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МАЈЧИНАТА ДЕБЕЛИНА, ВОЗРАСТА И ТИРОИДНИОТ СТАТУС-ИНТРИГАНТНА ВРСКА СО НЕОНАТАЛНИОТ ИСХОД

MATERNAL OBESITY, AGE AND MATERNAL THYROID STATUS - AN INTRIGUING CONNECTION TO THE NEONATAL OUTCOME

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Abstract

Introduction. Thyroid dysfunction is the second most common endocrine disorder affecting women of reproductive age. Higher body mass index (BMI>30 kg/m^2) is linked with many endocrine abnormalities, including thyroid dysfunction. Gestational age at birth (GAB) and birth weight (BW) are important predictors of neonatal mortality and morbidity. The objective of this prospective study was to determine the adverse neonatal outcomes of women [small for gestational age (SGA), intrauterine growth restriction (IUGR) and others] complicated with impaired thyroid function and obesity, when compared with those with normal function.

Methods. Dried blood spot and urine samples were analyzed for thyroid and iodine status in 358 pregnant women in any gestational week, without known thyroid disorders. They gave birth at the University Clinic of Gynecology and Obstetrics-Skopje. The blood samples were analyzed with time-resolved fluoroimmunoassay in Zurich, and UIC was analyzed by mass spectrometry in Helsinki.

Results. We found a significant positive correlation between total thyroxine (TT4) and GAB (p=0.045) and UIE and mother age (p=0.007), but a significant negative correlation between GAB and UIE (p=0.051), GAB and mother's age (p=0.01), GAB and BMI (p=0.02). There was an inverse correlation between BW and maternal age (βst=-0.0641, P=0.010) and between BW and maternal TT4 (βst=-3.3640, P=0.0016). We found a positive correlation between BW and maternal BMI (βst = 21.847, P = 0.006).

Conclusion. Overweight, obese and older women are at increased risk of thyroid dysfunction during pregnancy considered as high-risk pregnancies for adverse neonatal outcomes. We can use maternal TT4, BMI and age for predicting the BW.

Keywords: obesity, thyroid status, small for gestational age (SGA), intrauterine grow restriction (IUGR), neonatal outcome

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Апстракт

Вовед. Тироидната дисфункција е второто најчесто ендокрино нарушување, кое ги зафаќа жените во репродуктивна возраст. Повисокиот BMI (>30 кг/м^2) е поврзан со многу ендокрини абнормалности, вклучително и тироидна дисфункција. Гестациската возраст при раѓање (GAB) и родилната тежина се важни предиктори за неонаталниот морталитет и морбидитет. Целта на оваа проспективна студија беше да се утврди евентуалниот неповолен неонатален исход на жените, мали за гестациската возраст (SGA), интраутерин застој во растот (IUGR) и други комплицирани случаи, со нарушена функција на тироидната жлезда и дебелина, во споредба со тие со нормална функција.

Методи. Исушените капки крв и примероците на урина беа анализирани за тироидниот и јодниот статус кај 358 бремени жени во која било гестациска недела, без познати тироидни нарушувања. Тие се породија на Универзитетската клиника за гинекологија и акушерство-Скопје. Крвните примероци беа анализирани со флуороимунолошка анализа во Цирих, а уринарната јодна концентрација (UIC) беше анализирана со масна спектрометрија во Хелсинки.

Резултати. Откривме значајна позитивна корелација меѓу TT4 и GAB (p=0.045), UIE и возраста на мајката (p=0.007), но значајна негативна корелација меѓу GAB и UIE (p=0.051), GAB и возраста на мајката (p=0.01), GAB и BMI (p=0.02). Варијаблите на тироидната жлезда T4 (p=0.119) и UIE (p=0.367) не се разликуваат значајно меѓу предвремените и

повеќе предвремените бремености, освен TSH (p= 0.0394). Постои инверзна корелација меѓу BW и возраста на мајката (βst=-0.0641, P=0.010) и меѓу BW и мајчиниот TT4 (βst=-3.3640, P=0.0016). Најдовме позитивна корелација меѓу BW и мајчиниот BMI (βst=21.847, P=0.006).

Заклучок. Жените со прекумерна телесна тежина и обезните, се со зголемен ризик од тироидна дисфункција за време на бременоста, како и постарите жени, и затоа треба да се сметаат како високоризични бремености со неповолни акушерски исходи. Можеме да ги користиме TT4, BMI и возраста на мајката како предиктори за родилната тежина.

Клучни зборови: дебелина, тироиден статус, мали за гестациската возраст (СГА), интраутерин застој во растот (ИУГР), неонатален исход

Introduction

Thyroid hormones and their most important component, iodine are essential for fetal growth and development and play a vital role in the early growth and development of most organs, especially the brain [1,2]. Thyroid dysfunction is the second most common endocrine disorder affecting women of reproductive age. The recent studies have found an association between impaired maternal thyroid status and pregnancy outcome, but only few studies have studied the correlation between body mass index (BMI) and maternal thyroid dysfunction.
Higher BMI (>30 kg/m^2), according to the World Health Organization (WHO) [3], or obesity, especially central obesity, is linked to many endocrine abnormallities, including thyroid dysfunction. This is not uncommon, because triiodothyronine (T_3) regulates the energy metabolism and thermogenesis, playing a key role in glucose and lipid metabolism as well as the fatty acids oxidation [4].
Fat cells produce leptin and are considered as an active endocrine organ. Leptin physiologically regulates energy homeostasis by informing the central nervous system about adipose tissue reserves and is also an important neuroendocrine regulator of the hypothalamic-pituitary-thyroid axis [5]. Evidence suggests that slight variations in thyroid function contribute to the development of regional obesity and the tendency to gain weight, although this has not been confirmed by all studies [4,5].
Gestational age at birth and birth weight are important predictors of neonatal mortality and morbidity and evidence showed an increased risk of preterm birth in relation to maternal hyperthyroidism and hypothyroidism [6]. Some studies reported an increased risk of low-birth weight or small-for-gestational age (SGA) in mothers with hypothyroidism [7,8], while others found no association [6,9].

SGA is defined as weight below the 10th percentile or 2 standard deviation (SD) for the gestational age [10]. The term intrauterine growth restriction (IUGR) is used to describe a fetus that cannot reach its growth potential due to placental insufficiency. Preterm delivery was defined as delivery before 37 completed gestational weeks. Low Apgar score was considered if Apgar score at 1st and 5th min was less than 7.
The objective of this prospective study was to determine the adverse neonatal outcomes of women (SGA, IUGR and others) complicated with impaired thyroid function and obesity, when compared with those with normal function and to find the predictive impact of maternal demographic characteristics and thyroid parameters on neonatal outcome.

Material and methods

Studied population

This prospective study conducted in the period from April to July 2017 included 358 healthy pregnant women in any gestational week, without known thyroid disorders (mean age 30.15±5.26 years) who gave birth at the University Clinic of Gynecology and Obstetrics - Skopje.

Inclusion criteria

Inclusion criteria were singleton pregnancy in any gestational age without previous history of thyroid disease of the mother or treatment with thyroid drugs.

Exclusion criteria

The study did not include: mothers who smoke cigarettes, mothers with any chronic diseases, especially diabetes mellitus or hypertension, and any fetal anomaly diagnosed with amniocenteses or ultrasound.

Ethical Approval and informed consent

This study was approved by the Ethics Committee of the Faculty of Medicine in Skopje, Ss. Cyril and Methodius University in Skopje and an informed consent was obtained from all individual participants included in the study.
A sample of 2 mL (milliliter) of urine and five drops of heparinized blood of 5 μL (microliter) was taken from each participant and applied to a special type of filter paper. The samples were dried for 24 hours at room temperature and then they were frozen at -20° C, until sending them to the Department of Health Sciences and Technology in Zurich (Departement Gesundheitswissenschaften und Technologie-ETH Zürich). TSH and TT4 were analyzed with time-resolved fluoroimmunoassay with GSP 2021-0010; PerkinElmer, Turku, Finland [10].

Urine iodine concentration (IUC) in urine samples was analyzed by mass spectrometry (MS) using Agilent 7800 ICP-MS system, with the Pinell-modified Sandell Kolthoff method, at the National Institute for Health and Welfare (THL) in Helsinki (ICP) [11].
The data about maternal age, parity, obstetric history, gestational age at the time of birth as well as the way of birth were noted from the medical history. Birth weight and length were measured by the midwife attending the birth, while condition of the newborn after delivery and Apgar score was given by the neonatologist.

Statistical analysis

Data analyses were performed using MedCalc Statistical Software, version 19.1.3 (MedCalc Software bv, Ostend, Belgium). The results are presented as mean± SD, median and percentages (%). Bivariate Pearson's (parametric test) or Spearman's (non-parametric test) were used to measure the strength and direction of variables relationships. The comparison of pregnancy outcomes between the normal and abnormal groups was analyzed by Student's *t* test with equal or unequal variances. A *p* value of <0.05 was considered statistically significant. Multiple regression analysis was used to show predictable values of independent variables (age, BMI, TT4 and TSH) on the dependent variable BW.

Results

Demographic and clinical characteristics

The maternal demographic characteristics (Body Mass Index) and nationality, maternal thyroid function values (TSH, TT4, Tg and UIC), gestational week on birth, mode of delivery, birth characteristics and other essential data are shown in Table 1.

Table 1. Demographic, clinical and other characteristics of neonatal outcome

	Normal thyroid status n = 220	**Impaired thyroid status n = 139**	Range	P
Maternal age (years)	28.96 ± 5.22	29.75 ± 6.04	14 - 52	0.189
BMI (kg/cm^2)	26.7 ± 4.61	27.71 ± 5.00	17 - 47	0.081
Nationality				0.744
- Macedonian	130 (59.09%)	74 (53.23%)		0.275
- Albanian	61 (27.72%)	51 (36.69%)		0.074
- Gipsy	28 (12.72%)	12 (8.63%)		0.231
Gestational week at birth	38.46 ± 2.30	38.38 ± 2.89	20 - 42	0.798
Mode of delivery				
- Spontaneous, eutocic	127 (57.72%)	67 (48.20%)		0.078
- Emergency Cesarean Section	23 (10.45%)	11 (7.91%)		0.424
- Dystocic Cesarean Section	28 (12.72%)	13 (9.35%)		0.329
Preterm				
Yes	26 (11.81%)	15 (10.79%)		0.766
No	194 (88.18%)	124 (89.20%)		
Birth weight (g)	3093.47 ± 523.09	3184.14 ± 619.16	555 - 4470	0.153
Birth weight categories				0.289
SGA/IUGR	9 (4.09%)	3 (2.15%)		0.319
Sex				
- male	122 (55.45%)	62 (44.60%)		0.045
- female	98 (44.54%)	77 (55.39%)		
Apgar score (1 min)			5 - 9	
< 5	7 (3.18%)	8 (5.75%)		0.599
> 5	213 (96.81%)	131 (94.24%)		
Apgar score (5 min)			4 - 10	
< 5	5 (2.27%)	2 (1.43%)		0.575
> 5	215 (97.72%)	137 (98.56%)		
Thyroid function values				
TSH (mU/L)	0.555 ± 0.293	0.515 - 0.400	0.1-3.7	0.282
TT4 (nmol/L)	118.33 ± 23.51	80.956 ± 19.935	46.2 - 195.2	<0.0001
Tg (□g/L)	11.40 ± 7.645	11.909 ± 10.823	0.141 - 80.241	0.634
Iodine status				
UIC (μg/L)	261.83 ± 683.31	198.759± 121.687	13.5 - 558.120	0.183

The results are expressed as mean ± SD (standard deviation), mean and n (%), number (percent); BMI, body mass index; LBW, Low Birth Weight; IUGR, Intrauterine Growth Restriction; UIC, Urinary Iodine Concentration; P, value of significance

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 range 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, and we made two groups of participants (those with normal thyroid parameters-Group 1) and Group 2 with impaired thyroid function (participants with different levels from the reference ranges).

The mothers with normal thyroid status were of Macedonian nationality predominantly with lower BMI and lower age compared to the second group. The number of preterm births was greater in the group with normal thyroid status. All mentioned and the other results presented in Table 1 did not significantly differ between the two groups. We found a statistical significance only in the sex and TT4 of the neonate.

T – test for independent samples

Thyroid variables T4 (p=0.119) and UIE (p=0.367) did not differ significantly between premature and very premature pregnancies, except for TSH (p=0.0367).

Box plots of the mean and the results for 95% Confidence Interval (CI) of the mean, range, median, and the 25th and 75th percentiles for both subgroups [Spontaneous premature pregnancies (SPP) and Spontaneous very premature pregnancies (SVPP) are shown in Figure 1. The mean TSH of the SVPP (0.358±0.254 mU/L) was higher than the mean SPP (0.545±0.294 mU/L). The results from the unpaired t-test (for equal variances and unequal sample size): Test statistic t (d), Difference, P-value and F-test (that determines the equality of the variances) are shown in Figure 1, too.

There was a high statistical significance (P = 0.0394)

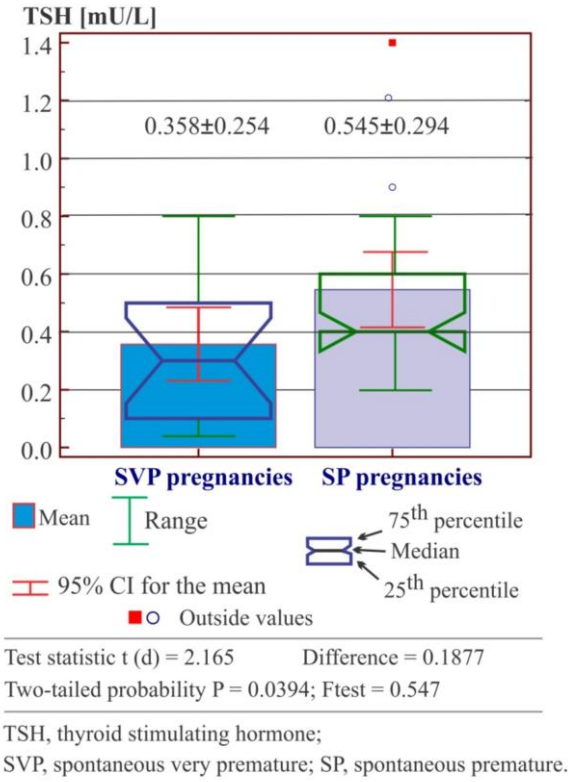

Fig. 1. Notched Box-and-Whisker diagram of SVP and SP pregnancies according to TSH values (independent samples t- test)

between TSH values among SVP and SP pregnancies.

Bivariate Pearson or Spearman correlation

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

Table 2. Bivariate correlation between thyroid and clinical parameters

	Mother age	BMI	GAB	Baby weight	Apgar 5 min	SGA	IUGR
TSH	r = - 0.249	r = - 0.107	r = 0.286	r = 0.286	r = 0.162	r = - 0.075	r = 0.146
	p = 0.1166	p = 0.506	p = 0.092	p = 0.069	p = 0.311	p = 0.642	p = 0.363
TT4	r = - 0.004	r = - 0.206	r = 0.314	r = 0.265	r = 0.198	p= 0.178	p = - 0.175
	p = 0.979	p = 0.071	p = 0.045	p = 0.094	p = 0.214	p = 0.264	p = 0.272
UIE	r = 0.413	r = 0.183	r = - 0.373	r = 0.265	r = - 0.247	ρ = 0.214	ρ = 0.096
	p = 0.007	p = 0.252	p = 0.051	p = 0.094	p = 0.119	p = 0.178	p = 0.552
GAB	r = - 0.395	r = - 0.359	/	r = 0.592	r = 0.238	ρ = 0.198	ρ = 0.287
	p = 0.01	p = 0.02	/	p< 0.0001	p = 0.134	p = 0.214	p = 0.068

BMI, body mass index; GAB, gestational age on birth; SGA, small-for-gestational age; IUGR, intrauterine growth restriction; TSH, thyroid stimulating hormone; TT4, total thyroxine; UIE, urinary iodine excretion

The positive value of product-moment correlation coefficient (r, ρ) as the measure of the strength of linear dependence between two variables indicated a *significant positive correlation* between T4 and GAB (r=0.314, p =0.045), UIE and mother's age (r=0.413, p=0.007) and between GAB and baby weight (p<0.0001). A *significant negative correlation* was found between GAB and UIE (r=-0.373, p=0.051), GAB and mother's age (r=-0.395, p=0.01) and GAB and BMI (r=-0.359, p=0.02).

Multiple regression analysis

Assessments [standardized coefficient β (βst), standard error of βst (Std. Error), t, and p-value] of the depen-

dent predictor "baby weight" or determinants (age, BMI, TT4, and TSH) for prognosis of the birth weight in group with impaired thyroid status after backward multiple regression analysis and the results from Analysis of Variance (F-ratio, degrees of freedom and significance level) are shown in Table 3.

Table 3. Multiple backward regression analysis in mothers with impaired thyroid status

Multiple regression (backward)				
Sample size	139			
Enter variable if P < 0.05, Remove variable if P > 0.5				
Dependent Y	Baby weight			
Coefficient of determination R^2	0.06690			
Multiple correlation coefficient	0.2587			
Regression equation				
Independent variables	*βst coefficient*	*Std. Error*	*t*	*P*
Age	-0.06401	0.02484	- 2.577	0.010
BMI	21.847	6.3473	3.442	0.006
TT4	-3.3640	1.0600	- 3.174	0.0016
TSH	98.2086	88.4056	1.111	0.2674
Variables thyroglobulin and urinary iodine excretion were not included in model				
Analysis of Variance	F -ratio	Significance level	DF	Residual
	6.13	P = 0.0001	2	136

βst, beta standardize; Std. error, standard error of the βst, DF, Degrees of freedom; BMI, body mass index; TT4, total thyroxine; TSH, thyroid stimulating hormone

There was an inverse correlation (negative βst coefficient, βst=-0.0641) between birth weight and maternal age (P=0.010) and inverse correlation (βst=-3.3640) between birth weight and maternal TT4 (P=0.0016). We found a positive correlation (positive βst=21.847) between birth weight and maternal BMI (P=0.006). The correlation between birth weight and maternal TSH was positive, but not statistically significant (P=0.2674).

The multiple correlation coefficient (0.2587) is a measure of how well a given variable (baby weight) can be predicted using linear function of a set of other variables (BMI, age and TT4). Only 25.87% from birth weight changes was dependent on BMI, age and TT4 as the predictors. The remaining from the total variability between them were not explained (74.13% of baby weight were dependent on other factors, which were not covered with the regression model).

The predictive impact of maternal demographic characteristics and thyroid parameters in predicting of birth weight were statistically significant (TT4, P=0.0016; BMI, P=0.006 and age, P=0.0100).

Discussion

In our study, similar to that of Ajmani SN *et al*. [14], women with impaired thyroid function had higher maternal age (29.75±6.04 *vs*. 28.96±5.22) compared to women in the normal group. Hence, the increased maternal age was associated with a higher incidence of thyroid dysfunction. The increase in prevalence of thyroid dysfunction in the older age group is due to current trend of becoming pregnant in older age.

Mannisto *et al*. [15] 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 higher BMI delivered earlier and that is connected to a lower birth weight.

According to the multiple regression results in our study we could predict the birth weight by maternal demographic characteristics and thyroid parameters such as TT4, BMI and age. We found an inverse correlation of birth weight with maternal age and TT4, and a positive correlation between birth weight and maternal BMI. The results presented by Brynhildsen *et al*. [16] suggested that BMI can explain trends in infants' weight, which is agreement with the results obtained in our study. Gois *et al.* [17] in a regression analysis predicted the risk of low birth weight in advanced maternal age. They found βst=1.8 for mothers which age was > 40 years.

This study has the following limitations. We have not taken into consideration the TPO Ab (Thyroid Peroxidase antibodies) as a possible factor of mother's impaired thyroid status. Also, missed deliveries outside the University Clinic of Gynecology and Obstetrics in Skopje reduced the accuracy of the statistical model further. Thirdly, the neonatal cord blood TSH levels were not examined, which can be done in further studies.

Conclusion

Based on the results of previous studies, and alongside with the results of our study, we can conclude that overweight and obese women are at an increased risk of thyroid dysfunction during pregnancy, as well as older women, and thus these should be considered as high risk pregnancies for adverse neonatal outcomes. We can use maternal TT4, BMI and age for predicting the birth weight.

Conflict of interest statement. None declared.

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