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Low Pregnancy Associated Plasma Protein A as a Predictive Tool for Pregnancy Outcome

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ABSTRACT

Objective: The objective of this study is to identify the predictive value of pregnancy-associated plasma protein A using univariate and multivariate regression analysis in identification of patients with low values (less than 0.4 MoM) in combined first-trimester screening for predicting disadvantaged perinatal outcome after exclusion of aneuploidy.

Methods: A study was conducted at the University clinic for gynecology and obstetrics in Skopje, over a one-year period (2018 y). Those with PAPP-A values (<0.4 MoM) of 64 and a control group of 50 patients with values ≥0.4 MoM. The concentration of PAPP-A was measured from peripheral blood and determined by Immulite 2000 HPi Systems Analyzer.

Results: Univariate and multivariate logistic regression analyses were used to assess the predictive role of PAPP-A. The unadjusted OR for PAPP-A for preterm delivery was 0.225, for antepartum complications was 0.138, for intrauterine growth restriction of 0.049. In the adjusted logistic regression analysis, PAPP-A was not found to be a significant predictor of respiratory distress syndrome, newborn infections, NICU stay and pH≤7.2. The adjusted OR for antepartum complications was 0.131, for intrauterine growth restriction was 0.053.

Conclusion: It can be concluded that PAPP-A levels in the first trimester are associated with intrauterine growth restriction and antepartum complications. The study suggests that caution is needed in pregnancies with PAPP-A values below 0.3 MoM.

Keywords: Perinatal Outcome; PAPP-A; First Trimester; Intrauterine Growth Restriction; Preterm Birth; Predictive

Abbreviations: PAPP –A: Pregnancy Associated Plasma Protein A; MoM: Multiple of Medians; OR: Odds Ratio; NICU: Neonatal Intensive Care Unit; PH: Potential of Hydrogen; LL: Low Level; CI: Confidence Interval

Introduction

Main obstetric entities that determine perinatal outcome are preterm births, small-for-gestational-age infants, hypertensive disorders, diabetes, and stillbirth [1]. The synthesis of specific placental substances are important for: the appropriate formation, maintenance and development of the conceptus in early pregnancy, the normal course of pregnancy and childbirth [2]. PAPP-A is a glycoprotein produced by the placenta and decidua. It has a role in protecting the fetus from recognition by the maternal immune system, mineralization of the extracellular matrix and angiogenesis. Thus, this protein is descriptive of insufficient early placentation resulting in placental-related complications, especially in the third trimester [3]. This is the predominant proteinase for IGFBP- 4 [4]. Intact IGFBP-4 is a potent

inhibitor of IGF in vitro, suggesting that proteolysis acts as a positive regulator of IGF availability. This protease has an important role in the local proliferative response, acting on accelerated cell divisions [5]. PAPP-A is a proven serum marker for aneuploidy in first-trimester screening. It is characterized by low values in the first trimester. There is no available pathophysiological explanation for these low values. Determining the concentration of PARR-A has a limited value in predicting certain complications such as threatened abortion, ectopic pregnancy, preeclampsia and diabetes [6]. Several studies have confirmed the finding that the serum level, in early pregnancy, can predict an unfavorable perinatal outcome and should be appropriately incorporated into recommendations for screening in the first trimester [7,8].

Low value of plasma protein A associated with pregnancy, less than or equal to 0.4 MoM is taken, which is represented in 8% of patients in the first trimester in whom biochemical screening is done, less than or equal to 0.37 MoM in 5 %, less than or equal to 0.3 MoM in 3% and less than or equal to 0.2 MoM in 1% [9]. According to the RCOG (HNS trust) in England, the fifth percentile is 0.415 MoM and the first 0.21 MoM [8]. At the Clinic for Gynecology and Obstetrics in Skopje, 9439 analyzes of the PRISCA (Prenatal risk assessment) 1 type were performed in 2018, of which 377 patients (about 3.99%) had a value lower than 0.4 MoM. The first results from the study included 35 patients with low level of PAPP A in conclusion, there was a significant difference in unfavorable outcome in the cases with PAPP-A under 0.4 MoM, particular in the group, with a PAPP-A value under 0.2 MoM. The patients delivered with SC with the main indications in utero hypoxia, growth restriction and elevated blood pressure had PAPP-A between 0.3-0.4 MoM. The patients with intrauterine fetal death and placental abruption in the most of the cases have PAPP-A value under 0.2 MoM [10]. After coming article from the same authors has shown the difference in frequency of complications, in the cases with PAPP-A under 0.4 MoM, such as premature birth, preeclampsia compound with SGA fetuses versus the control group. The difference for SGA newborn and premature birth among the groups has statistical significance. The patients delivered with cesarean section were with the main indications SGA or elevated blood pressure, often occurred combined with prematurity. The presence of other diseases which could damage placenta should be emphasized [11]. The studies in which the association of low level (LL) PAPP-A and preterm delivery are characterized by different patient numbers and different designs. An association was found with low PAPP-A below the 10th percentile and preterm delivery [12,13], while other cohort studies were not found prediction of LL PAPP-A for preterm labor [14,15]. Regarding the connection with birth weight and fetal growth, there are several studies that mostly prove the connection with LL PAPP-A below 0.4 MoM. A positive predictive value for SGA of 2.97 (95% CI 1.1 to 6.4) was found in a retrospective cohort study [14]. Another study did not demonstrate the role of low PAPP-A in predicting SGA [12].

Materials and Methods

A prospective study was conducted at the Clinic for Gynecology and Obstetrics in Skopje, over a period of one year - 2018. The selection of patients who were screened for aneuploidy in the first trimester from 10+6 to 13+6 gestational weeks. A total of 114 subjects (pregnant women) participated in the study, the control group 50, and the test group 64. The test group (n=64) had a PAPP-A level below 0.40 MoM, and the control group (n=50) greater or equal at 0.40 MoM. The patients in the study group were divided into two subgroups depending on the PAPP-A value: the first subgroup (n=24) below 0.30 MoM and the second subgroup (n=40) from 0.30 to 0.39 MoM. The analyzes were performed in the Biochemical Laboratory of the Clinic. Determination of plasma protein A concentration associated with pregnancy (PAPP-A) Plasma protein concentration associated with pregnancy (PAPP-A) is determined by in vitro diagnostics - Immulite 2000 HP Systems analyzer, Diagnostic Products Corporation, for quantitative measurement of pregnancy-associated plasma protein A (PAPP-A) in serum. It is about solid phase, enzyme-labeled chemiluminescent imunometric assay. Calibration range is up to 10mIU/mL with a low analytical sensitivity of 0.025 mIU/mL. When calculating the MoM, a correction is made depending on racial origin, mother's weight, IVF, smoker, multiple pregnancy, diabetes and obesity. Statistical methods - univariate and multivariate logistic regression analysis with determination of the value of the odds ratio (OR) and 95% Confidence Interval (CI), are used to identify significant predictive factors for unfavorable perinatal outcome; For all analyses, a p value < 0.05 was considered statistically significant.

Unconditional logistic regression analysis with adjustment for covariates. Variables were tested by univariate analysis, and significance was tested by Chi square test for categorical variables and with T test for continuous variables. Potential covariates were tested for inclusion in a multivariate model if p -value for association with any interval predictor, PAPP-A or the composite outcome is below 0.2 univariate analysis. Cut– off for p-value of univariate analysis is used to select variants that could have the potential to be associated with a modified model. OR and 95% Confidence interval (CI), will be estimated from logistic regression analysis.

Conclusion

The results from univariate logistic regression analysis and PAPP-A are in (Table 1). The unadjusted OR for PAPP-A for preterm delivery of 0.225 indicates that with a one unit increase in PAPP-A (MoM), the odds of preterm delivery decrease by 77.5% and for antepartum complications of 0.138 shows that with a one unit increase in PAPP-A (MoM), the chances of complications before delivery are reduced by 86.2%. The unadjusted OR for PAPP-A for SGA of 0.049 indicates that by one unit increase in PAPP-A (MoM), will reduced SGA by 85.1%. PAPP-A values in unadjusted logistic regression analysis showed no significant association with RDS, newborn infections,

stay in NICU and pH of neonatal umbilical artery for ≤7.2. Multivariate logistic regression analysis and the PAPP-A shows the results of the multivariate logistic regression, for determining the predictive role of PAPP-A for the three adverse outcomes (premature delivery, complications before delivery and SGA), in which it was performed adjusting for maternal age, body mass index and smoking state. In this adjusted analysis, PAPP-A was not confirmed as a significant predictor for premature birth.

Table 1: PAPP-A results from Univariate Logistic Regression Analysis.

Outcome	Odds Ratio	95% Confidence Interval OR	p = level
Premature delivery	0.225	0.044 – 0.294	0.042 sig
Complications before delivery	0.138	0.027 – 0.714	0.018 sig
SGA	0.049	0.043 – 0.891	0.042 sig
RDSy	0.215	0.030 – 1.540	0.126
Infections of the newborn	0.813	0.233 – 2.831	0.744
NICU	0.365	0.05 – 2.647	0.319
ph≤7.2	0.63	0.194 – 2.045	0.442

Table 2: Results from Multivariate Logistic Regression Analysis for PAPP A.

	Odds Ratio	95% Confidence Interval OR	p = level
Premature Delivery			
PAPP-A	0.205	0.037 – 1.136	0.070
Patient's age	1.065	0.968 – 1.172	0.195
BMI	0.967	0.886 – 1.056	0.461
Smoking ref (non-smoker)			
Smoker	1.581	0.531 – 4.707	0.411
Complications Before Delivery			
PAPP-A	0.131	0.024 – 0.709	0.018 sig
Patient's age	1.024	0.938 – 1.119	0.593
BMI	0.949	0.872 – 1.032	0.220
Smoking ref (non-smoker)			
Smoker	1.460	0.521 – 4.090	0.471
Small For Gestational Age			
PAPP-A	0.053	0.003 – 0.923	0.044 sig
Patient's age	0.979	0.868 – 1.105	0.735
BMI	0.810	0.701 – 0.936	0004 sig
Smoking ref (non-smoker)			
Smoker	2...292	0.625 – 8.402	0.211

The results showed a significantly lower chance of complications before labor and birth of an SGA fetus, with an increase in the value of PAPP-A. (Table 2) In this combination of factors and BMI was significantly associated with the birth of an SGA fetus, with an increase of its value by one unit, the chances of SGA decrease by 19%. From the above statistical analysis, it can be concluded that PAPP A below 0.4 MoM could be used as a additional predictive tool for SGA and expectance of above mention complication before delivery.

Assuming these results and results from the literature, it could be contributed for decrease perinatal morbidity and mortality.

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Conflict of Interest

I do not have any economic interest or any conflict of interest.

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