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Diagnostic validity of a marker model of first trimester in pregnancy in prediction of birth weight

Dijagnostička valjanost modela zasnovanog na markerima prvog trimestra trudnoće u predviđanju mase ploda na rođenju

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Abstract

Background/Aim. Nowadays, low birth weight is considered to be one of the main causes of cardiovascular diseases or metabolic syndrome occurring later in life. Many studies have shown a strong impact of abnormal birth weight onto the future development, however, due to its stronger influence onto the development, a special emphasis is placed on low birth weight as compared to higher one. There is still no high-percentage accuracy test that will clearly classify expectant women under the risk of giving birth to a child too low or too big for gestational age. The aim of this paper was to set up a model that may indicate future low or high birth weight. **Methods.** This study included 191 expectant women who were divided into three groups, based on the birth weight (group 1: < 3,000 g; group 2: 3,000–4,000 g; group 3: > 4,000 g). The values of biochemical (pregnancy associated plasma protein A – PAPP-A, free β human chorionic gonadotropin) and ultrasonographic markers (nuchal translucency) as well as their multiple of the median (MoM) were determined and compared among groups. **Results.** It was shown that the values of PAPP-A MoM were considerably lower in groups of expectant women that had a fetus with low body weight ($p = 0.003$, $p = 0.001$). Statistically significant correlation between PAPP-A MoM and the newborn's weight ($r_s = 0.221$, $p = 0.001$) was proven among the groups examined within this study. **Conclusion.** The usage of a combination of biochemical parameters, sonographic and demographic data in screening program increases the chances for early identification of fetuses that are under higher risk for growth restriction or increased growth. Also, the increase in the value of PAPP- A MoM causes the increase of fetus' body weight.

Key words:
chorionic gonadotropin, beta subunit, human; diagnosis; fetal growth retardation; forecasting; pregnancy; pregnancy-associated plasma protein-a; pregnancy trimester, first; ultrasonography.

Apstrakt

Uvod/Cilj. Danas se smanjena porođajna masa ploda smatra jednim od glavnih uzročnika nastanka kardiovaskularnih oboljenja ili metaboličkog sindroma koji nastupaju kasnije tokom života. Mnoge studije su pokazale jak uticaj abnormalne porođajne mase ploda na kasniji razvoj, međutim, zbog jačeg uticaja na razvoj jedinke, poseban akcenat se stavlja na smanjenu porođajnu masu u odnosu da povišenu. Još uvek ne postoji test koji bi sa visokoprocentnom tačnošću jasno klasifikovao trudnice sa visokim rizikom od rađanja deteta s manjom ili većom porođajnom masom s obzirom na gestacijsko doba. Cilj ovog rada je bio postavljanje modela koji bi mogao upućivati na buduću smanjenu ili prekomernu masu novorođenčeta. **Metode.** Studijom je bila obuhvaćena 191 trudnica, koje su na osnovu telesne mase novorođenčeta, bile podeljene u tri grupe: grupa 1 (> 3 000 g), grupa 2 (3 000–4 000 g), grupa 3 (> 4000 g). Za svaku grupu su određene i međusobno upoređene vrednosti biohemijskih markera (plazma proteina A povezanog sa trudnoćom – PAPP-A i slobodne β jedinice humanog horionskog gonadotropina) i ultrasonografskih markera (nuhalna translucencija), kao i njihovih multiplih medijana (MoM). **Rezultati.** Nađeno je da su vrednosti PAPP-A MoM bile znatno niže u grupama trudnica koje su imale plod sa

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malom telesnom masom ($p = 0,003$, $p = 0,011$). Među ispitivanim grupama je dokazana pozitivna, statistički značajna korelacija između PAPP-A MoM i mase novorođenčeta ($r_s = 0,221$, $p = 0,001$). **Zaključak.** Korišćenjem kombinacije biohemijskih parametara, sonografskih i demografskih podataka u *screening* programu uvećava se šansa za ranu identifikaciju fetusa koji su pod povišenim rizikom od restrikcije u rastu ili povećanog rasta. Takođe, sa porastom vrednosti PAPP-A MoM raste i telesna masa fetusa.

Ključne reči:
horionski gonadotropin, beta subjedinica; dijagnoza; fetus, zaostajanje u rastu; predviđanje; trudnoća; plazma, protein a, udružen sa trudnoćom; trudnoća, prvi trimestar; ultrasonografija.

Introduction

There are just few chapters in humane medicine that largely exceed the ambitions of a discipline that studies them. One of such examples is the entity of children born small or big for the gestational age. Although at first glance it may be regarded as a typical pediatric topic, these issues deserve greater interest of endocrinologists, biochemists, gynecologists.

Even though the impact of adverse factors from the external environment is undisputable, there are disorders that have the roots in the period of fetal growth. Hence, many pathological conditions or diseases during the phase of growing up or during middle age are actually the consequence of a disturbed fetal growth. We may say, fetal growth is a result of many factors, including genetics, nutrition, mother's metabolism, endocrinological factors, the goodness of placental function and perfusion, but also the ability of the fetus itself to respond to all the factors that influence it [1]. Nowadays, low birth weight is considered one of the main causes of cardiovascular diseases or metabolic syndrome that occur later in life. Low birth weight is an important determinant of child's health and a major risk factor for several noncommunicable diseases later in life including coronary heart disease, stroke, hypertension and type 2 diabetes [2].

Low levels of plasmatic pregnancy-associated plasma protein-A (PAPP-A) and high levels of free-beta human chorionic gonadotropin (fβ-hCG) could influence the outcome of pregnancy [3]. Abdel Moety et al. [4] study suggests that first-trimester uterine artery impedance, as measured by Doppler ultrasound as well as low serum biomarkers (β-hCG and PAPP-A) can be used for prediction of preeclampsia and birth weight. Until today, may researchers have tried to find an ideal combination of parameters which would be good indicators of birth weight, however, there is still no test that has high percentage of accuracy to clearly classify expectant women under high risk of giving birth to a child who is too small or too big for the gestational age. Law et al. [5] explain that the limitation of these studies is the usage of exclusively one marker in prediction, wrong combination of markers, or usage of a wrong parameter in wrong time. This paper examines the predictive ability of two biochemical markers (PAPP-A, fβ-hCG) in combination with ultrasonographic marker "nuchal translucency" (NT) measured at first trimester. Biochemical parameters may be good indicators of placental, fetal, but also motherly condition, hence biochemical screening may be used as an additional tool in diagnosing many complications in pregnancy such as: gestational diabetes, pregnancy-induced hypertension, intrauterine fetal suffering, etc. [6].

Low birth weight is a much serious issue compared to high birth weight. Existing scientific literature shows a strong correlation between low birth weight and neonatal mortality, which is why this issue is given a lot of significance within public health [7].

It was believed for many years that the fetus is a passive user of "uteroplacental capacities". Nowadays, fetal growth is explained as much more complex phenomenon, being a consequence of an active interaction among a mother, placenta and fetus in the process of providing nutrients. Termination or damage caused to any of these components damages the growth potentials. A mechanism of cell proliferation, hyperthrophy and differentiation is coordinated by peptide growth factors, but also by other intercellular intermediaries that act in paracrine and autocrine manner.

Many studies have shown that children born small for gestation age (SGA) face higher risk to later develop insulin resistance, obesity, arterial hypertension, dyslipidemia, metabolic disorders of carbohydrates i.e. all components of metabolic syndrome [8]. Epidemiological studies have proven the connection between adverse intrauterine effects and later risks of facing chronic diseases.

The aim of this study was to establish a model, based on first trimester marker, that could indicate future low or high birth weight.

Methods

Examinees, Ethics statement and clinical information

This study comprises 191 expectant women who had their regular checks in the Center for Women's Reproductive Health of the Primary Health Care Center in Podgorica, Montenegro. The study protocol was reviewed and approved by the Ethics Commission. All expectant women agreed to using the data for the purpose of scientific work. Combined screening for trisomy 21, 18 and 13 has been performed in the laboratory of the Clinical Center of Montenegro in Podgorica, between 10 and 13 weeks gestation.

Based on the birth weight, the examinees were divided into three groups (group 1: < 3,000 g; group 2: 3,000–4,000 g; group 3: > 4,000 g), so the parameters were analyzed and compared by the groups.

Study protocol and measurements

The screening implied the determination of the value of β-hCG and PAPP-A by using a commercial immunofluorescent test (AutoDELFIA), while the results have been expressed in mmol. An ultrasound for a routine ultrasound check of the examinees has been used to determine the dimension of NT (SIMENS, SC2000 ultrasound system).

All measurements of examined biochemical parameters were performed on a device Beckman Coulter Access2, Florida, USA.

Within the risk assessment performed by Double test, the results are expressed as multiple of median (MoM) for a given gestation week. MoM is a statistical measure showing to which extent the result differs from its median in population, and is calculated through a formula given below [9].

$$\text{MoM (patient)} = \frac{\text{Result (patient)}}{\text{Median (population)}}$$

A low PAPP-A is defined as a maternal serum PAPP-A value < 0.4 MoM, with increased frequency of adverse obstetrical outcomes noted below this level [10].

Pearson correlation coefficient was used to determine the correlation between biochemical parameters and future fetal weight.

In cases where a statistically significant difference was found between the methods, receiving operating characteristic (ROC) curves were made to determine the predictor potential of the parameters, while the values are plotted as curve with the corresponding *p* value.

Results

Table 1 shows mean values and SD, as well as minimum and maximum values in terms of examined variables for three examined groups.

Mean value of biochemical parameter PAPP-A in the group having the birth weight lower than 3,000 g was 1.00 (± 0.71), in the group having the birth weight from 3,000 g to 4,000 g was 1.25 (± 0.71), while in the group having the birth weight above 4,000 g was 1.36 (± 0.99) and that difference was statistically significant ($p = 0.003$) (Figure 1).

Table 1

Descriptive statistical indicators of multiple of median biochemical and ultrasonographic parameters of the examinees in the groups

Parameters	Group 1 (n = 77) < 3,000 g		Group 2 (n = 90) 3,000 g–4,000 g		Group 3 (n = 24) > 4,000 g	
	mean ± SD	median	mean ± SD	median	mean ± SD	median
Biochemical						
PAPP-A MoM	1.00 ± 0.71	0.86 (0.13–4.86)	1.25 ± 0.71	1.11 (0.31–4.56)	1.36 ± 0.99	1.08 (0.31–4.56)
fβ-hCG MoM	1.52 ± 9.02	1.17 (0.16–79.60)	1.24 ± 0.62	1.14 (0.22–3.69)	1.23 ± 0.55	1.11 (0.38–2.27)
Ultrasonographic						
NT MoM	0.99 ± 0.30	0.93 (0.45–1.69)	1.03 ± 0.28	1.03 (0.43–1.79)	1.11 ± 0.27	1.10 (0.61–1.69)

PAPP-A – pregnancy-associated plasma protein-A; MOM – multiple of median; fβ-hCG – free-beta human chorionic gonadotropin; NT – nuchal translucency; SD – standard deviaton.
Description of the groups is given in the paragraph Methods.

The hCG was considered raised if levels were more than 2MoM [11].

Statistical data processing

SPSS statistical program Windows 10 version was used for data processing, working under Microsoft Windows environment. A diagram in the form of curves and dendrograms has been done within Origin statistical program.

A hypothesis on the normality of results distribution has been firstly checked, and depending on that, parameter and nonparameter technics applied. Mann-Whitney *U* test and Kruskal Wallis H test (non-parameter test) were applied for parameters for which the hypothesis on the normality of results distribution does not apply. For those parameters to which the hypothesis on the normality of results distribution applies, *t*-test was applied to independent samples of one-factor analysis of the variance (parameter techniques).

Descriptive statistic measures were used for the description of significant parameters: frequency (n), percentage (%), mean value, standard deviation (SD), median and scope.

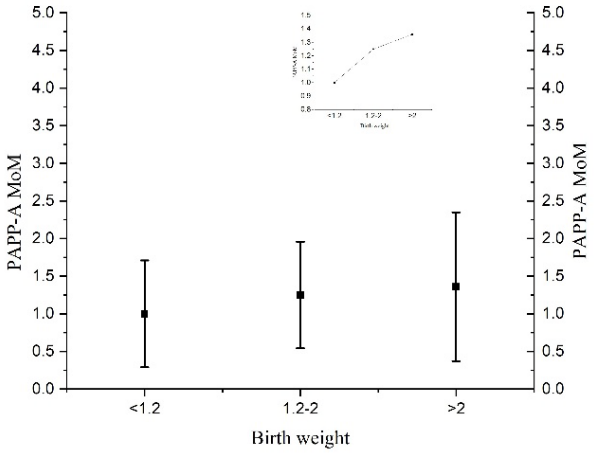


Fig. 1 – An overview of arithmetic mean and a standard deviation, as well as growth trend in terms of parameters PAPP-A MoM for three examined groups of expectant women.
For abbreviations see under Table 1.

In the group of examinees with newborn's birth weight lower than 3,000 g average value of PAPP-A MoM was 1.00, which is statistically considerably lower as compared to the values reached in the group where newborn's weight ranged between 3,000 g to 4,000 g ($p = 0.001$) and in the group higher than 4,000 g ($p = 0.025$), while PAPP-A MoM value did not statistically differ between the groups having the weight 3,000 g–4,000 g and > 4,000 g (Table 2).

Mean value of the biochemical parameter fβ-hCG MoM, in the group where the birth weight was lower than 3,000 g was 1.52 (± 9.02), in the group where birth weight ranged from 3,000 g to 4,000 g was 1.24 (± 0.62), while in the group where the birth weight was over 4,000 g was 1.23 (± 0.55). Statistically significant difference in terms of examined parameter among the three groups was not proven ($p = 0.830$) (Figure 2).

Mean value of the ultrasonographic parameter NT MoM in the group where the birth weight was lower than 3,000 g was 0.99 (± 0.30), in the group where the birth weight ranged from 3,000 g to 4,000 g was 1.03 (± 0.28), while in the group where the birth weight was over 4,000 g was 1.11 (± 0.27). Statistically significant difference in terms of examined parameter among the three examined groups was not proven ($p = 0.173$) (Figure 3).

Values of multiple of median PAPP-A lower than 1.2 in the group 1 were found with 61 examinees, interval MoM 1.2–2 was found with 9 examinees, while the values of MoM higher than 2 were found with 7 expectant women from the group 1.

Values of multiple of median PAPP -A lower than 1.2 in the group 2 were found with 62 examinees, interval MoM 1.2–2 was found with 40 examinees, while the values of MoM higher than 2 were found with 12 expectant women altogether from the group 2.

Values of MoM PAPP -A lower than 1.2 in the group 3 were found with 13 examinees, interval MoM 1.2–2 was found with 8 examinees, while the values of multiple of median higher than 2 were found with 3 expectant women altogether from the group 3.

Statistically significant difference was found in the percentage of the examinees of the group 1 for the interval of MoM lower than 1.2 as compared to the group 2 and the group 3. Intervals of MoM 1.2–2 and > 2 were statistically significantly less present in the group 1 as compared to the groups 2 or 3 ($\chi^2 = 15.03$, $p = 0.005$) (Figure 4).

In the group 1, 39 examinees had the values of fβ-hCG MoM lower than 1.2, 22 examinees had the value of this parameter in the interval from 1.2 to 2, while 16 examinees had the values of fβ-hCG MoM higher than 2.

In the group 2, 63 examinees had the values of fβ-hCG MoM lower than 1.2, 40 examinees had the value of this parameter in interval from 1.2 to 2, while 11 examinees had the values of fβ-hCG MoM higher than 2.

In the group 3, 14 examinees had the values of fβ-hCG

Table 2

Results of testing the difference in values of PAPP-A MoM among three examined groups

Comparison	Mann Whitney *U* test	*p*-value
Group 1/Group 2	3,159.00	0.001
Group 1/Group 3	643.50	0.025
Group 2/Group 3	1,358	0.957

Group 1: < 3,000 g; Group 2: 3,000 g–4,000 g; Group 3: > 4,000 g.
For abbreviations see under Table 1.
Description of the groups is given in the paragraph Methods.

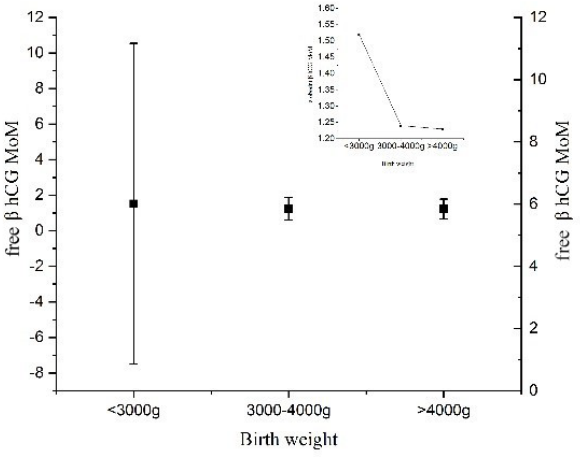


Fig. 2 – An overview of arithmetic mean and a standard deviation as well as a downward trend in terms of parameters fβ-hCG MoM for three examined groups of expectant women.
For abbreviations see under Table 1.

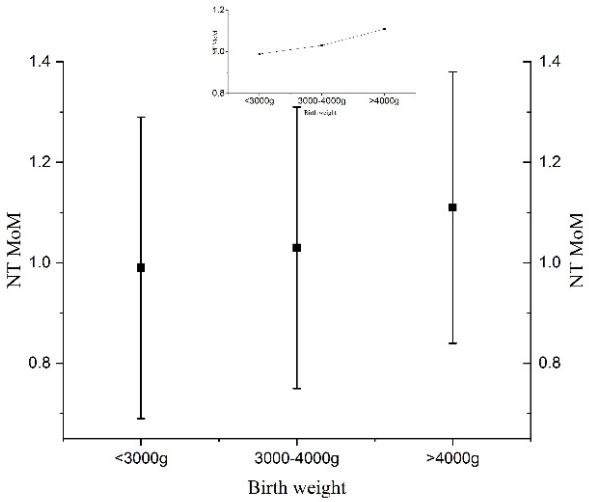
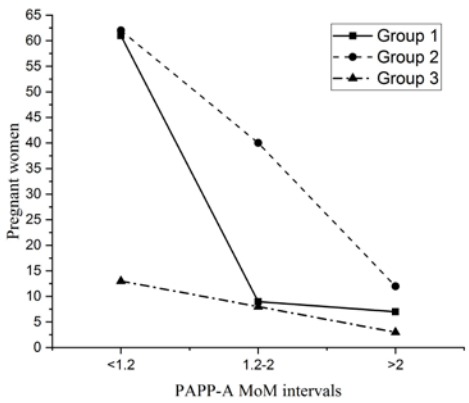
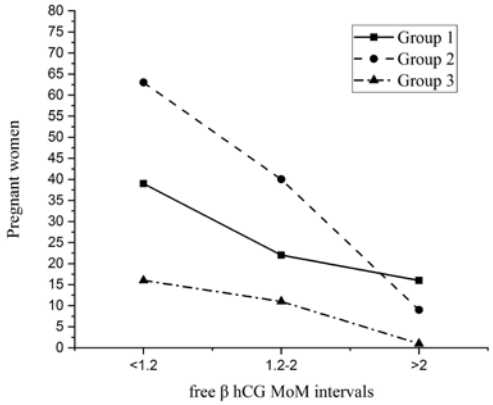


Fig. 3 – An overview of arithmetic mean and a standard deviation as well as the growth trend in terms of NT MoM parameters for three examined groups of expectant women.
For abbreviations see under Table 1.



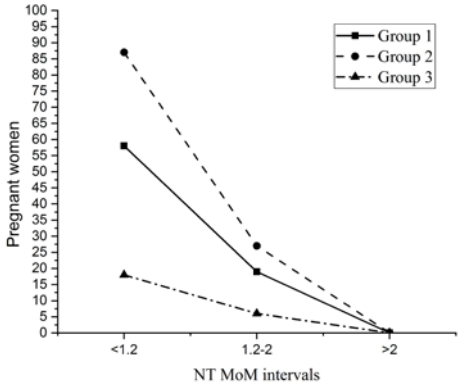
Group1: < 3,000 g; Group 2: 3,000 g–4,000 g; Group 3: > 4,000 g.

Fig. 4 – An overview of the number of examinees with different intervals of MoM PAPP-A in examined groups.
For abbreviations see under Table 1.
Description of the groups is given in the paragraph Methods.



Group1: < 3,000 g; Group 2: 3,000 g–4,000 g; Group 3: > 4,000 g.

Fig. 5 – An overview of the number of examinees with different intervals MoM of fβ-hCG in examined groups.
For abbreviations see under Table 1.
Description of the groups is given in the paragraph Methods.



Group 1: < 3,000 g; Group 2: 3,000 g–4,000 g; Group 3: > 4,000 g.

Fig. 6 – An overview of the number of examinees with different intervals of MoM NT in examined groups.
For abbreviations see under Table 1.
Description of the groups is given in the paragraph Methods.

MoM lower than 1.2, 9 examinees had the value of this parameter in interval from 1.2 to 2, while only 1 examinee had the values of fβ-hCG MoM higher than 2 (Figure 5).

The frequency of the value of fβ-hCG MoM according to different intervals of MoM (< 1.2, 1.2–2, > 2) did not statistically significantly differ as compared to three examined groups of examinees ($\chi^2 = 7.03$, $p = 0.134$).

In the group 1, the values of MoM NT lower than 1.2 were found with 58 examinees, values of MoM in the interval 1.2–2 were found with 19 examinees. None of the examinees in the group 1 had the value of MoM NT higher than 2.

In the group 2, the values of MoM NT lower than 1.2 were found with 87 examinees, values of MoM in the interval 1.2–2 were found with 27 examinees. None of the examinees in the group 2 had the value of MoM NT higher than 2.

In the group 3, the values of MoM NT lower than 1.2 were found with 18 examinees, values of MoM in the interval 1.2–2 were found with 6 examinees. None of the examinees in the group 3 had the value of MoM NT higher than 2.

The frequency of the value of NT MoM according to different intervals of MoM (< 1.2, 1.2–2, > 2) did not statistically significantly differ as compared to three examined groups of patients ($\chi^2 = 0.034$, $p = 0.983$) (Figure 6).

Correlation of NT MoM with PAPP-A MoM or fβ-hCG MoM ($p = > 0.05$) was not proven. What was proven is a weak, positive, statistically significant correlation between PAPP-A MoM and fβ-hCG MoM ($r_s = 0.207$, $p = 0.002$). Therefore, the increase of value in PAPP-A MoM triggers the increase of the value of fβ-hCG MoM.

A correlation of ultrasonographic parameter NT MoM and a biochemical parameter fβ-hCG MoM with birth weight

was not proven, however what was proven is a positive, statistically significant correlation between PAPP-A MoM and newborn's weight ($r_s = 0.221$, $p = 0.001$). The increase in the value of PAPP-A MoM triggers the increase of the fetal body weight (Table 3).

We used the ROC to examine diagnostic validity of the models NT MoM, PAPP-A MoM, fβ-hCG MoM in prediction of birth weight. Only one variable (PAPP-A MoM) gave a unique statistical contribution to the model (Figure 7).

tervals of MoM showed that the first group of examinees had considerably higher percentage of examinees whose values of PAPP-A MoM were lower than 1.2. ($p = 0.005$). Our results comply with the findings by previous studies [12–14].

Some authors also describe a significant positive correlation between concentration of PAPP-A in the first trimester and relative newborn's body weight, and between the concentration of PAPP-A in later pregnancy and newborn's body weight [14, 15]. Our results confirm these assertions

Table 3

Proven correlations between examined parameters, their correlation with birth weight and demographic characteristics

	NT MoM	PAPP-A MoM	fβ-hCG MoM	Birth weight
NT MoM	1.000			
correlation coefficient				
p-value				
PAPP-A MoM		1.000		
correlation coefficient	-0.008			
p-value	0.905			
fβ-hCG MoM			1.000	
correlation coefficient	-0.046	0.207		
p-value	0.499	0.002		
Birth weight				1.000
correlation coefficient	0.123	0.221	-0.033	
p-value	0.071	0.001	0.632	

For abbreviations see under Table 1.

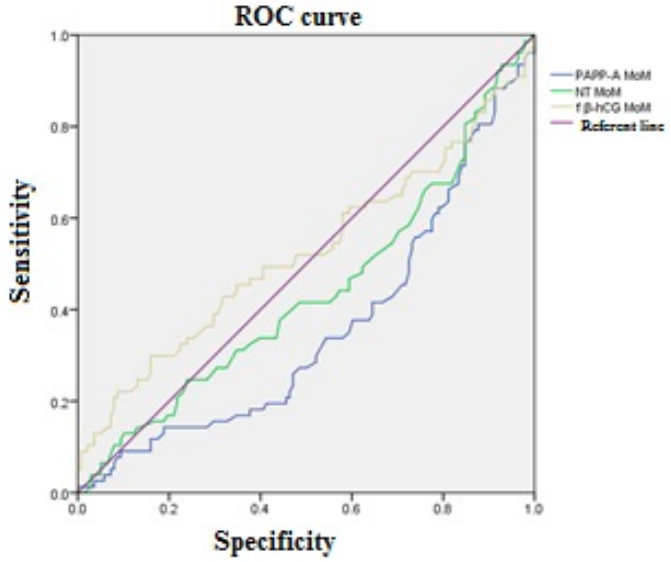


Fig. 7 – Receiver operating characteristic (ROC) curve for inflection points of PAPP-A MoM, fβ-hCG MoM and NT MoM in determining birth weight with 95% confidence interval [Area under ROC curve for PAPP-A MoM: 0.358 ($p = 0.001$); Area under ROC curve for fβ-hCG MoM: 0.044 ($p = 0.557$); Area under ROC curve for NT MoM: 0.042 ($p = 0.138$)].
For abbreviations see under Table 1.

Discussion

By analyzing the values of biochemical parameters among examined groups, this study was found that the values of PAPP-A MoM had been considerably lower in groups of expectant women whose fetus had small body weight ($p = 0.003$, $p = 0.011$). Additionally, comparison of the in-

($p = 0.001$). Low concentrations of PAPP-A in the first trimester envisage weak growth of the fetus, however this may indicate the birth of smaller, but completely healthy baby. On the other hand, we may say that smaller placenta is responsible for low fetal growth, therefore, there can exist a subgroup of normal pregnancies where the size and capacity of the placenta cause the fetal growth restriction [5].

There are opposing opinions related to predictive value of PAPP-A for the occurrence of macrosomia. While some cannot find statistically significant differences in the values of PAPP-A between the expectant women having physiological pregnancy and those with macrocosmic fetus, others talk about correlation between PAPP-A and macrosomia [10, 16]. They explain the correlation with large amount of insulin-like growth factor due to increased values of PAPP-A which stimulates intrauterine growth. We did not proven statistically significant difference in the values of PAPP-A among the examinees, however the analysis of the data clearly indicates the difference among the groups (G1 = 2.36, G4 = 2.65) which adheres to the results found in 2011 by Tarim et al. [17].

Another study's findings demonstrated that in pregnancies resulting in the birth of small for gestational age (SGA) infants, the maternal serum PAPP-A levels at 11+0 to 13+6 weeks of gestation decrease, and in normal pregnancies, there was a significant association between the serum levels of this metabolite and birth weight, which may be predetermined [18]. Our study's results are consistent with the hypothesis that impaired placentation plays a role in the pathogenesis of SGA.

The connection between low PAPP-A values in the first trimester of pregnancy and slow fetal growth, followed by low birth weight later on lies in specific function of pregnancy associated plasma protein A as IGFBP-4 protease. IGFBP-4 is a powerful inhibitor of insulin like growth factor (IGF). IGF plays a significant role in the invasion of trophoblast, influencing early development and vascularization of placenta. Under the influence of PAPP-A, IGF binding protein (IGFBP) cleaves, thus releasing IGF into circulation. In this way, high concentrations of PAPP-A lead to better development of the fetus [19].

Many studies have shown a strong correlation of fβ-hCG and birth weight. A study carried out by Barjaktarović et al. [2] indicates the existence of the connection between low values of free β-hCG in later stages of the first trimester of pregnancy and higher risk of SGA. A huge study carried out in the Netherlands on a sample of 8,195 expectant women showed a correlation between a fβ-hCG and uterine and fetal functions such as umbilical cord development, suppression of myometrial contractions, the promotion of growth and differentiation of fetal organs but also angiogenesis and regulation of immune tolerance. These findings underline the importance of hCG throughout gestational physiology and suggest that variations in hCG levels may be associated with adverse clinical outcomes such as fetal loss, preeclampsia, preterm delivery and fetal growth restriction and newborn's birth weight [20]. However, there are studies that prove not such a strong connection between the said parameter and birth weight. The correlation does exist, however, it is considerably lower from those between the PAPP-A and the birth weight [21]. Our research did not prove this connection ($p \geq 0.05$) and the results gained comply with Güducü et al. [22].

Information that low values of fβ-hCG may trigger low birth weight indicate that the birth weight is dependant on the development of placenta during the first and second trimester pregnancy. Free β-hCG is a hormone produced in placenta immediately after implantation, hence low values may indicate a slow or pathological placentation [23].

The results of this study are comparable with the results of the studies that show that the values of fβ-hCG in the serum of an expectant woman measured in the first trimester are almost equal between experimental and control group [24, 25]. By analyzing the data given in our research, we may notice an upward trend of this parameter with the increase of the body weight of the fetus, which may indicate that actually higher values of fβ-hCG may be predictors of low body weight at birth (body weight < 2,500 g = 78.84; body weight > 4,000 g = 69.41). Early vascular damage of the placenta also show decreased oxygenation, which leads to hyperplasia syncytiatrophoblast, and as a consequence of all of this there may occur an increased production of fβ-hCG [26]. Further research is needed to identify hCG receptor(s) and associated intracellular signaling cascades and to increase understanding of its role in achieving conception and in pregnancy-related disorders [27].

In their research, Poon et al. [28] found a considerable increase of fetal nuchal translucence with the increase of fetal weight, as well as that low NT is connected to low fetal body weight. However, our study did not render the same assumption, but we do notice an upward trend of growth of NT with the increase of fetal body weight. The examined groups in this research had little number of expectant women, hence it leaves the room to possibly believe that the conclusions drawn from our research is the result of a low number of samples, hence it requires further and deeper research on bigger study.

Conclusion

By analyzing the values of biochemical parameters among examined groups in this study, a positive, statistically significant correlation between PAPP-A MoM and the newborn's weight ($r_s = 0.221$, $p = 0.001$) has been established. Increase in value of the PAPP-A MoM causes the rise of fetus' body weight. It may be established that using the combination of biochemical parameters, sonographic and demographic data in screening programs increases the opportunity for early identification of fetuses that are exposed to higher risk of future low or high birth weight.

Conflict of interest

None of the authors of this manuscript have a conflict of interest.

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