy; 3) pregnancy resulting in delivery after 22 weeks gestation and/or weight > 600 g. Inclusion criteria for the second part of the study patients ($n=287$): 1) pregnant women, regardless of the stage of pregnancy, who have had a TSH test during pregnancy; 2) singleton pregnancy; 3) pregnancy resulting in delivery after 22 weeks gestation and/or weight > 600 g.

For the diagnosis of hypothyroidism during pregnancy, we used the Recommendations for Good Clinical Practice for Thyroid Disease of the Bulgarian Society of Endocrinology, published in 2019: elevated TSH concentration above the upper limit of the trimester-specific reference ranges in the respective population. In case such specific reference-ranges are not available, the following reference ranges may be used:

- First trimester: 0.1–2.5 mIU/L;
- Second trimester: 0.2–3.0 mIU/L;
- Third trimester: 0.3–3.0 mIU/L;

Subclinical hypothyroidism is defined as a condition characterized by mildly

to moderately elevated TSH values and normal fT4 and fT3 levels; and *clinical* hypothyroidism – by elevated TSH values and low fT4 and fT3 levels [5].

The statistical analysis was performed using SPSS version 13 for Windows, descriptive statistics.

Results. In the first part of the study, 133 patients were examined; universal screening was performed and TSH was tested in all of them in the first trimester at their first visit to an obstetrician-gynaecologist for pregnancy. The value of 2.5 mIU/L was accepted as the upper limit of the normal TSH reference range. As a result, thyroid disorder was detected in 28.6% (38/133) (Table 1).

T a b l e 1
Thyroid disorder detected during universal
screening

Thyroid disorder	<i>N</i>	%
No	95	71.4
Yes	38	28.6
Total	133	100.0

The disorders detected are distributed as follows in the group: Hashimoto’s thyroiditis – 17/38 (44.7%), Hypothyroidism – 19/38 (50.0%), Diffuse goiter – 1/38 (2.6%), and Hyperthyroidism – 1/38 (2.6%).

Some of the patients were additionally tested for fT4, Anti-Tg Ab and Anti-TPO Ab in the first trimester and it was found that 43.5% had elevated Anti-TPO Ab, 22.7% had elevated Anti-Tg Ab, and 25% had clinical hypothyroidism. The value of 34 IU/ml was accepted as the upper limit for Anti-TPO Ab, 116 IU/ml for Anti-Tg Ab, and a reference range of 10.6–22.7 pmol/L for fT4.

In a subsequent analysis of pregnant women with a disorder detected during universal screening ($n = 38$), it was found that 30/38 fell into the high-risk group for developing hypothyroidism during pregnancy. Therefore, in a targeted screening of female patients, 21.1% would have been missed because of the lack of stigmata for increased risk of developing thyroid disease according to the ETA criteria.

Due to the trend of changing the upper limit of normal TSH during pregnancy by the American Association of Endocrinology as well as by many similar organizations from countries in Asia, we found that if an upper limit of 4 mIU/L for the normal TSH reference range is accepted (in our study it was 2.5 mIU/L), the disease would be diagnosed in 4.51% (6/133) of the patients.

The second part of the study included 286 patients from the University Obstetrics and Gynaecology Hospital “Maichin Dom”. A retrospective analysis of the motivation for TSH testing in these patients was performed – 65.51% (188/287) had preventive testing, 31.36% (90/287) presented symptoms, and 3.13% (9/287) had family history of thoroid disease. We further divided the patients into two

T a b l e 2

Distribution of pregnant women according to the values of TSH, Anti-TPO Ab, Anti-Tg Ab, and fT4 in the first trimester

Indicator		1st trimester TSH		Total
		< 2.5 mIU/L	≥ 2.5 mIU/L	
Anti-Tg Ab ≤ 116 IU/ml	N	5	17	22
	%	71.4%	77.3%	75.9%
Anti-Tg Ab > 116 IU/ml	N	2	5	7
	%	28.6%	22.7%	24.1%
Total	N	7	22	29
	%	100.0%	100.0%	100.0%
Anti-TPO Ab ≤ 34 IU/ml	N	2	13	15
	%	28.6%	56.5%	50.0%
Anti-TPO Ab >34IU/ml	N	5	10	15
	%	71.4%	43.5%	50.0%
Total	N	7	23	30
	%	100.0%	100.0%	100.0%
fT4 < 10.67 pmol/L	N	0	2	2
	%	0.0%	25.0%	18.2%
fT4 10.6–22.77 pmol/L	N	3	6	9
	%	100.0%	75.0%	81.8%
Total	N	3	8	11
	%	100.0%	100.0%	100.0%

subgroups: patients with thyroid disease ($n = 190/287$), and patients who had normal TSH values and were not taking thyroid therapy ($n = 97/287$). In the first subgroup, 48.8% (92/190) had preventive testing, 47.4% (90/190) had symptoms, and 4.2% (8/190) had testing due to family history. In the second subgroup, 99% (96/97) of the patients had preventive testing and 1% (1/97) due to family history. Additional analysis was made in the first subgroup – 80.5% (153/190) of these patients fell into the high-risk group for developing hypothyroidism during pregnancy. Therefore, a targeted screening would have missed 19.5% (37/190) of them. Analyzing the criteria for placing the patient in the appropriate high-risk group, we found that 58.9% (112/190) of them met two or more criteria, and 28.9% (55/190) met at least one criterion. Most often it was age above 30 years – 63.2% (120/190) of the patients, followed by the presence of another autoimmune disease – 35.8% (68/190), and finally history of miscarriage – 31.1% (59/190). In this group, 64 (64/190) patients had clinical hypothyroidism, with 76.6% (49/64) of them being in the high-risk group, where a targeted screening would have missed 23.4% (15/69) of them.

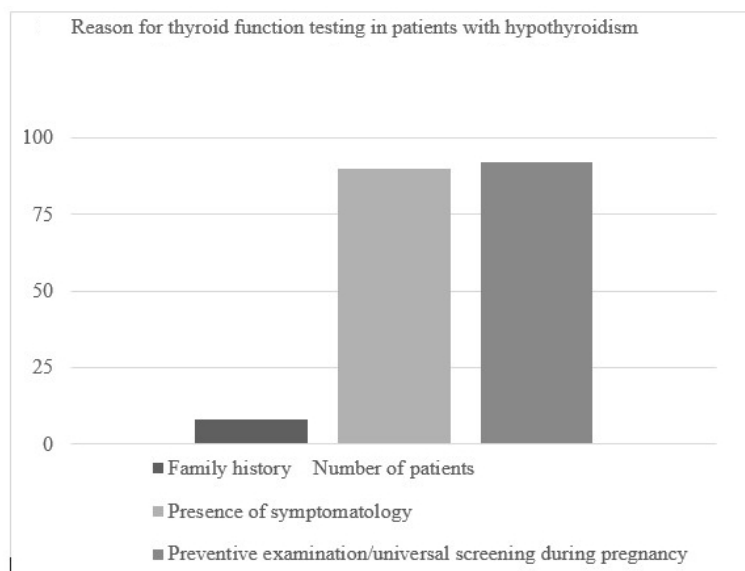


Fig. 1. Distribution of the reasons for which thyroid function was examined in patients with hypothyroidism

Discussion. In 2019, the Bulgarian Society of Endocrinology (BSE) issued Recommendations for Good Clinical Practice for Thyroid Disease. There are indications for screening (so-called targeted screening) for thyroid dysfunction during pregnancy only if risk factors are present and these indications are the same as those listed above in the European Thyroid Association (ETA) Guidelines. In summary, the investigations recommended by the BAE in high-risk patients are: TSH and fT4 shortly before becoming pregnant or in the first trimester of pregnancy, anti-TPO Ab, thyroid ultrasonography [1,5].

The question of the iodine status of Bulgarian population arises accordingly. Two international groups and studies classified the country's population as having optimal iodine intake [9,10]. Furthermore, a large-scale nationwide survey among 537 women has shown the following results: low urinary iodine concentration (UIC) in 221 pregnant women (41.1%), and normal and above-optimal – in 316 pregnant women (58.9%), the areas with the lowest concentration were Gotse Delchev, Gabrovo and Troyan [11]. Despite numerous Europe-wide studies, most regional ones report iodine deficiency for each individual country. Based on this, VELASCO and TAYLOR [12] highlight the need for universal screening in Europe, taking into account that most countries on the continent are iodine deficient, unlike America.

Since 2010, large-scale international research on the screening of pregnant women has started, based on which the first Recommendations and Guidelines of the Societies were issued. Two studies from this period, involving a total of 26

408 patients, should be highlighted. The results of both studies demonstrate that universal screening covers more patients with hypothyroidism, 2.8% [13] and 4.6% [14], versus 0.9% with targeted screening and 0 patients with no screening. NEGRO et al. [13] conclude that universal screening does not reduce severe complications in general, but since it has a chance of protecting even one patient from them, it is worthwhile. LAZARUS et al. [14] conclude that universal screening is most likely effective, but cannot assess whether conducting it would have a positive impact on maternal and foetal health.

Other European studies have established higher incidence rates – 10.3% in Poland, with 55% of patients likely to be missed if targeted screening is performed instead of universal one. There, too, the proportions of criteria that put the patient in the high-risk group were investigated, and in contrast to our study most often it was family history (31%), followed by miscarriage or preterm birth (14%) [15]. The Polish Society of Endocrinologists recommends measuring TSH either before becoming pregnant or in 4–8 weeks of pregnancy in all Polish women [16]. The Spanish Society of Obstetrics and Gynaecology, on the other hand, has recommended universal screening with TSH testing not later than the 10th week of pregnancy [17].

In Romania, there are no accepted national recommendations for the diagnosis and treatment of hypothyroidism during pregnancy, and their national associations have not come up with a statement to follow any of the international guidelines [18].

A large percentage of the European countries, especially those closer to Bulgaria, are just starting to develop population-based reference ranges for each trimester of pregnancy and do not have regulated screening programs on a national level. At the same time, a large survey among European endocrinologists showed that 42% of them examine all pregnant women and 43% conduct targeted screening [19].

In 2020, FERREIRA et al. [20] published an interesting literature review, covering a total of 393 articles, including Guidelines, meta-analyses of 5758 patients, and controlled trials. Summarized, the arguments in favour of universal screening introduction are: thyroid disorders are a frequent problem in the fertile population; selective screening requires careful and in-depth analysis of the criteria and yet misses a significant number of patients; readily available and inexpensive tests for diagnosis, safe, easy and inexpensive therapy; potential prevention of severe complications when therapy is employed; can be performed immediately before becoming pregnant or at the first visit to the gynaecologist; could prevent thyrotoxicosis in pregnant women with hyperthyroidism; and the few studies on cost effectiveness show that it is higher for universal screening. Summarized, the disadvantages of universal screening include: population-based and trimester-specific reference ranges for normal TSH are missing in many places (this also applies to Bulgaria, where the European reference ranges have been adopted, as well as to

a large percentage of the other countries in Europe and the Middle East); still insufficient data on the effectiveness of hypothyroidism therapy on the serious complications of pregnancy; questionable benefits in populations with sufficient iodine intake (as already mentioned just over 40% of Bulgarian pregnant women were deficient); significant drop in benefit from screening if not performed by mid-first trimester of pregnancy. In conclusion, they recommend universal screening [20].

Conclusion. It is appropriate to consider the introduction of universal screening at the first visit to a gynaecologist in Bulgaria and to ensure adequate iodine intake and monitoring of thyroid function to minimize maternal and foetal adverse events. There is a need to create trimester-specific reference ranges of TSH for the Bulgarian population.

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