

Original article

## Hypothyroidism and gestational diabetes mellitus: Is there a relationship?

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**Abstract:** *Background and Objective* — Subclinical gestational hypothyroidism (SGH) and gestational diabetes mellitus (GDM) constitute two most common endocrine pathologies encountered during pregnancy. SGH and GDM have common pathophysiological mechanisms, being interrelated pathological conditions that are capable of complicating the course of pregnancy, labor and the postpartum period both on the part of the mother and on the part of the fetus. We aimed to analyze the relationship between these pathologies and to assess the risk of developing GDM against the background of hypothyroidism.

*Materials and Methods* — the study included 200 pregnant women observed at the Perinatal Center of the Maternity Hospital the Bauman State Clinical Hospital No. 29 during 2018-2020. The main group consisted of 133 women who visited the perinatal center for hypothyroidism (both SGH and primary hypothyroidism, detected prior to pregnancy); the control group comprised 67 women without endocrine pathology. Both groups were comparable in terms of age, height, weight, and the number of pregnancies in the anamneses. The main group received levothyroxine sodium therapy with the achievement of the target trimester-specific level of thyroid-stimulating hormone (TSH). The criteria for the diagnosis of SGH were the TSH level above 2.5  $\mu$ U/mL in combination with an enlarged titer of antithyroid antibodies and/or a burdened medical history of thyroid pathology, or the TSH level above 4.0  $\mu$ U/mL in the absence of antithyroid antibodies [1]. The diagnosis of GDM was established on the basis of fasting hyperglycemia ( $\geq 5.1$  mmol/L), or based on the results of an oral glucose tolerance test (OGTT) with 75 g of glucose: fasting glucose level of  $\geq 5.1$  mmol/L; the concentration 1 hour after glucose intake  $\geq 10.0$  mmol/L; the content 2 hours after glucose intake  $\geq 8.5$  mmol/L [2]. In both groups, the frequency of developing GDM, the timing of diagnosis, and the need for insulin therapy were evaluated. Statistical data processing was carried out using the StatTech v. 2.1.0 software. Quantitative indicators were assessed for compliance with the normal distribution via Shapiro-Wilk criterion or Kolmogorov-Smirnov criterion. Intergroup comparison was performed using Mann-Whitney U test or Pearson's chi-squared test.

*Results* — We discovered that among women with a burdened family history of thyroid pathology and diabetes mellitus, as well as with thyroid pathology prior to pregnancy, the prevalence of hypothyroidism was higher. The presence of thyroid pathology in the anamnesis of pregnant women was associated with an earlier diagnosis of hypothyroidism. We revealed a significant difference in the prevalence of GDM between two groups of subjects. The chances of detecting GDM in the hypothyroidism group were 8.6 times higher than in the euthyroidism group. The threshold level of TSH for the first trimester, predicting the development of GDM, was identified. The sensitivity and specificity of the model were 71.4% and 63.1%, respectively.

*Conclusion* — Hypofunction of the thyroid and GDM are interrelated endocrine pathologies. In the presence of hypothyroidism (both primary and SGH), GDM develops significantly more often. The level of TSH in the first trimester  $\geq 2.7$   $\mu$ U/mL amplifies the chance of developing GDM by over 8 times; hence, it could be considered a signal for timely prevention and detection of this pathology.

**Keywords:** subclinical gestational hypothyroidism, primary hypothyroidism, gestational diabetes mellitus, insulin resistance, thyroid hormones.

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### Introduction

Hormonal and metabolic changes in the course of pregnancy lead to changes in the functioning of the thyroid. During physiological pregnancy in the first trimester, there is an increase in the synthesis of thyroid hormones due to the thyroid-stimulating effect of  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG), which helps thyroid gland adapting to an increase in circulating levels of thyroxine-binding globulin. In addition, there is a change in the peripheral metabolism of thyroid hormones, especially at

the level of the placenta [3]. Hypothyroidism occurs due to relative inability of maternal thyroid gland to adapt to the changes associated with pregnancy. In the contemporary world, against the background of an increase in the prevalence of autoimmune pathology, malnutrition, and iodine deficiency, the frequency of gestational hypothyroidism consistently increases.

The frequency of occurrence of subclinical gestational hypothyroidism (SGH) depends on the population and recognized diagnostic criteria for thyroid-stimulating hormone (TSH). When

using the trimester-specific criteria for the norm, recommended by American Thyroid Association and used in Russia since 2011, its prevalence reaches 15.5%, according to foreign studies [4], and 16.8%, according to domestic research [5]. In the case of expanding the limits of the TSH norm to the level, characteristic of nonpregnant women, the prevalence of SGH would be within 2-4% [5].

The negative impact of overt hypothyroidism on the health of the mother and fetus is beyond doubt: it was demonstrated by many studies [6,7]. Complications are less common in SGH than in overt hypothyroidism, but a number of studies have noted an increased risk of severe preeclampsia, preterm birth, placental abruption, infantile respiratory distress syndrome, and miscarriage in women with SGH, compared with euthyroid women [8]. Besides, according to a number of studies, SGH is associated with insulin resistance, which could contribute to the development of gestational diabetes mellitus (GDM) [9, 10].

GDM is the most common disorder of carbohydrate metabolism in obstetric practice, leading to the development of complications during pregnancy, childbirth, and fetal development [11, 12]. Pregnant women with GDM have an increased risk of threatened miscarriage, and premature and operative delivery; they have higher risks of developing polyhydramnios and severe preeclampsia [12]. Fetal complications include diabetic fetopathy, shoulder dystocia, traumatism during childbirth, severe asphyxia, and cerebrovascular accidents of traumatic origin [11]. In addition, the presence of diabetes mellitus in the mother increases the risk of developing long-term metabolic complications, including obesity and type 2 diabetes mellitus in children [13].

The objective of our study was to examine the relationship between subclinical gestational hypothyroidism and gestational diabetes mellitus in the Russian Federation population, along with the factors affecting the development of this pathology.

## Material and Methods

Our study was conducted at the maternity hospital of Bauman State Clinical Hospital No.29 (Moscow, Russia) from January of 2019 through December of 2020. The inclusion criteria for the study were the presence of a developing pregnancy in a woman, a normal level of fasting glycemia, and a normal or elevated level of TSH.

To assess the level of glycemia on an empty stomach, venous blood plasma was examined, and the level of glycemia on an empty stomach less than 5.1 mmol/L was considered normal [2].

To evaluate the thyroid status, the levels of TSH, antibodies to thyroid peroxidase (TPO Ab) and antibodies to thyroglobulin (TG Ab) were used. The criteria for diagnosing SGH was a TSH content above 2.5  $\mu\text{IU/mL}$  in combination with an enlarged titer of antithyroid antibodies and/or a burdened history of thyroid pathology, or the TSH level above 4.0  $\mu\text{IU/mL}$  in the absence of antithyroid antibodies [1].

The exclusion criteria were pregestational diabetes mellitus, GDM detected in early pregnancy, and cases when pregnant women dropped out of observation.

We studied 218 medical records of pregnant women observed at the Perinatal Center of Maternity Hospital No.29 in the period of 2019-2020. The main group consisted of 133 women who visited the perinatal center for hypothyroidism (primary and SGH), the control group included 67 women without endocrine

pathology at the time of seeing the physician. The presence of endocrine pathology in the control group was excluded based on the level of TSH within the reference values for pregnant women [1] and the normal content of fasting glycemia [2]. In the absence of a return visit, the patients were called to, in order to learn the further history of their pregnancies. At this stage, 18 pregnant women dropped out of observation due to lack of data.

The main group received therapy with levothyroxine sodium; dose titration was carried out under the control of the TSH content with the achievement of the target level [1]. The diagnosis of GDM was established on the basis of fasting hyperglycemia in venous plasma (fasting glucose level  $\geq 5.1$  mmol/L), or based on the results of an oral glucose tolerance test (OGTT) with 75 g of glucose at 24-28 weeks gestation: fasting glucose level of  $\geq 5.1$  mmol/L; the concentration 1 hour after glucose intake  $\geq 10.0$  mmol/L; the content 2 hours after glucose intake  $\geq 8.5$  mmol/L [2]. In both groups, the frequency and timing of GDM development, along with the need for insulin therapy were evaluated.

The study was retrospective and therefore did not require ethics committee approval. Statistical data processing was carried out using the StatTech v. 2.1.0 (StatTech LLC, Kazan, Russia).

Quantitative indicators were assessed for compliance with the normal distribution using the Shapiro-Wilk test (with the number of subjects under 50), or the Kolmogorov-Smirnov test (with the number of subjects over 50). In the absence of a normal distribution, quantitative data were described using the median (Me) and the interquartile range (Q1 – Q3). Categorical data were described with absolute values and percentages.

Comparison of two groups in terms of a quantitative indicator, the distribution of which was non-normal, was performed using the Mann-Whitney U test. Comparison of percentages in the analysis of four-field contingency tables was carried out using Pearson's chi-squared test (with values of the expected phenomenon more than 10). Comparison of percentages in the analysis of multifield contingency tables was performed using Pearson's chi-squared test.

## Results

The study included 200 women, the main characteristics of which are presented in *Table 1*. The main group consisted of 133 women who visited the Perinatal Center of the Maternity Hospital at Bauman State Clinical Hospital No.29 for hypothyroidism (both SGH and primary, detected before pregnancy). The control group included 67 women without endocrine pathology.

The median first trimester TSH level in the groups was 1.44 [0.77-2.06]  $\mu\text{IU/mL}$  for the euthyroid group and 3.84 [2.77-4.71]  $\mu\text{IU/mL}$  in the hypothyroid group ( $p < 0.001$ ).

Both groups were comparable in terms of age, height, weight, and number of pregnancies in anamneses; however, some differences were found between the groups (*Table 1*).

We discovered a higher value of body mass index (BMI) in the hypothyroidism group ( $p = 0.020$ ), which could be explained by the effect of hypothyroidism on body weight. However, when analyzing the distribution of the shares of underweight, normal, overweight and obese pregnant women, no differences between the groups were detected ( $p = 0.717$ ), i.e., the groups were comparable in terms of the proportion of patients with different categories of body weight.

**Table 1. Comparison of patient parameters in main and control groups**

Parameters	Categories	Thyroid status			p
		Me	Q <sub>1</sub> – Q <sub>3</sub>	n	
Age at the time of visiting a doctor, full years	Hypothyroidism	31	27-34	133	0.230
	Euthyroidism	32	29-34	67	
Height, m	Hypothyroidism	1.65	1.61-1.70	133	0.237
	Euthyroidism	1.67	1.63-1.71	67	
Weight before pregnancy, kg	Hypothyroidism	63	55-73	133	0.088
	Euthyroidism	58	54-68	67	
BMI, kg/m <sup>2</sup>	Hypothyroidism	22.90	20.20-26.20	133	0.020*
	Euthyroidism	21.20	19.00-25.00	67	
Number of pregnancies	Hypothyroidism	2	1-3	132	0.361
	Euthyroidism	2	1-2	67	

\* Statistically significant differences (p<0.05).

**Table 2. Analysis of the presence of burdened heredity vs. thyroid status**

PARAMETERS	CATEGORIES	THYROID STATUS		P	OR; 95% CI
		Hypothyroidism N (%)	Euthyroidism N (%)		
Heredity for thyroid disease	Absence	105 (79.5)	64 (95.5)	0.003*	5.49; 1.6-18.9
	Presence	27 (20.5)	3 (4.5)		
Heredity for diabetes mellitus	Absence	88 (66.7)	60 (89.6)	<0.001*	4.29; 1.8-10.2
	Presence	44 (33.3)	7 (10.4)		

OR, odds ratio; CI, confidence interval.

**Table 3. Analysis of the timing of subclinical gestational hypothyroidism diagnosis vs. heredity for thyroid diseases**

Parameters	Categories	Diagnosis timing for hypothyroidism, weeks			p
		Me	Q <sub>1</sub> – Q <sub>3</sub>	n	
Heredity for thyroid disease	Absence	12	10-15	156	0.003*
	Presence	9	8-12	21	

**Table 4. Analysis of thyroid disease before pregnancy vs. thyroid status**

PARAMETERS	CATEGORIES	THYROID STATUS		P	OR 95% CI
		Hypothyroidism N (%)	Euthyroidism N (%)		
Thyroid disease before pregnancy	Absence	92 (69.7%)	64 (95.5%)	<0.001*	9.27; 2.75-31.25
	Presence	40 (30.3%)	3 (4.5%)		

OR, odds ratio; CI, confidence interval.

In the hypothyroidism group, there was more often a burdened family history of both thyroid pathology (p=0.003) and diabetes mellitus (p<0.001) (Table 2). This finding, probably, points to common genetic factors underlying hypothyroidism and diabetes mellitus.

Heredity, burdened by thyroid pathology, yielded a 5.5-fold increase in the chance of developing hypothyroidism, and the odds ratio was statistically significant (OR=5.49; 95% CI: 1.6-18.9). Moreover, in the presence of heredity, burdened by the pathology of the thyroid, SGH in patients was detected significantly earlier (Table 3).

The groups differed in the presence of pregestational thyroid pathology in the patients (Table 4).

Just as we expected, a patient's history of thyroid disease increased the chance of developing hypothyroidism (Table 4). The chances of developing hypothyroidism were 9.3 times higher in the presence of thyroid disease prior to the pregnancy, and the difference in these chances was statistically significant (OR=9.27; 95% CI: 2.75-31.25).

In the hypothyroidism group, GDM was detected significantly more often than in the euthyroid group: 57.3% vs. 13.4% (p<0.001) (Figure 1).

The odds of developing GDM in the presence of hypothyroidism were 8.6 times higher, compared with euthyroidism, and the odds ratios were statistically significant (OR=8.62; 95% CI: 3.95-18.87). Moreover, GDM was detected more often in the hypothyroidism group, regardless of whether a woman had SGH or primary hypothyroidism before her pregnancy (p<0.001). When assessing the nature of the GDM course depending on the thyroid status, we revealed no difference in the timing of GDM detection or in the need for insulin therapy (p=0.183 and p=0.214, respectively).

To determine the specific level of TSH in the first trimester, which increased the risk of developing GDM, an analysis of TSH in the first trimester was performed versus the presence of GDM. Based on obtained data, when comparing the level of TSH in the first trimester, depending on the presence of GDM, we detected statistically significant differences (p=0.003) (Figure 2).

When estimating the dependence of the probability of detecting gestational diabetes on the TSH level in the first trimester via ROC analysis, the following curve was obtained (Figure 3).

The area under the ROC curve was 0.628±0.042 with 95% CI of 0.546-0.710. The resulting model was statistically significant (p=0.003).

The threshold value of TSH in the first trimester, which corresponded to the highest value of the Youden's index, was 2.7 μIU/mL (Figure 4). GDM was predicted when the TSH value in the first trimester was greater than, or equal to, that value. The sensitivity and specificity of the model were 71.4% and 63.1%, correspondingly.

## Discussion

Lately, the close relationship of thyroid dysfunction with insulin resistance, metabolic syndrome and the risk of developing diabetes mellitus was actively studied. The objective of our study was to investigate the relationship between hypofunction of the thyroid and GDM as one of insulin resistance manifestations.

Our study yielded several interesting results. First, we established that both heredity for thyroid pathology and heredity for diabetes mellitus increased the chances of developing SGH. These data suggested possible common genetic factors underlying the pathology of the thyroid and disorders of carbohydrate metabolism. Such assumptions were made in the prospective population-based cohort study in Rotterdam, in which higher TSH levels were associated with a higher risk of developing diabetes and the progression from prediabetes to diabetes [14]. By now, a number of studies with conflicting results were conducted on searching for a link between hypothyroidism and diabetes mellitus. Some studies confirmed such relationship [14, 15], while other studies did not find it [16, 17].

Thyroid hormones are not only insulin antagonists, implementing their hyperglycemic effect via enhancing gluconeogenesis, glycogenolysis, and the release of glucose from the liver into the blood due to an increase in GLUT2 expression, but are also insulin synergists, facilitating the transport and utilization of glucose by peripheral tissues (muscle and fat) via increasing the expression of GLUT4.

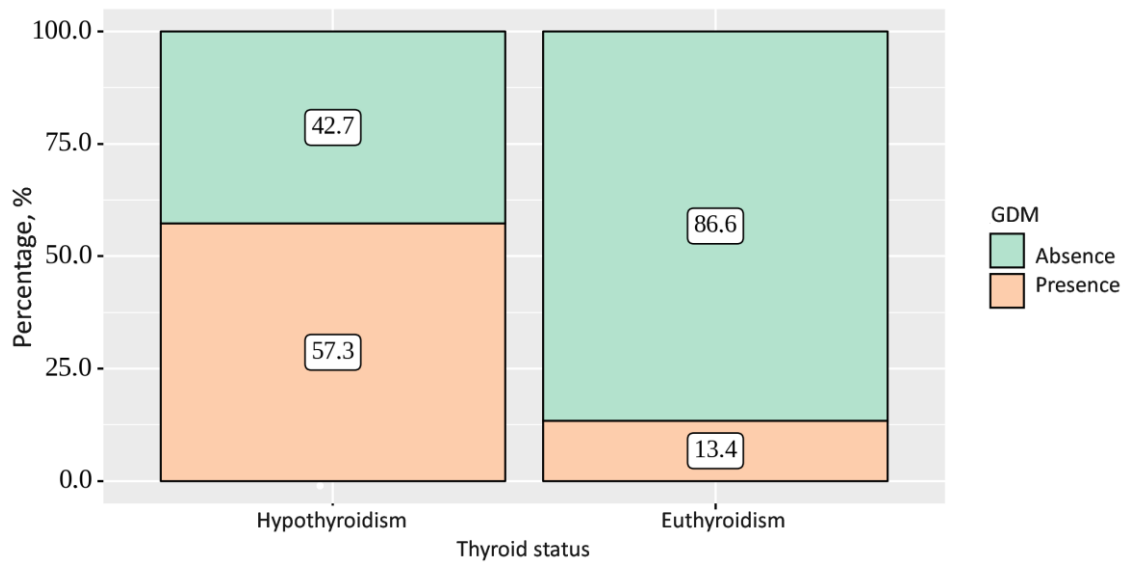


Figure 1. Analysis of the presence of gestational diabetes mellitus vs. thyroid status.

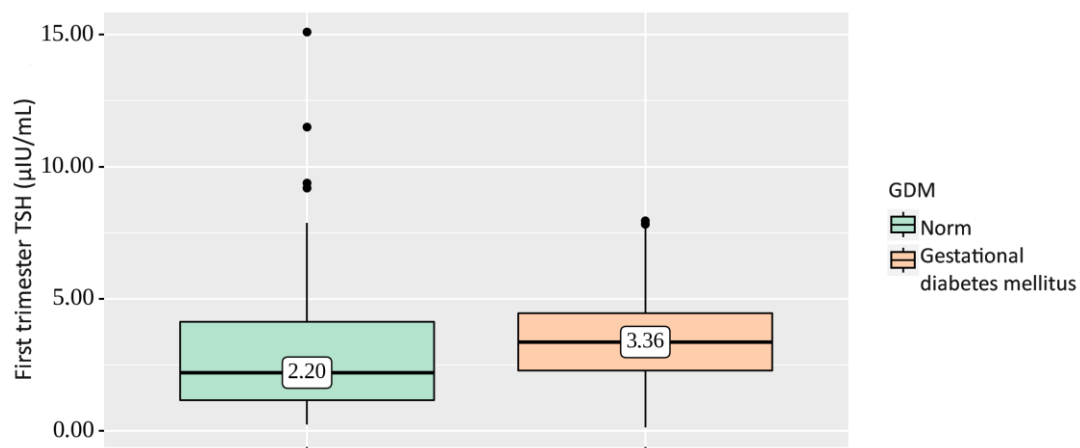


Figure 2. Analysis of the first trimester thyroid-stimulating hormone concentration vs. presence of gestational diabetes mellitus.

Possible pathogenetic mechanisms of carbohydrate metabolism disorders in hypothyroidism include a decrease in GLUT4 expression, a direct effect on insulin degradation, an impaired ratio between glucose release by the liver and its utilization by peripheral tissues, and an increase in circulating free fatty acids [14]. Data on the effect of hypothyroidism on the level of insulin secretion are contradictory, but some studies indicated a reduction in the latter [18].

Besides, in a study by Gupta et al. subclinical hypothyroidism was associated with an increased level of proinflammatory cytokines (CRP and IL-6), their level was directly related to TSH content, which implied the association of SGH with systemic inflammation and resulting insulin resistance [19].

Our study confirmed the association of hypothyroidism with the development of GDM. In the group of pregnant women with hypothyroidism, GDM was detected significantly more often. The odds of developing GDM in the presence of hypothyroidism were 8.6 times higher, compared with euthyroidism; and the difference in odds was statistically significant (OR=8.62; 95% CI: 3.95-18.87). Furthermore, GDM was detected more habitually in the hypothyroidism group, regardless of whether it was SGH or

primary hypothyroidism preceding pregnancy. However, the presence of hypothyroidism did not affect the characteristics of GDM course: there were no differences between the groups either in the timing of GDM detection or in the need for insulin therapy.

Another important result of our study was the identification of a relationship between the first trimester TSH level and the prediction of the GDM risk. TSH level in the first trimester greater than, or equal to, 2.7 µIU/mL predicted the development of GDM with a sensitivity of 71.4% and a specificity of 63.1%. Some studies did not confirm the relationship between the level of TSH and the incidence of GDM. For example, in a study by Popova et al. the level of TSH did not correlate with the incidence of GDM; however, a direct relationship with the level of TPO Ab and an inverse relationship with the level of free T4 [3].

Our study did not aim at identifying the reference values of TSH for the Russian population of pregnant women. For that purpose, it would be necessary to conduct large epidemiological research. However, we think that TSH level above 2.7 µmol/L in the first trimester should contribute to a more active detection of carbohydrate metabolism disorders in pregnant women, as well as to a timely prevention of such disorders.

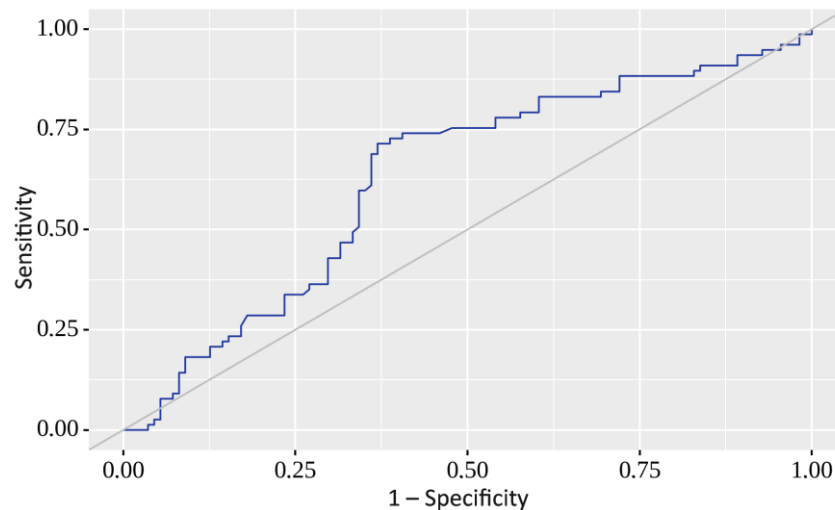


Figure 3. ROC-curve characterizing the dependence of the probability of developing gestational diabetes mellitus on the level of thyroid-stimulating hormone in the first trimester.

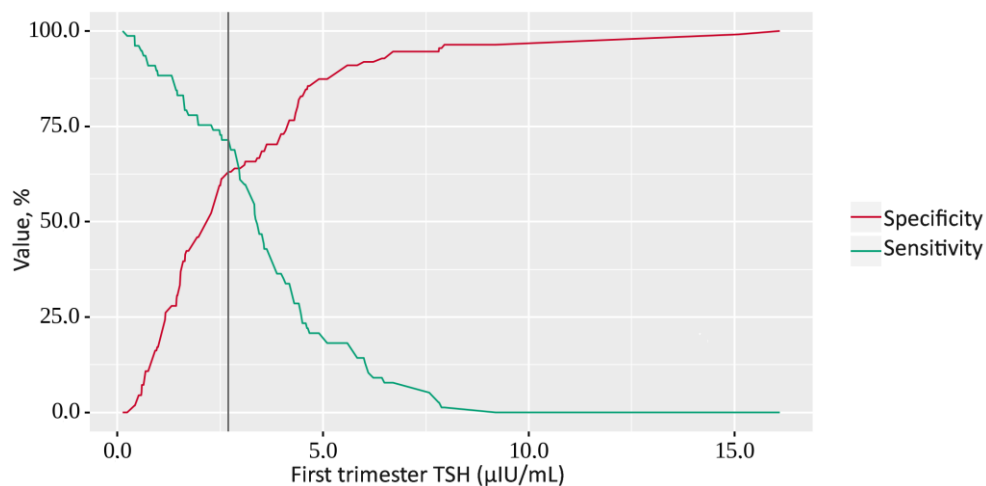


Figure 4. Sensitivity and specificity analysis of the model vs. the threshold concentration values of thyroid-stimulating hormone in the first trimester.

### Conclusion

Hypothyroidism and gestational diabetes mellitus are interrelated endocrine pathologies. The revealed relationship is probably based on mutual genetic factors, as well as on the negative effect of hypothyroidism on carbohydrate metabolism. The result is a more frequent development of GDM in the presence of hypothyroidism in pregnant women. The first trimester TSH concentration of  $\geq 2.7 \mu\text{IU/mL}$  increases the chance of developing GDM by over 8 times: hence, it should be considered a signal for timely prevention and detection of this pathology.

### Ethical approval

Formal consent is not required for this type of study.

### Study limitations

Since it was a retrospective study, it had a number of limitations. First, it was not always possible to fully determine the anamnestic data that could affect the development of hypothyroidism in pregnant women. For the same reason, the study did not include data on the content of antithyroid antibodies in the subjects. The second limitation was that TSH

concentration was determined at different times, as the patients went to the doctor to be registered for pregnancy. For statistical analysis, we considered TSH level separately for each of two periods: the first trimester and the second trimester.

### Conflict of Interest

None declared.

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