РЕФЕРЕНТНЫЕ ЗНАЧЕНИЯ ПОКАЗАТЕЛЕЙ ФУНКЦИИ ЩИТОВИДНОЙ ЖЕЛЕЗЫ В ПЕРВОМ ТРИМЕСТРЕ БЕРЕМЕННОСТИ И РИСК РАЗВИТИЯ ГЕСТАЦИОННОГО САХАРНОГО ДИАБЕТА У ЖЕНЩИН САНКТ-ПЕТЕРБУРГА

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ОБОСНОВАНИЕ. Субклинический гипотиреоз (СГТ) и гестационный сахарный диабет (ГСД) ассоциированы с рисками для здоровья матери и ребенка. Встречаемость СГТ зависит от популяции и принятых референтных значений тиреотропного гормона (ТТГ). Вместо универсальных фиксированных референтных значений ТТГ во время беременности в настоящее время предложено использовать нормы ТТГ, специфичные для каждой популяции и триместра беременности. Специфичные для беременных женщин Северо-Запада России нормы ТТГ в настоящее время не определены. Данные относительно взаимосвязи функции щитовидной железы и ГСД противоречивы и требуют уточнения.

ЦЕЛЬ. Определение референтных значений для уровня ТТГ и свободного тироксина (св.Т4) в первом триместре беременности у женщин, проживающих в г. Санкт-Петербурге, а также оценка взаимосвязи между тиреоидным статусом в I триместре беременности и риском развития ГСД.

МЕТОДЫ. У 503 женщин на сроке беременности до 14 нед был определен уровень ТТГ, св.Т4 и антител к тиреопероксидазе (АТ к ТПО). На сроке 24–28 нед участницам исследования был выполнен пероральный глюкозотолерантный тест (ПГТТ) для скрининга на ГСД. Оценена взаимосвязь между функцией щитовидной железы, маркерами аутоиммунного процесса в щитовидной железе и выявленным ГСД.

РЕЗУЛЬТАТЫ. Были определены референтные значения для ТТГ (0,07–4,40 мМЕ/л) и для св.Т4 (11,7–20,3 пмоль/л). Распространенность СГТ составила 16,9% исходя из диагностического критерия ТТГ>2,5 мМЕ/л в I триместре и 3,8% при использовании рассчитанного в ходе исследования референтного интервала. Гипотироксинемия встречалась у 5,3% женщин при учете референтных значений для св. Т4, предложенных производителем наборов, и у 2,8% женщин при использовании рассчитанных нами референтных значений св.Т4. ГСД был выявлен у 23,5% женщин, пришедших на ПГТТ. Анализ логистической регрессии выявил связь ГСД с гипотироксинемией [ОШ=7,39; p=0,026; 95% ДИ 1,27–42,93] и с повышенным уровнем АТ к ТПО [ОШ=2,02; p=0,047; 95% ДИ 1,01–4,04], значимую после переоценки с учетом возраста и ИМТ.

ЗАКЛЮЧЕНИЕ. В ходе исследования были получены референтные значения ТТГ в I триместре беременности для женщин, проживающих в Санкт-Петербурге, выявлена взаимосвязь риска ГСД с повышенным уровнем антиТПО и гипотироксинемией.

КЛЮЧЕВЫЕ СЛОВА: гестационный сахарный диабет; тиреотропный гормон; тироксин; референтные значения

FIRST TRIMESTER THYROID FUNCTION IN PREGNANT WOMEN RESIDING IN SAINT PETERSBURG (RUSSIA): REFERENCE VALUES AND RISK OF GESTATIONAL DIABETES

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BACKGROUND. Subclinical hypothyroidism during pregnancy and gestational diabetes mellitus (GDM) is known to be associated with maternal and child morbidity. The concept of subclinical dysfunction of the thyroid gland in pregnant women depends on the population-specific and trimester-specific reference values so fixed universal cutoff concentrations for thyroid-stimulating hormone (TSH) that were recommended earlier now are put under the question. Population-specific and trimester-specific reference values have not been defined for pregnant women residing in Saint Petersburg. The data concerning the association of maternal thyroid status with GDM development are controversial.

AIMS. The aim of the study was to determine the reference values of TSH and free thyroxin (fT4) in the first trimester of pregnancy in women living in St. Petersburg, and to assess the relationship between thyroid status and the risk of subsequent development of GDM.

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MATERIALS AND METHODS. The levels of TSH, fT4 and thyroid peroxidase antibodies (TPO-Ab) were analyzed in 503 pregnant women before the 14th week of gestation. The women underwent oral glucose tolerance test (OGTT) at 24–28 weeks to find out those with GDM. The association between thyroid function, thyroid autoimmunity and the risk of GDM we estimated.

RESULTS. The reference values for TSH were 0.07 – 4.40 mU /L, and for fT4 11.7 – 20.3 pmol/L. The prevalence of subclinical hypothyroidism in the 503 pregnant women was 16.9% according to the diagnostic criteria of TSH> 2.5 mIU / L and 3.8% using our calculated reference interval. Hypothyroxinemia was registered in 5,3% using reference values recommended by diagnostic tests manufacturer and in 2,8% according to our calculated reference interval for fT4. GDM was diagnosed in 23% of women. Logistic regression analysis showed associations of hypothyroxinemia and TPO-Ab-positivity with the increased risk of GDM that remained significant after adjustments on age and body mass index (BMI) [adjusted OR (95% CI) = 7.39 (1.27–42.93) for hypothyroxinemia, p=0.026; and adjusted OR (95% CI) = 2.02 (1.01–4.04) for TPO-Ab-positivity, p=0.047).

CONCLUSIONS. Reference intervals for first trimester TSH and fT4 have been established for pregnant women living in St. Petersburg. Hypothyroxinemia and TPO-Ab-positivity were associated with the increased risk of GDM.

KEYWORDS: gestational diabetes mellitus; thyrotropin; thyroxine; reference values

Subclinical hypothyroidism is defined as a condition where serum thyroid stimulating hormone (TSH) level is above the upper limit of the reference range, with serum thyroid hormones within the normal limits.[1, 2] Subclinical hypothyroidism is associated with health risks for both mother and child, including premature birth, spontaneous abortion, and problems with intellectual development of the child.[3, 4] The prevalence of subclinical hypothyroidism depends on the population group, gestational age, and the accepted TSH reference values.[3] For example, when using the reference range for TSH accepted until recently (<2.5 mU/L in the first trimester of pregnancy and <3.0 mU/L in the second and third trimesters), the estimated prevalence of subclinical hypothyroidism may reach 15.5% in some populations.[1, 5] The existing strict reference limits for TSH during pregnancy have been questioned by the American Thyroid Association.[4] Implementation of wider population-specific and trimester-specific reference ranges for TSH would decrease the prevalence of subclinical hypothyroidism to 2%–4%,[3, 6] which would reduce the medical, financial and psychological burden on a pregnant woman. Pregnancy-specific reference ranges for TSH in woman from the Northwest region of Russia need to be assessed.

According to the International Diabetes Federation, nearly 16.9% of pregnant women have hyperglycaemia; of those, 85% have gestational diabetes mellitus (GDM).[7] GDM is associated with an increased risk of unfavourable neonatal outcomes[8] The results of currently available studies on the correlation between thyroid function and GDM are controversial. [2, 9, 10] Both subclinical and overt hypothyroidism are associated with insulin resistance and facilitate the development of GDM in pregnant women.[9, 10] However, a study involving 10,000 pregnant women conducted by Cleary-Goldman et al. found no association between subclinical hypothyroidism and the risk of GDM .[11]

AIM

The aim of this study was to determine the reference ranges for TSH and free thyroxine (fT4) in the first trimester of pregnancy in women residing in Saint Petersburg and to assess the association between thyroid status in the first trimester of pregnancy and the risk of developing GDM.

METHODS

Study design

The study was conducted at the V.A. Almazov Federal North-West Medical Research Center and Saint Petersburg Women's Health Clinic No. 22 between March 2012 and April 2017. The study included 503 pregnant women who were registered for antenatal care before 14 weeks of gestation and consented to an oral glucose tolerance test (OGTT) at 24–28 weeks of gestation.

Eligibility criteria

The exclusion criteria for the study were as follows: (a) type-1 or type-2 diabetes mellitus, (b) other diseases affecting glucose metabolism, and (c) refusal to participate in the study. In assessing reference values for TSH and fT4, we also excluded (d) women previously diagnosed with thyroid diseases, (e) women with multiple pregnancy, (f) women receiving drugs that affect thyroid function, and (f) foetal death

Study conditions

Women from all districts of Saint Petersburg were followed up at the V.A. Almazov Federal North-West Medical Research Center.

Study duration

The study was performed between March 2012 and April 2017.

Description of medical intervention

At enrolment, all women underwent venous blood collection; serum specimens were frozen at −70°C and stored until testing. Serum levels of TSH, fT4, and anti-thyroid peroxidase antibodies (anti-TPO) were measured in March 2017. Serum anti-TPO above the upper limit of the reference interval given by the manufacturer (>34 IU/mL) was considered elevated.

Table 1. Demographic and Clinical Characteristics of Patients

Characteristics	Mean (SD)	Range
Mean age (years)	1.61±1.34	0.01-11.48
BMI (kg/m^2)	15.14±3.02	9.38-58.52
Gestational age at the time of blood collection (weeks)	28.06±73.72	0.00-611.00
TSH (mIU/L)	29.43±4.70	19-46
fT4 (pmol/L)	23.82±4.97	15.04-48.86
anti-TPO (IU/mL)	10.33±2.33	5.00-14.00
Frequency of miscarriages during the study, (n, %)	1.40 (7)	
Frequency of miscarriages in the past (n, %)		
1	13.50 (68)	
2	1.0 (5)	
≥3	0.20 (1)	

BMI, body mass index; TSH, thyroid stimulating hormone; fT4, free thyroxine; anti-TPO, anti-thyroid peroxidase antibodies; SD, standard deviation.

All women were screened for GDM using OGTT at 24–32 weeks of gestation. During OGTT, we measured the fasting glucose level as well as glucose levels at 1 and 2 hours after a 75 g oral glucose load.

We estimated the correlation between thyroid function (TSH and fT4) and autoimmune thyroid markers (anti-TPO), and GDM. An isolated increase in serum TSH (up to 10 mIU/L) with normal fT4 was considered subclinical hypothyroidism; a serum TSH greater than 10 mIU/L and decreased fT4 was defined as overt hypothyroidism; a fT4 below the reference values and normal TSH as hypothyroxinemia; and a TSH below the reference values as hyperthyroidism.[1, 2, 4] We also estimated the incidence of thyroid disorders according to the accepted reference values. To identify the optimal normal limits of TSH and fT4, we used the following reference values: (1) TSH reference range recommended by the European Thyroid Association for the first trimester of pregnancy (0.1–2.5 mIU/L)[1]; (2) reference range for fT4 (12–22 pmol/L) given by the kit manufacturer (Roche Diagnostics GmbH); and (3) reference range for TSH and fT4 calculated during the study and based on the distribution of results in women with serum anti-TPO levels of ≤34 IU/mL (using 2.5th and 97.5th percentiles as lower and upper limits).

Main outcome

The main outcome measure was the presence or absence of GDM.

Subgroup analysis

All patients were divided into two groups according to OGTT results: patients with GDM and patients with normal glucose metabolism. The diagnosis of GDM for treatment initiation was based on the OGTT results. Prior to 2013, the accepted diagnosis criteria for GDM was the standard WHO criteria (fasting glucose levels ≥7.0 mmol/L and/or postprandial (after 2 hours) glucose levels ≥7.8 mmol/L).[12]. After January 2013, the accepted diagnosis criteria was based on the recommendations of the Russian National Consensus (fasting glucose levels ≥5.1 mmol/L and/or postprandial glucose levels ≥10.0 mmol/L after 1 hour and/or ≥8.5 mmol/L after 2 hours.[13] Women diagnosed with GDM were treated and followed up in the Perinatal Center of the V.A. Almazov Federal North-West Medical Research Center. For statistical purposes, we retrospectively assessed all study participants for GDM using the criteria of the Russian National Consensus.

Ethical review

The study protocol was approved by the Ethics Committee of the V.A. Almazov Federal North-West Medical Research Center (Protocol No. 119 from 13.07.15).

Statistical analysis

Data analysis was performed using the SPSS 22.0 software (SPSS Inc., USA). Data were expressed as M ± SD, where M is the mean value and SD is the standard deviation. Table 1 also represents the minimum and maximum values. Pearson's $\chi 2$ test was used to assess differences in the distribution of categorical variables between the two groups. Student's t test was used to compare continuous variables. The differences were considered significant at p-value <0.05. Binomial logistic regression was used to assess the association between the thyroid status and GDM.

RESULTS

Study population

The demographic and clinical characteristics of the 503 women included in the study are shown in Table 1. The mean age of the participants was 29.4 years and the mean gestational age at the time of blood collection was 10 weeks.

Results

After excluding women with elevated anti-TPO (n = 65), no data on anti-TPO (n = 9), multiple pregnancy

Table 2. Reference Limits for TSH and fT4 in the First Trimester of Pregnancy

Hormone	Mean	2.5 percentile Add number and %	5th percentile Add number and %	Median	95th percentile Add number and %	97.5th percentile Add number and %
TSH, mIU/L	1.49±1.05	0.07	1.16	1.34	3.51	4.40
ft4, pmol/L	15.15±3.07	11.74	12.16	14.77	18.96	20.28

TSH, thyroid stimulating hormone; fT4, free thyroxine

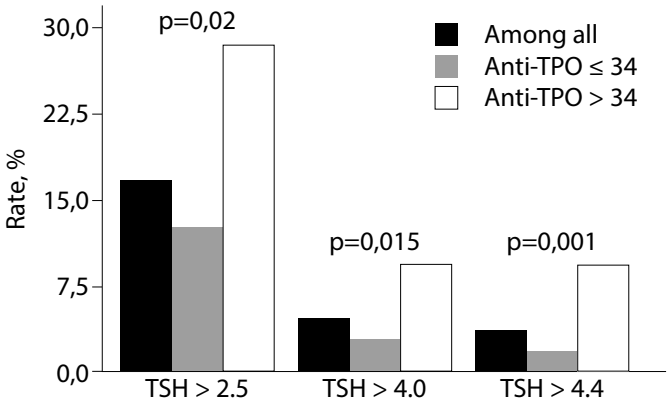

Figure 1. Prevalence of Subclinical Hypothyroidism by TSH Reference Values and Anti-TPO Levels
TSH, thyroid stimulating hormone; fT4, free thyroxine; anti-TPO, anti-thyroid peroxidase antibodies

(n = 5), miscarriage (n = 7), and previously identified thyroid diseases (n = 7), the reference values for TSH (0.07–4.40 mIU/L) and fT4 (11.7–20.3 pmol/L) for the eligible population was determined (Table 2).

The prevalence of subclinical hypothyroidism in the study population (n = 503) in the first trimester of pregnancy was 16.9% when using the accepted criteria (TSH > 2.5 mIU/L) and 3.8% when using the values calculated in the current study. Subclinical hypothyroidism was more frequent among women with increased anti-TPO levels, regardless of the reference values (Figure 1).

The prevalence of hypothyroxinemia also varied depending on the accepted reference values for fT4. The prevalence using the reference range specified by the kit manufacturer (12–22 pmol/L) was 5.3% and the prevalence using the reference values calculated in this study (11.7–20.3 pmol/L) was 2.8%. Patients with elevated anti-TPO levels were more likely to have hypothyroxinemia regardless of the fT4 reference values used (Figure 2).

GDM was diagnosed in 102 women (23.5%) that underwent OGTT (n = 434) (Table 3). Women with GDM were older than women without GDM (30.8 ± 4.4 vs. 29.0 ± 4.8 years, p = 0.001) and had greater body mass index (BMI) (25.2 ± 5.0 vs. 23.5 ± 4.9 kg/m2, p = 0.003). Hypothyroxinemia, diagnosed using the reference limits calculated in this study, was significantly more frequent in patients with GDM than in participants with normal glucose metabolism (6.1% vs. 1.2%, p = 0.005) and elevated anti-TPO levels (18.9% vs. 9.4%, p = 0.012). We found no significant difference between the levels of TSH, fT4 and anti-TPO, and the frequency of subclinical and overt hypothyroidism between these groups.

Logistic regression analysis demonstrated an association between hypothyroxinemia and the risk of developing GDM; the association remained statistically significant after adjusting for age and BMI (odds ratio [OR]: 7.39; p = 0.026; 95% confidence interval [CI] 1.27–42.93). In addition, we observed an association between elevated ant-TPO levels and the risk of GDM, which remained significant after adjusting for age and BMI (OR: 2.02; p = 0.047; 95% CI 1.01–4.04). No association was found between the level of TSH and the risk of GDM (Figure 3). We also observed no significant correlation between thyroid function and the risk of miscarriage.

DISCUSSION

To our knowledge, this is the first study that calculated reference values for TSH and fT4 for the first trimester of pregnancy in women living in the

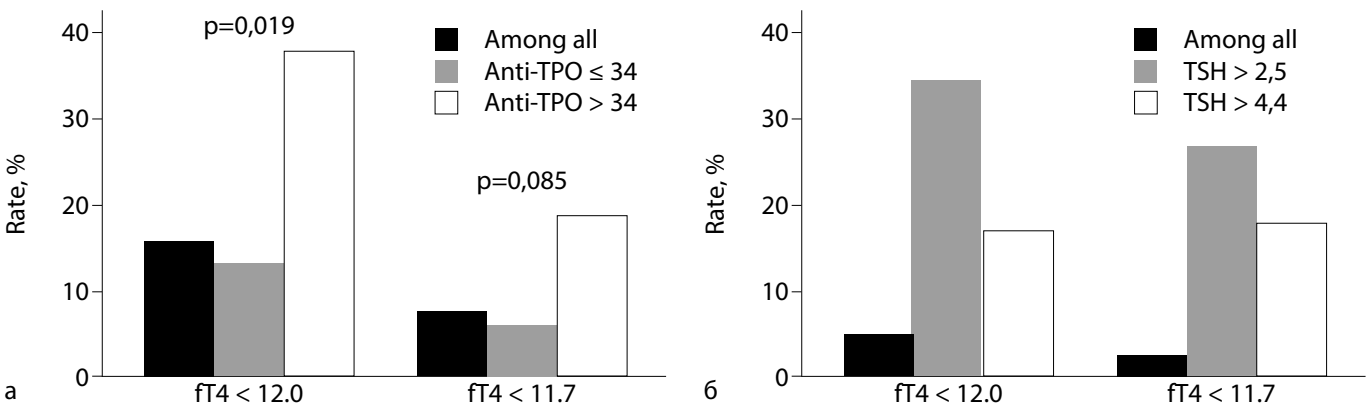

Figure 2. Prevalence of Hypothyroxinemia Using Various Reference Values for fT4 A, With and Without Elevated Anti-TPO levels; B. By TSH Levels
TSH, thyroid stimulating hormone; fT4, free thyroxine; anti-TPO, anti-thyroid peroxidase antibodies

Table 3. Characteristics of Patients With and Without GDM

Characteristics	GDM (n = 102)	No GDM (n = 332)	P-value
Mean age (years)	30.8±4.4	29.0±4.8	p=0.001
BMI (kg/m^2)	25.2±5.0	23.5±4.9	p=0.003
TSH (mIU/L)	1.4±1.3	1.7±1.4	p=0.066
ft4 (pmol/L)	15.1±5.0	15.3±2.3	p=0.687
anti-TPO (IU/mL)	42.4±94.3	26.6±72.8	p=0.128
Prevalence of subclinical hypothyroidism, %			
TSH > 2.5	11.8	17.8	p=0.151
TSH > 4.4	1.0	4.5	p=0.097
Prevalence of overt hypothyroidism (n, %)			
TSH > 2.5	2.0	0.9	p=0.362
TSH > 4.4	1.0	0.6	p=0.668
Prevalence of hypothyroxinemia (n, %)			
fT4 < 12.0	9.2	3.3	p=0.016
fT4 < 11.7	6.1	1.2	p=0.005
Prevalence of elevated anti-TPO (n, %)	18.9	9.4	p=0.012

BMI, body mass index; TSH, thyroid stimulating hormone; fT4, free thyroxine; anti-TPO, anti-thyroid peroxidase antibodies.

Northwest region of Russia. Our reference limits were wider than the currently accepted reference limits. We found an association between the risk of GDM and elevated levels of anti-TPO and hypothyroxinemia. However, no significant association was observed between the risk of GDM and TSH levels, hypothyroidism and hyperthyroidism.

The existing strict reference limits for TSH during pregnancy have been questioned by the American Thyroid Association in 2017.[4] Diagnostic criteria for subclinical hypothyroidism were revised after several studies demonstrated significant differences in the reference values for TSH in different populations,[4, 6, 14] which are probably owing to variations in ethnic characteristics, regional levels of iodine supply and geographical location.[4] The reference range for TSH determined in this study is significantly wider than the reference range recommended for pregnant women. [1, 2] The prevalence of subclinical hypothyroidism (using reference values calculated in this study) is comparable with data of other studies.[5] In our opinion, reference values for TSH in pregnant women seem to be too low.

The American Thyroid Association recommends calculating population-specific reference values for TSH in samples with sufficient iodine supply. [4] Saint Petersburg is a region characterized by mild iodine deficiency.[15] The study by Soboleva et al. that included 103 pregnant women from Saint Petersburg, reported median ioduria of 117.00 μg/L (range: 75.00–170.90 μg/L) indicating iodine deficiency with ioduria less than 150 μg/L in 69.8% of patients. In 2013–2014, the proportion of new-born children with TSH greater than 5 mIU/L was 6.9%, which also suggests mild iodine deficiency in the region.[15]

More than 23% of women in our study were diagnosed with GDM by OGTT, which significantly exceeds the prevalence of GDM observed in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study (17.8%)[8] and in studies from European population (12.4%).[16]. This difference might be explained by the fact that women at higher risk of

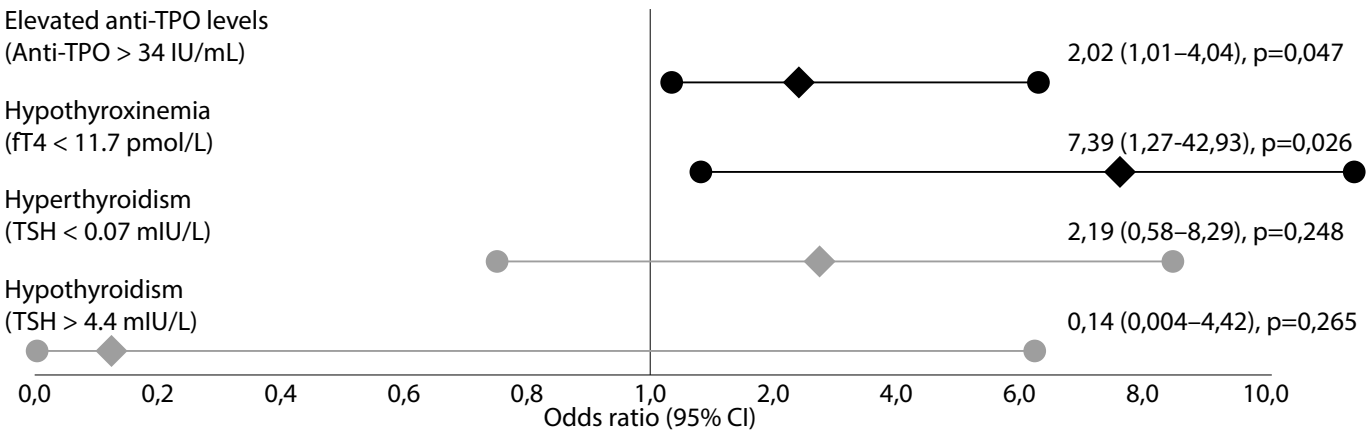

Figure 3. Regression Analysis: Association Between Thyroid Function and the Risk of Developing GDM

developing GDM undergo OGTT more frequently. Until 2013, universal screening for GDM was not recommended in Russia, and this recommendation is still not fully implemented in Saint Petersburg. Therefore, women without risk factors for diabetes often refuse OGTT. Thus, the prevalence of GDM in Saint Petersburg is not representative of the entire population as not all women are screened.

The mechanism underlying the relationship between autoimmune processes of the thyroid and the risk of GDM is poorly understood.[17]. Patients with subclinical and overt hypothyroidism have increased peripheral resistance to insulin and increased serum insulin,[11]. Studies have confirmed that women with reduced thyroid function are at increased risk for developing GDM. [9, 10]. A large study by Tudela at al. demonstrated a statistically significant association between the level of TSH and the risk of developing GDM, even after adjusting for age, IMT, and ethnicity. In this study, women with subclinical hypothyroidism were at higher risk of developing GDM; however, this correlation failed to reach statistical significance after adjustment ($p = 0.056$).[9] In contrast, Cleary–Goldman et al. examined over 10,000 women in the first trimester of pregnancy and found no significant correlation between subclinical hypothyroidism and the risk of GDM; this lack of association was likely because this population was more ethnically homogeneous and had lower levels of serum anti-TPO compared with the population from the Tudela study. [11]. In the current study, we found no association between TSH levels and GMD.

Several studies reported an association between hypothyroxinemia and GDM in euthyroid women during the second and third trimesters of pregnancy], but not during first trimester of pregnancy.[10, 11] In our study, we found an association between hypothyroxinemia and GDM, which is consistent with the results from two studies. [18, 19]. The lack of consistent findings between hypothyroxinemia and GDM suggests the need to further evaluate the prognostic value of fT4 to assess the risk of GDM.

The results of studies assessing the association between the autoimmune process of the thyroid and GDM are inconsistent.[17, 20] Our findings, showing an association between elevated levels of anti-TPO and the risk of GDM are consistent with some studies. [17, 20]. However, a meta-analysis of 20 studies that included a total of 34,566 patients revealed only a weak association between the level of anti-TPO and the risk of developing GDM (hazard ratio [HR]: 1.12; 95% CI: 1.03–1.22).[17] On the contrary, there was a strong association between reduced thyroid function and GDM in women with increased levels of anti-TPO (HR: 1.35, 95% CI 1.06–1.71) [17]. In other studies, women with elevated TSH and anti-TPO had 3.2 times higher risk of developing GDM compared with euthyroid women showing no signs of autoimmune process in the thyroid.[20]. This kind of an association was not found in our study, likely due to the relatively small sample size.

Limitations

The small sample size and lack of data on the iodine status (median ioduria) in our study limited our ability to generalize the use of these reference values for the entire population of women in this region.

CONCLUSION

Reference values for TSH vary considerably depending on the population and gestational age. These values have not yet been confirmed for different regions of Russia. In our study, we calculated reference intervals for TSH in the first trimester of pregnancy in women residing in Saint Petersburg (0.07–4.40 mIU/L). Our reference range for TSH was significantly wider than the currently accepted range; therefore, further research with larger sample sizes involving patients from other regions of Russia is warranted.

The association between autoimmune thyroid diseases and the risk of GDM remains poorly defined, and the results of the existing studies are inconsistent. We identified an association between the risk of GDM and increased levels of anti-TPO and hypothyroxinemia, but not between the levels of TSH. Additional studies with larger samples to assess the prognostic value of thyroid status and autoimmune thyroid markers for GDM are warranted.

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Author contributions. Popova P.V: developed study design, performed statistical analysis and drafted the manuscript; Shilova E.S.: performed data collection and analysis and drafted the manuscript; Tkachuk A.A.: consulted patients and performed data collection; Dronova A.V.: consulted patients and performed data collection, Anopova A.D.: performed data collection; Nikolaeva A.E.: performed data collection; Kutaeva F.R.:–performed data collection; Grineva E.N.–managed the study and analysed the results.

СПИСОК ЛИТЕРАТУРЫ | REFERENCES

1. Lazarus J, Brown RS, Daumerie C, et al. 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *Eur Thyroid J*. 2014;3(2):76-94. doi: 10.1159/000362597
2. Фадеев В.В. По материалам клинических рекомендаций по диагностике и лечению заболеваний щитовидной железы во время беременности и в послеродовом периоде Американской тиреоидной ассоциации // *Клиническая и экспериментальная тиреоидология*. — 2012. — Т. 8. — №1. — С. 7-18. [Fadeyev VV. Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum. *Clinical and experimental thyroidology*. 2012;8(1):7-18. (In Russ.)] doi: 10.14341/ket2012817-18
3. Maraka S, Ospina NM, O'Keeffe DT, et al. Subclinical Hypothyroidism in Pregnancy: A Systematic Review and Meta-Analysis. *Thyroid*. 2016;26(4):580-590. doi: 10.1089/thy.2015.0418
4. Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. *Thyroid*. 2017;27(3):315-389. doi: 10.1089/thy.2016.0457
5. Blatt AJ, Nakamoto JM, Kaufman HW. National status of testing for hypothyroidism during pregnancy and postpartum. *J Clin Endocrinol Metab*. 2012;97(3):777-784. doi: 10.1210/jc.2011-2038
6. Li C, Shan Z, Mao J, et al. Assessment of thyroid function during first-trimester pregnancy: what is the rational upper limit of serum TSH during the first trimester in Chinese pregnant women? *J Clin Endocrinol Metab*. 2014;99(1):73-79. doi: 10.1210/jc.2013-1674
7. Guariguata L, Linnenkamp U, Beagley J, et al. Global estimates of the prevalence of hyperglycaemia in pregnancy. *Diabetes Res Clin Pract*. 2014;103(2):176-185. doi: 10.1016/j.diabres.2013.11.003
8. Group HSCR, Metzger BE, Lowe LP, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. 2008;358(19):1991-2002. doi: 10.1056/NEJMoa0707943
9. Tudela CM, Casey BM, McIntire DD, Cunningham FG. Relationship of subclinical thyroid disease to the incidence of gestational diabetes. *Obstet Gynecol*. 2012;119(5):983-988. doi: 10.1097/AOG.0b013e318250aeeb
10. Gorar S, Abanonu GB, Uysal A, et al. Comparison of thyroid function tests and blood count in pregnant women with versus without gestational diabetes mellitus. *J Obstet Gynaecol Res*. 2017;43(5):848-854. doi: 10.1111/jog.13280
11. Cleary-Goldman J, Malone FD, Lambert-Messerlian G, et al. Maternal thyroid hypofunction and pregnancy outcome. *Obstet Gynecol*. 2008;112(1):85-92. doi: 10.1097/AOG.0b013e3181788dd7
12. *Эндокринология: национальное руководство*. / Под ред. Дедова И.И., Мельниченко Г.А. — М.: ГЭОТАР-Медиа; 2008. [Dedov II, Mel'nichenko GA, editors. *Endokrinologiya: natsional'noe rukovodstvo*. Moscow: GEOTAR-Media; 2008. (In Russ.)]
13. Дедов И.И., Краснопольский В.И., Сухих Г.Т. Российский национальный консенсус «Гестационный сахарный диабет: диагностика, лечение, послеродовое наблюдение» // *Сахарный диабет*. — 2012. — Т. 15. — №4. — С. 4-10. [Dedov II, Krasnopol'skiy VI, Sukhikh GT. Russian National Consensus Statement on gestational diabetes: diagnostics, treatment and postnatal care. *Diabetes Mellitus*. 2012;15(4):4-10. (In Russ.)] doi: 10.14341/2072-0351-5531
14. Gilbert RM, Hadlow NC, Walsh JP, et al. Assessment of thyroid function during pregnancy: first-trimester (weeks 9-13) reference intervals derived from Western Australian women. *Med J Aust*. 2008;189(5):250-253.
15. Соболева Д.Е., Дора С.В., Волкова А.Р., и др. Йодообеспечение беременных женщин Санкт-Петербурга. Эффективность профилактики развития йододефицитных заболеваний в группе риска // Проблемы женского здоровья. — 2015. — Т. 10. — №2. — С. 25-31. [Soboleva DE, Dora SV, Volkova AR, et al. Iodine status of pregnant women living in Saint Petersburg. The effectiveness of iodine prevention in risk group. *Problemy zhenskogo zdorov'ya*. 2015;10(2):25-31. (In Russ.)]
16. Avalos GE, Owens LA, Dunne F, Collaborators AD. Applying current screening tools for gestational diabetes mellitus to a European population: is it time for change? *Diabetes Care*. 2013;36(10):3040-3044. doi: 10.2337/dc12-2669
17. Yang Y, Li Q, Wang Q, Ma X. Thyroid antibodies and gestational diabetes mellitus: a meta-analysis. *Fertil Steril*. 2015;104(3):665-671 e663. doi: 10.1016/j.fertnstert.2015.06.003
18. Yang S, Shi FT, Leung PC, et al. Low Thyroid Hormone in Early Pregnancy Is Associated With an Increased Risk of Gestational Diabetes Mellitus. *J Clin Endocrinol Metab*. 2016;101(11):4237-4243. doi: 10.1210/jc.2016-1506
19. Oguz A, Tuzun D, Sahin M, et al. Frequency of isolated maternal hypothyroxinemia in women with gestational diabetes mellitus in a moderately iodine-deficient area. *Gynecol Endocrinol*. 2015;31(10):792-795. doi: 10.3109/09513590.2015.1054801
20. Ying H, Tang YP, Bao YR, et al. Maternal TSH level and TPOAb status in early pregnancy and their relationship to the risk of gestational diabetes mellitus. *Endocrine*. 2016;54(3):742-750. doi: 10.1007/s12020-016-1022-6

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