Point Prevalence of Abnormal Thyroid-Stimulating Hormone during the First Trimester of Pregnancy in Israel

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ABSTRACT: **Background:** The prevalence of thyroid dysfunction in early pregnancy in Israel is not known.

Objectives: To assess the rate of abnormal thyroid-stimulating hormone (TSH) tests in low risk pregnant women attending a community clinic in Israel.

Methods: We conducted a retrospective analysis of the charts of low risk pregnant women (n=303) who had undergone a TSH screening during the first trimester of pregnancy at Clalit Health Services Women's Health Centers in Ashkelon and Tel Aviv. TSH of 0.1–2.5 mIU/L during the first trimester was considered to be normal.

Results: The TSH levels ranged from 0.04 to 13.3 mIU/L (median 1.73 mIU/L, mean 1.88 mIU/L). The rate of abnormal TSH was 25.6%, with low TSH 2.3% and high TSH 23.4%. The prevalence of abnormal TSH was not influenced by gravidity (primigravidas versus multigravidas) or place of residence (Ashkelon or Tel Aviv).

Conclusions: In view of the high prevalence of abnormal TSH (25.6%) in pregnant women in Israel during the first trimester, a universal country-wide screening should be considered.

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Normal maternal thyroid function is imperative for fetal neurodevelopment as well as for optimal maternal health [1]. Both overt and subclinical hypothyroidism and hyperthyroidism were reported to be associated with poor pregnancy outcome [2]. Hyperthyroidism during pregnancy is associated with adverse outcomes such as spontaneous abortions, premature labor, low birth weight, stillbirth, preeclampsia, and heart failure [2,3]. Hypothyroidism in pregnancy is linked to an increased rate of spontaneous abortion, preterm birth, intrauterine growth restriction, and neurodevelopmental deficits in the children [2,4-6]. It was recently suggested that maternal thyroid dysfunction during pregnancy affects thyroid function parameters of the offspring in adolescence even without definite proof of an increase in the risk of thyroid disease in the children [7].

TSH alone is considered the most sensitive test to reliably detect thyroid function abnormalities [2]. Furthermore, TSH measurements were shown to be useful in detecting even subtle thyroid dysfunction associated with poor pregnancy outcome [2]. Still, there is an ongoing debate regarding the need for universal screening for thyroid dysfunction during pregnancy [8,9]. One of the objections is the limited evidence that levothyroxine treatment is beneficial in pregnant women with subclinical hypothyroidism, isolated hypothyroxinemia, or thyroid autoimmunity [9]. For example, a recent study reported that antenatal screening in early pregnancy and maternal treatment for hypothyroidism did not result in improved cognitive function in children at age 3 years [10]. Another consideration for universal screening is the prevalence of overt or subclinical dysfunction in pregnancy. A recent study has demonstrated that TSH levels differ significantly according to ethnicity in pregnant women living even in an iodine-sufficient area [11].

The prevalence of thyroid dysfunction in early pregnancy in Israel is not known. The primary goal of this study was to assess the rate of abnormal TSH test in low risk pregnant women attending a community clinic. The secondary goal was to compare abnormal TSH rates in different areas with possible diverse socioeconomic status.

PATIENTS AND METHODS

The study, designed as a retrospective case series, was conducted in the Women's Health Centers of Clalit Health Services in Ashkelon and Tel Aviv. Data were collected by reviewing the charts of low risk pregnant women who had undergone a TSH screening during the first trimester of pregnancy in 2012 or the beginning of 2013. A total of 303 pregnant women were enrolled in the study, 150 from Ashkelon and 153 from Tel Aviv. The primary outcome measure was the rate of abnormal TSH test. The study protocol was approved by the Meir Medical Center, Kfar Saba Institutional Review Board Committee (protocol number 123/2012).

TSH TEST

The TSH test was performed as a standard laboratory procedure. The TSH normal range during the first trimester of pregnancy was defined in accordance with the guidelines of the American Thyroid Association, namely between 0.1 miU/L and 2.5 mIU/L [10]. Thus, low levels suggesting hyperthyroidism were considered as ≤ 0.09 mIU/L, and high levels suggesting hypothyroidism as ≥ 2.51 mIU/L.

STATISTICAL ANALYSIS

For continuous variables, descriptive statistics were calculated and reported as mean ± standard deviation and were compared by using the *t*-test for independent samples. Proportions were compared using the chi-square test with Yate's correction for small numbers. All tests were two-sided and considered significant at $P < 0.05$.

RESULTS

The age of the 303 women enrolled in the study ranged from 18 to 46 years (mean 30.6 years). The pregnancy order ranged from 1 to 7, with a median of 2, and for 147 women (48.5%) this was their first pregnancy. At the time of TSH analysis, the gestational age ranged from 4 to 14 weeks (mean 8.3 weeks). The TSH levels ranged from 0.04 to 13.3 mIU/L (median 1.73 mIU/L, mean 1.88 mIU/L). The rate of abnormal TSH was 25.6%, with low TSH (≤ 0.09 mIU/L) of 2.3% (7 of 303) and high TSH (≥ 2.51 mIU/L) of 23.4% (71 of 303).

The comparison of TSH between primigravidas and multigravidas is shown in Table 1. Multiparas were older and underwent the TSH test at a later gestational age. The mean TSH was similar in primigravidas and multigravidas with statistically insignificant differences in the rate of low or high TSH. The comparison of TSH between pregnant women in Ashkelon and Tel Aviv is shown in Table 2. Pregnant women from Ashkelon were younger, of a higher order of pregnancy, and underwent the TSH test at a later gestational age. The mean TSH was similar in pregnant women from Ashkelon and Tel Aviv with statistically insignificant differences in the rate of low or high TSH.

The rate of abnormal TSH in Israel compared to other countries as reported in the literature [11-18] is presented in Table 3.

Table 1. TSH in primigravidas compared to multigravidas

	Primigravidas (n=147)	Multigravidas (n=156)	*P* value
Age (yr)	29.4 ± 4.2	31.7 ± 4.4	< 0.001
Gestational age at analysis (wk)	8.1 ± 2.1	9.2 ± 2.6	< 0.001
TSH (mIU/L)	1.9 ± 1.2	1.8 ± 1.5	0.526
Abnormal TSH (%)	40 (27.2%)	38 (25.7%)	0.578
Low TSH (≤ 0.09 mIU/L)	3 (2.0%)	4 (2.6%)	0.935
High TSH (≥ 2.51 mIU/L)	37 (25.2%)	34 (21.8%)	0.504

P < 0.05 was considered statistically significant
TSH = thyroid-stimulating hormone

Table 2. TSH in pregnant women from Ashkelon compared to those from Tel Aviv

	Women from Ashkelon (n=150)	Women from Tel Aviv (n=153)	*P* value
Age (yr)	29.4 ± 4.4	31.8 ± 4.1	< 0.001
Gravidity (n)	2.4 ± 1.4	1.6 ± 0.9	< 0.001
Gestational age at analysis (wk)	9.4 ± 2.2	7.8 ± 2.4	< 0.001
TSH (mIU/L)	1.8 ± 1.3	1.9 ± 1.4	0.522
Abnormal TSH (%)	37 (24.7%)	41 (26.8%)	0.675
Low TSH (≤ 0.09 mIU/L)	6 (4.0%)	1 (0.7%)	0.116
High TSH (≥ 2.51 mIU/L)	31 (20.7%)	40 (26.1%)	0.259

P < 0.05 was considered statistically significant

Table 3. Rate of high TSH in pregnant women around the world as reported in the literature

Country [ref]	High TSH rate	No. of women Screened
Netherlands, Moroccan ethnicity [13]	2.7%	308
Tunis [14]	2.7%	147
Russia [15]	6.3%	1588
Netherlands, Turkish ethnicity [13]	10.8%	421
Brazil [16]	11.3%	115
Poland [17]	14.0%	62
North India [18]	14.3%	1000
Netherlands, Dutch ethnicity [13]	15.5%	2765
USA [19]	15.5%	117,892
Netherlands, Surinamese ethnicity [13]	17.7%	450
Israel (current study)	23.4%	303
Czeck Republic [20]	28.8%	73

In some studies high TSH level was defined as > 4.5 mIU/L

DISCUSSION

This study aimed to evaluate TSH levels during the first trimester of pregnancy in a cohort of low risk Israeli women. The main finding is that 25.6% of low risk women attending routine pregnancy care in Israel have an abnormal TSH in the first trimester of pregnancy. Of these women, 2.3% have low TSH and 23.4% have high TSH. The prevalence of abnormal TSH was not influenced by gravidity (primigravidas versus multigravidas) or place of residence (Ashkelon or Tel Aviv). The rate of low TSH in our study is similar to that reported in the literature, 1%–3% [9]. Low or suppressed TSH at the beginning of pregnancy is usually attributed to transient hyperthyroidism

secondary to elevated human chorionic gonadotropin levels [19]. High TSH at the beginning of pregnancy is of greater significant clinical importance since it may indicate hypothyroidism that is linked to adverse pregnancy outcome, such as increased rate of spontaneous abortion, preterm birth, intrauterine growth restriction, and neurodevelopmental deficits in the children [2-6].

Elevated TSH concentration during pregnancy with rare exceptions (such as TSH-secreting pituitary tumor, thyroid hormone resistance, or central hypothyroidism with biologically inactive TSH) indicates overt or subclinical hypothyroidism [9]. Another major cause of hypothyroidism in pregnancy is iodine deficiency [2]. In pregnancy, the iodine excretion rate is increased, probably in parallel with an increased glomerular filtration rate [20]. This would suggest that in the absence of increased dietary iodine intake during pregnancy, pregnant women would have a more prominent negative iodine balance. The different prevalence of iodine deficiency across the world may be one of the explanations for the wide reported range (2.7%–28.8%) of high TSH in different countries [Table 3] [11-18]. A study performed in Israel in 2004 revealed that the iodine content of drinking water was on average > 10 μg/L, a cutoff considered acceptable by the World Health Organization, with one-third of the samples being below this cutoff [21]. Mild to moderate iodine deficiency was present in up to 27% of pregnant as well as non-pregnant subjects in that study [21]. Thus, iodine deficiency may be one of the reasons for the relatively high prevalence of elevated TSH (23.4%) during the first trimester of pregnancy in Israel.

Another explanation for the relatively high prevalence of elevated TSH during the first trimester in Israel may be the previously reported ethnic differences in TSH [11,22]. It was argued that the reported ethnic differences in TSH might be associated with different iodine intake. The "generation R study" eliminated the iodine intake factor by investigating different ethnic groups in the same geographic area [11]. The study demonstrated a different ethnic prevalence of elevated TSH: 2.75%, 10.8%, 15.5% and 17.7% in Moroccan, Turkish, Dutch and Surinamese ethnic groups, respectively [11]. Theoretically, the reported ethnic differences in TSH during pregnancy may be explained by genetic differences in thyroid hormone pathway genes [23], as inter-individual variation in TSH levels was previously reported to be due to genetic factors [24].

Another reason for the wide reported range (2.7–28.8%) of high TSH in different countries [Table 3] [11-18] could be the different cutoffs for defining high TSH. In some studies high TSH level was defined as > 4.5 mIU/L [18] or as > 3.67 mIU/L [18]. We used the guidelines of the American Thyroid Association for TSH normal range during the first trimester of pregnancy, namely between 0.1 and 2.5 mIU/L [9].

Additional confounding factors that might influence the use of TSH in determining thyroid disease during pregnancy have been reported [2], namely, laboratory assessment, age, diet, education level, medications, socioeconomic status, body mass index, and smoking. The use of monoclonal antibodies for TSH assessment reduced the previously experienced cross-reactivity with other glycoprotein hormones such as luteinzing hormone or hCG [2]. Still, the use of different TSH immunoassay kits with different monoclonal antibodies recognizing various circulating TSH isoforms can result in the reporting of TSH values that may differ by as much as 1.0 mIU/L for a given serum sample [25]. Despite the above mentioned obstacles, the guidelines of the American Thyroid Association clearly state that serum TSH testing is a reliable test in pregnancy, assuming that trimester-specific reference ranges are applied [9].

Is there a benefit of screening for thyroid function in pregnant women in Israel? In order for any screening program to be worthwhile, the condition (in this case thyroid disorder) must be prevalent in asymptomatic individuals, there must be a reliable and readily available test to identify the condition, and identification of the condition must result in a beneficial intervention. The TSH test is a reliable test in pregnancy [9], thyroid dysfunction either overt or subclinical during pregnancy can and should be successfully treated [1], and the finding of abnormal TSH in 25.6% of otherwise asymptomatic pregnant women certainly warrants universal screening.

The main limitation of the study is that we did not carry out complete thyroid function evaluation (like free thyroxine or thyroid peroxidase antibodies) or ultrasound of thyroid, and the causes for abnormal TSH were therefore not evaluated. The advantage of the study is that it assessed, for the first time in Israel, the rate of abnormal TSH test in low risk pregnant women attending a community clinic. We conclude that in view of the high prevalence of abnormal TSH (25.6%) in pregnant women in Israel, universal screening should be considered.

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hCG = human chorionic gonadotropin

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