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КОРЕЛАЦИЈА НА НИВОТО НА ТИРЕОСТИМУЛИРАЧКИОТ ХОРМОН (TSH), ТИРОКСИНОТ (TT4), УРИНАРНАТА ЈОДНА КОНЦЕНТРАЦИЈА И ПРЕДВРЕМЕНОТО ПОРОДУВАЊЕ

THE IMPACT OF THYROID STIMULATING HORMONE(TSH), TOTAL THYROXINE (TT4) AND URINARY IODINE CONCENTRATION (UIC) ON NEONATAL OUTCOME AND PRETERM DELIVERY

Maja Avramovska[1], Borislav Karanfilski[2], Olivija Vaskova[3], Goran Dimitrov[4], GligorTofoski[4], Elena Dzikova[4], Katerina Nikoloska[4], Ana Daneva Markova[4] and Aleksandar Sikole[5]

[1]Clinical Hospital "Dr. Trifun Panovski" - Bitola, [2]National Committee for Iodine Deficiency, Ministry of Health, Skopje,[3]Institute for Pathophysiology and Nuclear Medicine, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, [4]Clinic for Gynecology and Obstetrics, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, [5]University Clinic for Nephrology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, Republic of North Macedonia

Abstract

Introduction. Impaired maternal thyroid metabolism is associated with poor outcomes for the mother, the developing newborn and preterm delivery. The aim of this study was to investigate the impact of thyroid stimulating hormone (TSH), total thyroxine (TT4) and urinary iodine concentration (UIC) on neonatal outcome and preterm delivery.

Methods. From the cohort of 358 healthy pregnant women (mean age 30.15±5.26 years)three subgroups were formed accordingto gestational week of pregnancy. TSH and TT4 were analyzed with time-resolved fluoroimmunoassay and UIC by mass spectrometry. Correlation of thyroid parameters with other variables was analyzed by Pierson's correlation test. Logistic regressionwas used to predict the neonatal outcome and preterm delivery. Receiver operating characteristics curve analysis was used to calculate cut-off value of TT4 as predictors of treating preterm delivery (TPD).

Results. There was a statistically significant difference in TSH (0.471±0.82 mIU/L *vs*. 0.544±0.337 mIU/L, P=0.016) betweenprematurely delivered and delivered atterm. TSH had a statistically significant predictive impact on the TPD in the second trimester (Exp β=-0.0532, Wald=4.6003, P=0.032). TT4 assumed a predictive impact in thethird trimester (Exp β=1.0227, Wald=6.0254, P=0.014). The cut-off point of TT4 in detecting of TPD was131.3 nmol/L, area under the curve =0.66.

Conclusion. The results of this study suggest that values of maternal TT4 and TSH show possible predictive impact of preterm birthin the second and third trimester, which varies by gestational age.

Correspondence to: Maja Avramovska, Clinical Hospital "Dr. Trifun Panovski"-Bitola; „Partizanska" nn, 7000 Bitola, R. N. Macedonia, Phone: +389 77 945 407; E-mail: dr.avramovska@gmail.com

Keywords: thyroid stimulating hormone, total thyroxine, urinary iodine concentration, preterm delivery

Апстракт

Вовед. Нарушениот метаболизам на мајчината тироидната жлезда е поврзан со лошисходза мајката, развојот на новороденчето и предвременото породување. Целта на оваа студија беше да се испита корелацијата помеѓутиреостимулирачкиот хормон (TSH), вкупниот тироксин (TT4) и уринарната јодна концентрација (UIC) со неонаталниот исход и предвременото породување.

Методи. Од групата 358 здрави бремени жени (средна возраст од 30,15±5,26 години) беа формирани три подгрупи според гестациската недела од бременоста. TSH и TT4 беа анализирани со автоматска флуороимунолошка анализа, а UIC со масна спектрометрија. Корелацијата на тироидните параметри со другите варијабли беше анализирана со Пирсоновиот тест за корелација. За да се предвиди неонаталниот исход и предвременото породување беше користена логистичка регресија. Анализата на ROC криватабеше употребена за да се пресмета пресечената вредност на TT4 како предиктор за заканувачко предвремено породување (TPD).

Резултати. Откривме статистички значајна разлика кај TSH (0.471±0.82 mIU/L vs. 0.544±0.337 mIU/L, P=0.016) помеѓу предвреме родените и родените во термин. TSH има статистички значајно предиктивно влијание на предвременото породување во вториот триместар (Exp β=-0.0532, Wald=4.6003, P=0.032). TT4 има можно предикторно влијание во третиот триместар (Exp β=1.0227, Wald=6.0254, P=0.014). Пресечната точка на TT4 во откривање на TPL е 131.3 nmol/L, површината под кривата = 0.66.

Заклучок. Резултатите од оваа студија сугерираат дека вредностите на TT4 и TSH на мајката покажуваат можно предиктивно влијание на предвременото породување во втор и трет триместар, кое варира според гестациската возраст.

Клучни зборови: тиреостимулирачки хормон, тотален тироксин, уринарна јодна концентрација, предвремено породување

Introduction

Preterm birth, defined as birth prior to 37 weeks of gestation, complicates 5-15% of pregnancies worldwide. It is the leading cause of morbidity and mortality in children younger than 5 years, and is an important risk factor for psychiatric, metabolic, cardiovascular and renal disease later in life [1]. However, in the majority of cases, no known risk factors can be found.

Every year 15 million babies in the world, more than one in 10 births, are born prematurely [2]. More than one million of those babies die shortly after birth due to complications of preterm birth. “Being born too soon is an unrecognized killer”, says Joy Lawn [2]. Many survivors face a lifetime of disability, including learning disabilities and visual and hearing problems [3].

According to the results of the Republic Center for Reproductive Health, in 2018 in our country a total of 1670 preterm births (8.07%) out of the total of 20697 births were recorded, which is almost identical to the number in2017. However,in 2013 this percentage was slightly lower (7.42%), or 1664 preterm births out of a total of 22433 births [4].

Solving the mystery of preterm labor, which compromises the health of future generations, is a formidable scientific challenge worthy of investment [1,5]. Numerous literature data found a connection between maternal thyroid status and preterm delivery. Thyroid dysfunction often is overlooked in pregnant women, because of nonspecific symptoms and the hypermetabolic state of normal pregnancy [6]. Thyroid hormone levels in the mother are very important in the growth and development of the baby. Research has shown that impaired maternal thyroid metabolism and thyroid hormones status are associated with poor outcomes for the mother and the developing newborn, and preterm delivery as well [7].

The aim of this study was to investigate the impact of thyroid parameters [thyroid stimulating hormone (TSH), total thyroxine (TT4) and urinary iodine concentration (UIC)] on neonatal outcome and preterm delivery.

Material and methods

Studied population

A total of 358 healthy pregnant women (mean age 30.15±5.26 years) were examined in this prospective study, divided into three subgroups depending on the trimester they were in at the time of sampling: first trimester [up to 12 gestational week (g.w.)], second trimester (12-28 g.w. and third trimester 28 g.w. to end of pregnancy. They had no known thyroid disorders and they gave birth at the University Clinic for Gynecology and Obstetrics-Skopje. An informed consent was obtained from each woman included in the study and the study protocol conformed to the ethical guidelines of the Declaration of Helsinki.

In the period April-July 2017, from each participant a sample of five drops of heparinized blood of 5 μL (microliter) was taken and applied to a special type of filter paper as well as 2 mL (milliliter) of urine. The next phase was to dye the samples for 24 hours and keep them atthe constant temperature of-20° C. The analyses (TSH and TT4) were forwarded to the Department of Health Sciences and Technology in Zurich (ETH Zürich) and were analyzed with GSP 2021-0010; PerkinElmer, Turku, Finlandwith time-resolved fluoroimmunoassay [8].

At the National Institute for Health and Welfare (THL) in Helsinki (ICP), theUIC in urine samples was analyzed by mass spectrometry (MS), using Agilent 7800 ICP-MS system, with the Pinell-modified Sandell Kolthoff method [8].

Postpartum data and data about maternal age, parity, obstetric history, gestational age at the time of birth and the way of birth were entered for each of these patients from their medical histories. Condition of the newborn after delivery and Apgar score was given by the neonatologist, while baby's birth weight and length weremeasured by the midwives.

Results

Demographic data

From the cohort of 358 pregnant women 41(11.45%) were elected that delivered prematurely (before 37 gestational week), as well as those who gave birth after 37 gestational weeks, 317 or 88.55%. The mean age of the participants in the first group (preterm labored patients) was 30.15±5.26 years, theirbody mass index (BMI) was 27.0±4.59 kg/m^2 and the mean age of gestational week at the time of delivery was 33.2±3.5 weeks. The premature newborns (24 male or 58.53%) had mean birth weight of 2199.5±526.5 g and mean length of 44.8±4.9 cm. The mean age of the second group (labored at term) was 39.09 ±1.3 weeks, with mean birth weight of 3246.7±445.9 g and mean length of 50.18±2.68 cm. The rests of the demographic and laboratory characteristics of the mothers and the newborns are presented in Table 1.

There were no statistically significant differences between the mothers' age, although it wasnoticeable that mothers who delivered pretermwereolder than mothers who

Table 1. Demographic and laboratory characteristics of mothers and newborns

Characteristics	Preterm labored patients (< 37 week); N = 41			Labored at term (>37 week); N = 317		
	VALUE [Mean, SD, n (%)]	Median	Range	VALUE [Mean, SD, n (%)]	Median	Range
Age, years	30.15 ± 5.26	30.9	20.6 - 45.4	29.12 ± 5.57	29	14 - 52
BMI, kg/m^2	27.0 ± 4.59	26.9	19.63 - 41.4	27.17 ± 4.82	26.6	17.26 - 47.6
Gestational age at blood sampling, weeks	27.3 ± 7.6	28	9 - 37	29.23 ± 10.9	33	5 - 42
Gestational age at birth, weeks	33.2 ± 3.5	34	20 - 37.5	39.09 ± 1.3	39	35.3 - 42
Thyroid parameters						
TSH, mU/L	0.471 ± 0.82	0.4	0.09 - 1.4	0.544 ± 0.337	0.5	0.1 - 3.7
TT4 (nmol/L)	114.12 ± 32.06	112.3	39.2 - 191.5	102.63 ± 28.06	100.8	24 - 195
UIC, µg/L	188.08 ± 117.05	164.05	40.9 - 558.1	274.79 ± 793.5	189.23	13 -
Premature pregnancies (34 < PP ≤ 37 weeks)	35.4±0.9; 22 (53.66)	35.3	34 - 37			
A. Spontaneous pregnancies	7 (31.81)			Spontaneous term deliveries		179 (56.4%)
B. With Cesarean section	15 (68.19)			Cesarean section term deliveries		138 (43.53%)
Very premature pregnancies (< 34 weeks)	30.7±3.7; 19 (46.34)	32.4	20 - 33.5			
A. Spontaneous very premature pregnancies	7 (36.84)					
B. With Cesarean section	12 (63.16)					
NICU admission, days	12.3 ± 15.3	12	0 - 81			
Weight, g	2199.5 ± 526.5	2260	555 - 3090	3246.7 ± 445.9	3250	2150 - 4470
Length, cm	44.8 ± 4.9	46	25 - 50	50.18 ± 2.68	50	45 - 89
Apgar score						
1 min	6.9 ± 1.5	7	1 - 9	7.7 ± 0.96	8	0 - 9
5 min	7.8 ± 1.53	8	1 - 9	8.7 ± 0.81	9	4 - 10
SGA	3 (7.31)					
IUGR	2 (4.87)					
Fetal Distress	10 (24.39)					

SD, standard deviation; n, number; %, percentage; BMI, body mass index; TSH, thyroid stimulating hormone; IUGR, Intrauterine Growth Restriction; SGA, Small for Gestational Age; TT4, total thyroxine; UIC, Urinary Iodine Concentration; NICU, neonatal intensive care unit

delivered at term (P=0.263); also that mothers who delivered preterm had a significantly higher BMI (P=0.831); and that the TSH value did not differ significantly between the two groups (P=0.296), as well as the UIE value (P=0.339).

There was a statistically significant difference between the values of TT4 (P=0.016), birth weight (P=0.0001), birth length (P=0.0001) and Apgar score at 1 and 5 minutes (P=0.0001) between mothers who gave birth prematurely and mothers who gave birth at term. The results for "p" wereobtained by t-test for independent samples, two-way probability.

Our study population according to the World Health Organization (WHO) was predominantly overweight; pregnant women delivered average at 33.2 gestational weeks [10]. Both premature and very premature pregnancies ended mostly with Cesarean section (68.19% and 63.16%, respectively), with more than 24% cases of fetal distress. The average stay of the newborns in neonatal intensive care unit (NICU) was 12.3±15.3 days (median 12 days). The newborn weight was classified in low birth weight category (less than 2500 g) [11]. Apgar score was reassuring both at1 and 5 minutes, according to the American College of Obstetrics and Gynecology (ACOG) [12]. Only 7.31% of the newborns were small for gestational age (SGA) and 4.87% were with intrauterine growth restriction (IUGR).

According to the guideline of the American Thyroid Association (ATA) for the diagnosis and management of thyroid disease during pregnancy and postpartum [13], the reference values for TSH and FT4 was ranged from 0.1 to 3.7 mIU/L and 65/97.5-165-247.5 nmol/L,

respectively. We compared our TSH and TT4 results in accordance with ATA reference values during appropriate trimester of pregnancy. We presented the matches or deviations of TSH and TT4 for each trimester.

In the first trimester of pregnancy (upto 12 g.w.), a totalof 64 women were examined, and TSH values did not deviate from normal reference values, with a mean 0.483±0.335 mIU/mL, where as for TT4 values only 2 pregnant women deviated from the reference values (3.12%). In the second trimester (12-28 g.w.), a totalof 100 women were examined, with TSH values within the reference range, mean 0.485± 0.274 mIU/L, while 31 pregnant women deviated from the reference values of TT4 or 31%. In the third trimester (28 g.w.), a total of 194 women were examined, with TSH values within the reference range, mean 0.563±0.369 mIU/L, with 54 pregnant or 27 pregnant women deviated from the reference values of TT4or 27%.

Bivariate Pearson's (r) or Spearman rho (ρ) correlation

Appropriate correlation coefficients [Pearson's (r) or Spearman rho (ρ)] as a measure of the strength for linear relationship according to distribution of the variables for each trimester are shown in Table 2.

Table 2. Bivariate correlation between thyroid status parameters and clinical parameters by each trimester

Trimester	Thy. P	Mother age	BMI	GAB	Baby weight	Apgar 5 min	SGA	IUGR	PPI
First	TSH	r=-0.114	r=0.062	r=- 0.094	r=0.067	r=0.126	ρ=-0.035	ρ=0.055	ρ=0.053
		p=0.370	p=0.319	p=0.460	p=0.597	p=0.319	p=0.780	p=0.665	p=0.676
	TT4	r=-0.157	r=-0.201	r=-0.188	r=-0.292	r=-0.279	p=-0.074	ρ=-0.084	ρ=0.156
N = 64		p=0.214	p=0.111	p=0.136	**p=0.019**	**p=0.025**	p=0.563	p=0.507	r=0.217
	UIC	r=-0.12	r=-0.005	r=0.094	r=0.141	r=0.100	r=0.023	r=-0.051	r=-0.039
		p=0.346	p=0.970	p=0.461	p=0.268	p=0.431	p=0.857	p=0.691	p=0.757
Second	TSH	r=-0.02	r=0.24	r=0.203	r=0.081	r=0.212	r=0.186	ρ=0.049	ρ=-0.212
		p=0.844	**p=0.016**	**p=0.043**	p=0.425	**p=0.034**	p=0.0644	p=0.678	**p=0.034**
	TT4	r=-0.030	r=-0.024	r=0.021	r=0.265	r=0.155	r=0.012	ρ=0.087	ρ=0.045
N = 100		p=0.766	p=0.809	p=0.835	p=0.094	p=0.124	p=0.998	p=0.165	p=0.653
	UIE	r=-0.151	r=0.010	r=-0.373	r=0.099	r=0.025	r=0.057	r=-0.003	r=-0.054
		p=0.133	p=0.923	p=0.471	p=0.327	p=0.804	p=0.575	p=0.892	p=0.595
Third	TSH	r=-0.103	r=0.069	r=- 0.018	r=0.020	r=0.035	r=-0.075	ρ=0.035	ρ=-0.007
		p=0.152	p=0.340	p=0.799	p=0.783	p=0.311	p=0.625	p=0.627	p=0.925
	TT4	r=-0.118	r=-0.146	r=- 0.087	r=-0.156	r=-0.114	r=-0.175	ρ=0.096	ρ=0.184
N = 194		p=0.100	**p=0.043**	p=0.227	**p=0.030**	p=0.114	**p=0.013**	p=0.183	**p=0.012**
	UIE	r=0.029	r=0.033	r=0.078	r=0.043	r=-0.247	r=0.037	r=-0.001	r=-0.037
		p=0.683	p=0.644	p=0.278	p=0.094	p=0.546	p=0.603	p=0.984	p=0.603

Thy. P, thyroid parameters; BMI, Body Mass Index; GAB, Gestational Age on Birth; SGA, Small for Gestational Age; IUGR, Intrauterine Growth Restriction; PPI, Partus Praetemporarius imminens; TSH, thyroid stimulating hormone; TT4, total thyroxine; UIC, Urinary Iodine Concentration

The negative value of product-moment correlation coefficient (r, ρ) as the measure of the strength of linear dependence between two variables indicated a *significant negative correlation* between TT4 in the **first trimester** and baby weight (r=-0.292, p=0.019), as well as TT4 in the first trimester and Apgar score at5 minute (r=-0.279, p=0.025). In the second trimester, a *significant negative correlation* was found between TSH and BMI (r=-0.24, p=0.016), TSH and PPI (ρ=-0.212, p=0.034). Also, in the **second trimester**, a significant positive correlation was found between TSH and GAB (r=0.203, p=0.043) and TSH with Apgar score at 5 minute (r=0.212, p=0.0342). In the**third trimester**, a *significant negative correlation* was found between TT4 and BMI (r=-0.146, p=0.043), with baby weight (r=-0.156, p=0.030) and SGA (r=-0.175, p=0.013), as well as a significant positive correlation between TT4 and PPI (r=0.184; ρ=0.012).

Urinary iodine concentration did nothave a statistically significant correlation in prediction of preterm birth, and no correlation with the other variables (mother age, BMI, GAB, SGA, Apgar score, baby weight) in each trimester.

Logistic regression

The binary dependent variable (labor) is determined by two values: 0 (those who gave birth after 37 g.w.) and 1 (premature-births before 37 g.w.). Due to the categorical nature of this variable, we used a logistic regression model. The coefficient β, standard error (Std. Error), Wald, P and odds ratio coefficients (exp β) and their confidence interval (CI) are shown in Table 3, for each trimester separately.

Table 3. Logistic regression of categorically dependent variables (PPI) depending on TSH and TT4 levels

LOGISTIC REGRESSION					
		Coefficients and standard errors			
FIRST TRIMESTER	Variable	β coefficient	Stand.error	Wald	P
	TSH, mIU/L	0.70634	1.29506	0.2975	0.585
	TT4, nmol/L	0.023157	0.018269	1.6067	0.205
	Constant	-5.3317			
		Odds Ratios and 95% Confidence Intervals			
	Variable	Odds ratio (exp β)			95% CI
	TSH, mIU/L	2.0266			0.1601 -25.6527
	TT4, nmol/L	1.0234			0.9874 -1.0607
		Coefficients and standard errors			
SECOND TRIMESTER	Variable	β coefficient	Stand.error	Wald	P
	TSH, mIU/L	-2.93347	1.36769	4.6003	**0.032**
	TT4, nmol/L	0.0058666	0.0088878	0.4357	0.509
	Constant	-0.8813			
		Odds Ratios and 95% Confidence Intervals			
	Variable	Odds ratio (exp β)			95% CI
	TSH, mIU/L	-0.0532			0.0036 -0.7766
	TT4, nmol/L	1.0059			0.9885 -1.0236
		Coefficients and standard errors			
THIRD TRIMESTER	Variable	β coefficient	Stand.error	Wald	P
	TSH, mIU/L	-0.38772	0.8391	0.2135	0.644
	TT4, nmol/L	0.022481	0.0091586	6.0254	**0.014**
	Constant	-4.5785			
		Odds Ratios and 95% Confidence Intervals			
	Variable	Odds ratio (exp β)			95% CI
	TSH, mIU/L	0.6786			0.1310 -3.5146
	TT4, nmol/L	1.0227			1.0045 -1.0413

TSH, thyroid stimulating hormone; TT4, total thyroxine; Stand. Error, standard error; (exp β) = e^{β}; CI, confidence interval; Variable UIC was not included in the model (P > 0.7).

The **first trimester** logistic regression model showed that TT4 and TSH had no statistical significance (p> 0.05) in predicting preterm delivery. In the **second trimester** TSH had a statistical significance (p<0.05), with a predictive impact on the outcome of preterm delivery. The higher value of the Wald test (4,6003) for TSH gavegreater predictive importance in predicting PPI in the second trimester than that of TT4 (Wald= 0.4357). Unlike the predictive significance of TSH in thesecond trimester, TT4 assumed a predictive impact in the **third trimester**. The lower P-value (0.014 *vs*. 0.644) and the higher Wald value (6.0254 *vs*. 0.2135) in TT4 compared to TSH, confirmed TT4 in prediction of PPI. Logistic regression results of the full cohort of 358 pregnant women, no matter in which trimester blood samples were taken, showed a more expressive predictive effect of TT4 on PPI (TT4, β=0.016401, Exp (β)= 1.0165, Wald=7.288, P=0.007) than predictive effect of TSH on PPI (P=0.061).

This statistical model distinguishes between mothers delivered at term and those who gave birth prematurely. The area under the curve (AUC) wasgreater than 0.5 (0.66) and gavea predictive effect of TT4 as a variable in the logistic regression model. The maximum sensitivity (39.02%) and specificity (84.54%) of the method

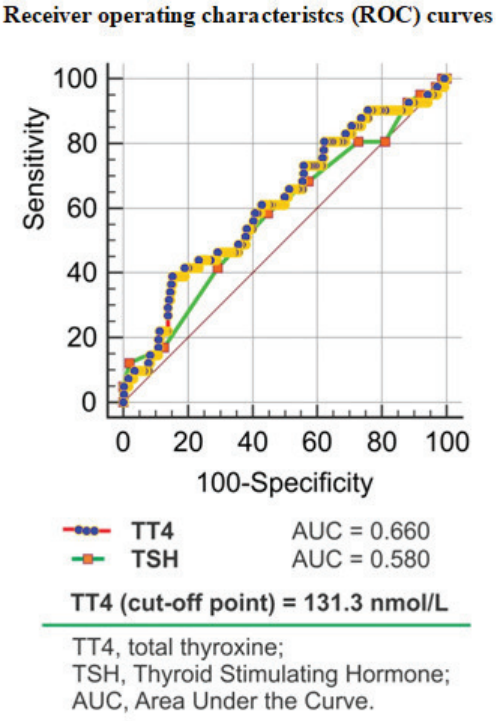

Fig. 1. ROC Curve [Receiver operating characteristics (ROC)] for comparisonof predictive meaning of TT4 and TSH in preterm labor

in detecting the impact of TT4 on the event wasat TT4= 131.3 nmol/L, which was essentially the cut-off point of TT4. Each single increase in TT4 above the cut-off value of 131.3 nmol/L significantly increased the risk of preterm delivery by 1.65% (OR=1.0165, CI=0.608-0.710). The larger and more significant predictive impact of PPI is also seen by the larger area under the TT4 curve of the TT4 and TSH specificity and sensitivity diagram as predictors of PPI event prediction.

Discussion

This study has evaluated the incidence of preterm birth in correlation with changes of TT4 and TSH levels in specific trimesters of pregnancy as well as UIC in preant women. In our group, 11.45% of the total of 358 women gave birth prematurely, usually by cesarean section (63-65%), with an average stay in the NICU of 12 days.

Over the last 20 years, multiple adverse pregnancy and neonatal outcomes, including preterm birth, have been connected with many categories of abnormal thyroid function testing [14]. Thyroid dysfunction often is overlooked in pregnant women, because of nonspecific symptoms and hypermetabolic state of normal physiology of pregnancy [6]. According to Leung, exploring the thyroid function in pregnancy remains a controversial issue [15,16].

However, given the potential obstetric and neonatal complications of untreated thyroid disorders in pregnancy, Leung recommends determining eventual presence of maternal thyroid dysfunction as early as possible in pregnancy [15,16].

The statistically significant difference in TSH levels (p=0.032) in the second trimester and TT4 (P=0.014) in the third trimester in mothers who delivered at term and preterm, demonstrated its potential impact on the neonatal outcome. Logistic regression analysis in this study showed that TT4 and TSH could be used as predictors of preterm delivery, depending on which trimester thesethyroid parameterswere examined. TT4 expresses a greater predictive impact on preterm delivery than TSH, independently of blood sampling time during different gestational age.

According to Leung, TSH concentrations in serum should be interpreted in the context of pregnancy physiology of the thyroid gland. During pregnancy, total TT4 levels are appropriately elevated above the non-pregnant reference ranges, due to the increased serum TBG levels through pregnancy [15,16].

Our results correlated with the results presented inthe study of Medici *et al*. [18] who demonstrated that higher maternal TT4 values were negatively correlated with birth weight and were associated with an increased risk for SGA, although our data were divided by specific trimesters. We found a negative correlation for these variables (r=-0.175, P=0.013) for the third trimester results. Mannisto *et al.* [19] in their study found that maternal BMI was related to thyroid function: obese pregnant women had higher serum concentrations of TSH and TT4, which is consistent with the results of our study, in which we found a significant negative correlation between gestational age at birth (GAB) and BMI (r=-0.359, p=0.02). Patients with larger BMI delivered earlier in a smaller gestational week [20,21].

The relationship between maternal and fetal thyroid function with adverse neonatal outcome and the long-term effects of the newborn require further detailed and comprehensive analysis. A multidisciplinary approach (endocrinologists with gynecologists), review of literature and future guidelines are needed [22,23].

Limitations of the study

The first limitation of this study was the small number of patients, especially the small number of women that delivered prematurely. Taking blood and urine tests only once throughout the pregnancy reduce the accuracy of predicting the impact of thyroid markers on the neonatal outcome and preterm delivery, which is the second limitation. The third limitation in our study wasthe inability to screen for the presence of thyroid peroxidase antibody (TPO-Ab) in pregnant women because its impact onthe risk of preterm delivery is known [23]. The fourth limitation was missing data of deliveries outside the University Clinic forGynecology and Obstetrics-Skopje, where the examination was performed, that reduced the accuracy of logistic regression model.

Conclusion

There was a statistically significant difference in maternal TT4 levels between preterm and term deliveries in the third trimester, and a statistically significant difference in TSH in the second trimester. TT4 has a possible predictive effect on the preterm delivery outcome for pregnant women in the third trimester, and TSH has a possible predictive effect on the outcome of preterm delivery in the second trimester.

TT4 expresses a greater predictive impact on preterm delivery than TSH, independently of blood sampling time during different gestational age.

Conflict of interest statement. None declared.

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