Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2022.48861

Turk J Obstet Gynecol 2022;19:287-94

The relationship between the first trimester maternal serum PAPP-A and β-hCG values and newborn intensive care needs in low-risk pregnancies

Düşük riskli gebeliklerde birinci trimester maternal serum PAPP-A ve serbest β-hCG değerleri ile yenidoğan yoğun bakım ihtiyacı arasındaki ilişki

Burak Elmas, Bergen Laleli Koç, Duygu Tuğrul Ersak, Uğurcan Zorlu, Ece Aydoğdu, Gamze Yılmaz, Eda Üreyen Özdemir, Necati Hançerlioğulları, Özlem Moraloğlu Tekin

University of Health Sciences Turkey, Ankara City Hospital, Clinic of Gynecology and Obstetrics, Ankara, Turkey

Abstract

Objective: The purpose of the study was to look at the connection between newborn intensive care requirements in low-risk pregnancies and maternal blood pregnancy-associated plasma protein (PAPP-A) and free human chorionic gonadotropin (hCG) levels, which are elements of screening tests within the first trimester.

Materials and Methods: In the delivery unit of our hospital, pregnant women between the years of 18 and 35 had singleton pregnancies who delivered between 37 and 41 weeks of pregnancy between July 2021 and January 2022 were split into 2 groups. One hundred eighty two pregnant women with infants who required neonatal intensive care (NICU) were enrolled in the first group, whereas 890 pregnant women with infants who did not require NICU were enrolled in the second. These two groups' maternal blood PAPP-A and free hCG levels, which are among the first trimester screening procedures, were examined. Additionally, subgroup analysis were performed in terms of cesarean section indications and NICU admission indications. Logistic regression analysis and ROC analysis were performed with related variables for estimating NICU need.

Results: The mean serum PAPP-A value was found to be 0.91±0.34 multiples of the median (MoM) in the blood taken from the infant mothers who needed NICU, while the mean serum PAPP-A value in the blood taken from infant mothers who did not need NICU was 1.12±0.59 MoM (p<0.000). The PAPP-A MoM mean of the group with Apgar 5th minute score ≥8 (1.09±0.57) was higher than the PAPP-A mean (0.84±0.27) of the Apgar 5th minute score <7 group (p=0.013). According to the results of our study, in groups with a PAPP-A value below 0.95, the possibility of increased NICU need of newborns is higher.

Conclusion: The low serum PAPP-A level, which is used as a screening test among pregnant women, demonstrates that it is successful in predicting perinatal outcomes in the low-risk pregnancy group.

Keywords: PAPP-A, neonatal outcome, free hCG, low-risk pregnancy, neonatal intensive care

Öz

Amaç: Çalışmanın amacı düşük riskli gebeliklerde ilk trimesterde tarama testleri bileşenlerinden maternal serum gebelikle ilişkili plazma proteini (PAPP-A) ve serbest insan koryonik gonadotropin (hCG) seviyeleri ile bebeklerin yenidoğan yoğun bakım (YDYB) ihtiyacı ilişkisinin araştırılmasıdır.

Gereç ve Yöntemler: Temmuz 2021-Ocak 2022 tarihleri arasında arasında hastanemiz doğum ünitesinde 37.-41. gebelik haftası arasında doğum yapmış olan 18-35 yaşları arasındaki tekil gebeliği olan ve YDYB ihtiyacı olan 182 bebeğe sahip olan gebeler ile YDYB ihtiyacı olmayan 890 bebeğe sahip olan gebelerin ilk trimester tarama testlerinden maternal serum PAPP-A ve serbest hCG değerleri karşılaştırılmıştır. Ayrıca sezaryen endikasyonları ve YDYB kabul endikasyonları bakımından da subgrup analizler yapılmıştır. YDYB ihtiyacının tahmini için ilişkili bulunan değişkenlerle lojistik regresyon analizi ve ROC analizi yapılmıştır.

PRECIS: In this study, the relationship between first trimester maternal serum PAPP-A and free β-hCG levels and postpartum neonatal intensive care needs in low-risk pregnancies was investigated.

Address for Correspondence/Yazışma Adresi: Burak Elmas, MD,
University of Health Sciences Turkey, Ankara City Hospital, Clinic of Gynecology and Obstetrics, Ankara, Turkey
Phone: +90 537 236 73 65 **E-mail:** burak_elmas88@hotmail.com **ORCID ID:** orcid.org/0000-0001-7977-4364
Received/Geliş Tarihi: 22.07.2022 **Accepted/Kabul Tarihi:** 11.09.2022

Bulgular: YDYB ihtiyacı olan bebeklerin ortalama PAPP-A değeri 0,91±0,34 medyanın katları (MoM) iken, YDYB ihtiyacı olmayan bebeklerin ortalama PAPP-A değeri 1,12±0,59 MoM olarak bulunmuştur (p<0,000). Apgar 5. dk skoru ≥8 grubunun PAPP-A MoM ortalaması (1,09±0,57), Apgar 5. dk skoru <7 grubunun PAPP-A ortalamasından (0,84±0,27) daha yüksektir (p=0,013). Çalışmamız sonuçlarına göre PAPP-A değeri 0,95 MoM altında olanların YDYB ihtiyacı olması ihtimali daha yüksektir.

Sonuç: Düşük riskli gebelik grubunda, PAPP-A düzeyinin düşük olması tarama testi olarak kullanılan bu parametrenin aynı zamanda perinatal sonuçları ön görmede etkin olduğunu göstermektedir.

Anahtar Kelimeler: PAPP-A, neonatal sonuçlar, serbest hCG, düşük riskli gebelik, yenidoğan yoğun bakım

Introduction

Serum concentrations of free human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein (PAPP-A) are used as indicators of chromosomal defects within the context of the first trimester screening test. However, maternal and pregnancy-related characteristics, such as maternal age, ethnicity, smoking habits, weight, and conception procedures, impact these tests. Multiples of the median (MoM) are calculated using each of these variables[1]. Recent studies have also discovered a link between poor obstetric outcomes and maternal serum-free hCG and PAPP-A levels used in chromosomal abnormality screening in the first trimester[1]. Placental dysfunction may be indicated by a low PAPP-A result. PAPP-A and free hCG levels are produced in the placenta shortly after implantation, and low levels may signify improper placentation, which explains why these hormones are associated with poor obstetric outcomes. Low PAPP-A levels have been linked to diseases including preeclampsia, stillbirth, preterm delivery, and fetal growth retardation in much more extensive investigations on PAPP-A from these two markers. However, there is ongoing debate over the findings of research using free-hCG[2-4]. Infants delivered in births with poor obstetric outcomes are becoming more in need of neonatal intensive care. As part of the first trimester screening tests, the levels of free hCG and PAPP-A were examined in this study to determine their association with low-risk pregnancy's requirement for neonatal intensive care.

Materials and Methods

The patient data were accessed using the automation system after receiving the hospital's ethical authorization. The study comprised singleton pregnant women between the ages of 18 and 35 who gave birth in our hospital's maternity ward in the 37th and 41st week of gestation between July 2021 and January 2022. Patients with placental pathologies such as ablation placenta, placenta previa, and vasa previa, pregnant women with an anomaly in their infants, and pregnant women with high-risk circumstances such as gestational diabetes mellitus, preeclampsia, multiple pregnancies, diabetes mellitus, hypertension, polyhydramnios, and oligohydramnios were excluded from the study. The study also eliminated patients whose complete follow-ups were not conducted at our institution. Body mass index (BMI), smoking status, age, method of birth, gravida, parity, and the weight, gender, Apgar score, and requirement for neonatal intensive care of the newborns were all collected from patient data. The MoMs of PAPP-A and free hCG values in the results of first-trimester screening test performed during the antenatal follow-up of infants in need of neonatal intensive care and healthy infants who did not were compared. In our clinic, during the 11th and 14th weeks of pregnancy, within the scope of the first trimester screening test, PAPP-A and hCG tests from blood samples taken from the antecubital vein were studied in our hospital laboratory (Siemens Immulte 2000 XPi) without waiting. In the first trimester screening test, crown-rump length measurement and nuchal translucency were added to serum markers as ultrasonographic measurements. The results of the tests were recorded in both ng/dL and MoM. The MoM value was determined using the prenatal risk calculation program (PRISCA software) used in the laboratory of our hospital by questioning the gestational age, maternal age and weight, smoking status, consanguineous marriage status and conception methods.

Information about the follow-up of newborns was obtained retrospectively from the data system of our hospital. Apgar scores, heights, weights, whether resuscitation done, whether there is a need for neonatal intensive care, and the postnatal laboratory parameters and daily clinical course of the infants of mothers who gave birth in our hospital are recorded on the infant screening system, which is used by pediatricians and obstetricians. All newborns were evaluated postnatally by specialist pediatrics and neonatal physicians. Information about infants in need of neonatal intensive care (NICU), vital follow-ups, indications for intensive care hospitalization and laboratory data, imaging results and physical examination findings are recorded by the specialists by filling in the NICU admission and discharge form. These forms are completed for all newborns admitted to the NICU post-birth, and the database contains all the information to including all medical conditions throughout admission, hospitalization, and repatriation. The international classification of diseases is also used to code all treatments and diagnoses (ICD-10). The admission to the NICU (NICU levels 2 and 3) within the first four weeks after delivery was referred to as a neonatal admission. The following conditions must be met for NICU admission in this study: Cardiorespiratory monitoring of neonates with transient problems, the requirement for intravenous fluid therapy, external intravenous fluid therapy, and closer monitoring of jaundiced infants, respiratory distress syndrome and neonatal septicemia, and continuous supported ventilation. One of the most frequent causes for an infant being admitted to the neonatal critical care unit is respiratory distress. One or more indicators of increased labor of breathing, such as tachypnea, cyanosis, chest retractions, stridor, nasal flaring,

stertor, or grunting, are characterized as respiratory distress in newborns. The ICD-10 code for infant distress was P22.0.

Based on measurements of the quantity of unconjugated bilirubin in the serum and the regional treatment recommendations, neonatal jaundice was characterized as a requirement for phototherapy. In the ICD-10, neonatal jaundice is coded as P59.9. A blood glucose level with less than 2.5 mmol/L, combined tube feeding, or management of hypoglycemia with parenteral glucose infusion was considered as indicators of neonatal hypoglycemia. The ICD-10 code for neonatal hypoglycemia is P70.3, P70.4, P70.8, or P70.9. Neonatal infection was categorized under the ICD-10 subheadings P36 and P39.9 and was described as a combination of clinical symptoms or cultural confirmation of infection requiring systemic antibiotic therapy. The presence of at least three of the following symptoms -inadequate body temperature, tachypnea (>70/min), eating reluctance, abdominal distention, lethargy, hepatosplenomegaly, tachycardia (HR >190 bpm), dyspnea, and bradycardia (HR 90 bpm)- was required for the diagnosis of sepsis. Asphyxia was measured using a low Apgar score, which was classified as less than 7 after 5 min. In the ICD-10, neonatal asphyxia is coded as P21.0, P21.1, and P19.9. Births with low birth weight are classified as P07.1 in the ICD-10 and is described as birth weight below 2500 g.ICD-10 code P92 is used to classify newborn feeding problems.

Statistical Analysis

The IBM SPSS (version 20.0) package application was used in a computer setting to analyze the data collected for our investigation. Cross tables and descriptive statistical data in the form of percentages and numbers were used to depict the research group's socio-demographic characteristics. For continuous variables, the standard deviation and mean values are provided. The Kolmogorov-Smirnov test was used to determine whether the data were in accordance with a normal distribution. To compare categorical variables, chi-square analysis was used. A t-test was performed to examine the normally distributed data between the two groups to compare non-normally distributed data between two groups, the Mann-Whitney U test was applied, and the Kruskal-Wallis test was used in the case of more than two groups. For investigating the linked variables, correlation analysis was performed. Order to estimate the NICU need, a logistic regression analysis was carried out with the corresponding factors. The PAPP-A value's NICU requirement was predicted using ROC analysis. The threshold for statistical significance was set at $p<0.05$.

Results

Of the 1.072 newborn babies included in the research, 17% required NICU care. Of the 1.072 babies, 496 (46.3%) were born vaginally, while 576 (53.7%) were delivered through cesarean section.

In the research, mothers of infants who required NICU had a mean age of 29.49±4.32 and mothers of infants whose did not have a mean age of 29.32±4.57. In terms of mother age, there wasn't any statistically meaningful difference between the two groups (p=0.656). The gravida variable and the requirement for NICU have a statistically significant connection (p=0.001). The parity variable and the requirement for NICU have a statistically significant connection (p=0.002). Multigravid women make up 63.7% of moms of infants who require NICU care and 74.2% of mothers of newborns who do not (p=0.004). Newborns of multigravid mothers had a lower requirement for NICU care. Additionally, there was a statistically significant link (p=0.036) between multiparity and the requirement for a NICU. Infants born to multiparous pregnant mothers had lower NICU needs. Between these two groups, there wasn't a statistically significant difference in the mean maternal BMI (p=0.181). The average gestational week for mothers of infants who require NICU is 38.19±1.17 weeks at the time of delivery, compared to 38.36±1.11 weeks for mothers of infants who do not. When it came to the mothers' gestational week at birth, there wasn't any statistically meaningful difference between the two groups (p=0.056). Whether or whether the infant requires a NICU is significantly correlated with smoking status (p=0.027). Infants of smokers require more NICU care (8.8% vs. 4.7%). 56.6% of mothers of infants who required NICU care underwent a cesarean section, compared to 53.61% of mothers of infants whose did not (p=0.395). The gender of the newborns and the requirement for NICU have a statistically significant link (p=0.007). Newborn boys require more NICU care than infant females. Newborns that require NICU have an average birth weight of 3187.66±661.76 gr, whereas healthy infants have an average birth weight of 3357,12430.47 gr. However, there wasn't any statistically significant link between the requirement for a NICU and fetal macrosomia (p=0.457). Infants who required NICU care had an average PAPP-A value of 0.91±0.34 MoM. Infants who do not require NICU care have an average PAPP-A value of 1.12±0.59 MoM. In terms of PAPP-A value, there is a statistically significant disparity between the requirement for NICU (p=0.000). The subgroup that does not require NICU has a PAPP-A value that is, on average, greater than the subgroup that does. However, the difference between the requirement for NICU and the free hCG value was not statistically significant (p=0.134) (Table 1).

Cesarean section grounds were studied in our study as a subgroup, and they are displayed in Table 2. The necessity for an NICU is statistically different from the criteria for a cesarean section (χ^2=21.723; p<0.001). Infants who had cesarean delivery with fetal distress indication require NICU care the most. Cesarean grounds and PAPP-A (MoM) values did not differ in a way that was statistically significant (F=1.407; p=0.230). Cesarean grounds and hCG (MoM) value did not change in a way that was statistically significant (F=1.517; p=0.196).

The between infant hospitalization causes and hCG (MoM) levels, there wasn't any statistically significant difference

(F=0.852; p=0.545). There wasn't any statistically significant relationship between the PAPP-A (MoM) value and neonatal hospitalization indications (F=1.878; p=0.087) (Table 3).

A statistically significant distinction existed between the PAPP-A (MoM) mean of the Apgar 5th minute score <7 group and the PAPP-A (MoM) mean of the Apgar 5th minute score greater than or equal to 8 group (p=0.013). A statistically significant distinction existed between the mean of the hCG (MoM) of the Apgar 5th minute score <7 group and the hCG (MoM) mean of the Apgar 5th minute score greater than or equal to 8 group (p=0.019) (Table 4).

Table 5 lists correlation analysis results. PAPP-A value has a strongly negative statistical connection (r=-0.102, p=0.001) with age, gravida (r=-0.147, p=0.001), and parity factors (r=-0.125, p=0.001). PAPP-A value has a positive and extremely weak statistical correlation with BMI (r=0.073, p=0.017), gestational week at delivery (r=0.067, p=0.029), and birth weight (r=0.099, p=0.001) variables. PAPP-A value and free hCG have a positive and statistically weakly significant connection (r=0.246, p=0.001), as do PAPP-A value and Apgar 5th minute score (r=0.159, p=0.001).

Our regression model (χ^2=15.038; p<0.000) was significant due to the forward (wald) approach logistic regression analysis. According to Nagelkerke, our binary logistic regression model, which was created to forecast the requirement for newborn intensive care, has a 26.9% explanation rate. Smoking and the need for a NICU had a significant positive connection, using the established model (B=2.069; p=0.001). When we look at the odds ratios (to the quantity) of this link, we find that infants of smoker mothers are more likely to need an NICU than those of non-smokers to be 7.055 times more likely. PAPP-A value and NICU necessity have a compelling negative connection in our constructed model (B=-1.227; p=0.000). In this connection, NICU requirement increases by 0.370 times for every unit reduction in PAPP-A score. Low birth weight and the requirement for NICU were positively and significantly correlated (B=3.198; p=0.000). Low birth weight infants cause NICU use to increase by 24.473 times. The need for a NICU was significantly negatively correlated with the need for a cesarean section (B=-0.943; p=0.001). Comparing individuals who have had prior uterine surgery to those who have fetal distress owing to cesarean indication, the requirement for NICU is increased by 0.390 times (Table 6).

The area under curve =0.593 was used to calculate the proportion of PAPP-A variables that predicted the requirement for NICU care. This determined PAPP-A value allows an accurate estimation of the NICU need at a rate of 59.3%. The test's cut-off point was 0.955, its specificity was 45.2%, and it

Table 1. Comparison of demographic and clinical characteristics of the groups

	NICU (+) (n=182)	NICU (-) (n=890)	p
Age**	29.49±4.32	29.32±4.57	0.656
Gravida***	2 (1-11)	2 (1-8)	<0.001
Parity***	1 (0-3)	1 (0-5)	0.002
Multigravida***	116 (63.7)	660 (74.2)	0.004
Multiparity***	47 (25.8)	301 (33.8)	0.036
BMI (kg/m^2)*	29.60±3.57	29.22±3.48	0.181
Obesity***	87 (47.8)	387 (43.5)	0.285
Gestational age (week)**	38.19±1.17	38.36±1.11	0.056
Smoking***	16 (8.8)	42 (4.7)	0.027
Cesarean delivery***	103 (56.6)	473 (53.1)	0.395
Infant gender*** Female Male	 80 (44.0) 102 (56.0)	 488 (54.8) 402 (45.2)	0.007
Birth weight (gr)**	3187.66±661.76	3357.12±430.47	<0.001
LBW***	40 (22.0)	6 (0.7)	<0.001
Macrosomia***	18 (9.9)	73 (8.2)	0.457
PAPP-A (MoM)**	0.91±0.34	1.12±0.59	<0.001
Free hCG (MoM)**	1.05±0.46	1.11±0.49	0.134

NICU: Neonatal intensive care unit, BMI: Body mass index, LBW: Low birth weight, PAPP-A: Pregnancy-associated plasma protein A, MoM: Multiples of the median, hCG: Human chorionic gonadotropin, *Continuous variable with normal distribution; t-test, **Continuous variables not normally distributed; Mann-Whitney U test, ***Categorical variable; chi-square test, p<0.05 was considered statistically significant

Table 2. Evaluation of the relationship between cesarean indications and the need for neonatal intensive care

	NICU (+) (n=182)	NICU (-) (n=890)	Total
Fetal distress	45 (26.2)	127 (73.8)	172 (100.0)
Malpresentation	2 (7.7)	24 (92.3)	26 (100.0)
Previous uterine surgery	40 (12.3)	284 (87.7)	324 (100.0)
CPD	12 (30.0)	28 (70.0)	40 (100.0)
Macrosomic fetus	4 (28.6)	10 (71.4)	14 (100.0)
Total	103 (17.9)	473 (82.1)	576 (100.0)
χ^2=21.723 p<0.001*			

NICU: Neonatal intensive care unit, CPD: Cephalopelvic disproportion, *chi-square test was used. P<0.05 was considered statistically significant

Table 3. Evaluation of the relationships between indications for hospitalization of newborns and PAPP-A and hCG values

	N	PAPP-A (MoM) Mean ± standard deviation	hCG (MoM) Mean ± standard deviation
Respiratory distress	53	0.82±0.32	0.93±0.33
Indirect hyperbilirubinemia	63	0.92±0.36	1.04±0.46
Low birth weight	40	0.94±0.25	1.17±0.57
Neonatal infection	8	0.98±0.43	1.22±0.53
Neonatal hypoglycemia	6	1.15±0.33	1.22±0.40
Asphyxia	4	0.89±0.19	1.11±0.58
Nutritional intolerance	8	1.20±0.58	0.85±0.16
		F=1.878 p=0.087*	F=1.463 p=0.194*

PAPP-A: Pregnancy-associated plasma protein A, hCG: Human chorionic gonadotropin, MoM: Multiples of the median, *Kruskal-Wallis multiple comparison test. P<0.05 was considered statistically significant

Table 4. Evaluation of the relationships between the fifth-minute Apgar score and PAPP-A values

	n	PAPP-A (MoM) Mean ± standard deviation	hCG (MoM) Mean ± standard deviation
Apgar score 5th min <7	32	0.84±0.27	0.89±0.23
Apgar score 5th min ≥8	1.040	1.09±0.57	1.10±0.49
		p=0.013*	p=0.019*

PAPP-A: Pregnancy-associated plasma protein A, MoM: Multiples of the median, hCG: Human chorionic gonadotropin. *Continuous variable not normally distributed; Mann-Whitney U test. P<0.05 was considered statistically significant

had a 52.7% sensitivity rate (Figure 1). Our study's findings indicate that individuals with PAPP-A values below 0.95 are more likely to have an increase in their demand for NICU care.

Discussion

PAPP-A and hCG, two of the first trimester blood screening tests, are linked to pregnancy problems in addition to being predictive of fetal defects[5]. In our investigation, blood samples from mothers of infants who required NICU care and had an Apgar score at the five-minute mark below seven had a substantially lower PAPP-A value. Additionally, despite a correlation between the hCG value and the Apgar score in the fifth minute, it was believed that this circumstance was caused by a discrepancy in the distribution of the data because it did not result in a greater requirement for NICU care. There are a few research looking at the connection between PAPP-A and various poor neonatal and perinatal results in the literature. According to these studies, low PAPP-A levels in the first trimester of pregnancy are linked to an increased risk of miscarriage, preeclampsia, pregnancy-induced hypertension, small-for-gestational-age delivery, stillbirth, premature membrane rupture, and placental abruption[3,6]. Although it is possible that the need for NICU for newborns might be connected with low PAPP-A levels, this is unlikely given that the study group in our study was made up of a low-risk group and there were no concomitant events that would enhance the need for NICU in infants throughout this group. This relationship can be explained by low placental size and decreased placental perfusion, which is probably associated with decreased PAPP-A production[7,8].

People who are most prone to stillbirth, IUGR, and early labor have smaller placentas and higher levels of alpha-fetoprotein in the absence of damaged uterine artery Doppler velocimetry in those with low PAPP-A levels[9]. PAPP-A levels are expected to be associated with a disturbance of placental circulation, even if the AFP quantity and Doppler measurements were excluded from our analysis. The neonatal outcomes of 9.450

Table 5. Evaluation of the relationships between PAPP-A and other parameters

	r	p
Age	-0.102	0.001
Gravida*	-0.147	<0.001
Parity*	-0.125	<0.001
BMI (kg/m^2)	0.073	0.017
Pregnancy week	0.067	0.029
Birth weight (gr)	0.099	0.001
Free hCG (MoM)	0.246	<0.001
Apgar 5th min score	0.159	<0.001

r: Corelation coefficient, MoM: Multiples of the median, BMI: Body mass index, hCG: Human chorionic gonadotropin, *Spearman correlation analysis was used, p<0.05 was considered statistically significant

singleton pregnant women who participated in the prenatal screening program were also studied by Kirkegaard et al.[10]. They asserted a high correlation between low PAPP-A levels and neonatal diseases, such as the requirement for NICU admission and hypoglycemia. PAPP-A and hCG values were examined with newborn critical care hospitalization indications in our investigation, but no significant correlation between the variables was discovered. Examining the studies on this topic shows that the connection between pregnancy issues such preterm birth, SGA, preeclampsia, and IUGR as well as first trimester screening tests are studied, and negative newborn outcomes are disclosed based on these results[6-9]. Fox and Chasen[11] looked at the connection between PAPP-A levels, the second trimester growth restriction, associated problems, and NICU admissions. Although there are not enough patients with lower PAPP-A values, it has been demonstrated a need for NICU rises in these infants. But we found that there wasn't a parameter we identified as a risk factor, like smoking. Although the results are similar to our findings, this study is not entirely appropriate for comparison because our study only looked at low-risk pregnant women[11]. However, an association between low birth weight and low PAPP-A values was noticed in a study with a huge number in which the findings of 12,592 pregnant women across Britain were published, comparable to our study[12]. A few studies, in particular, have suggested that elements like premature delivery and SGA impact negative newborn outcomes[13-16]. Since the low-risk pregnancy population was the focus of our study, there shouldn't be a significant NICU demand. The pregnant women in the NICU-required group, however, should be noted since they smoked, and smoking was linked to low birth weight and poor PAPP-A readings. All these findings clearly imply that placental perfusion dysfunction may be the etiology of the disease. The requirement for NICU has increased because of multigravida and multiparity rates, which is another finding of our study.

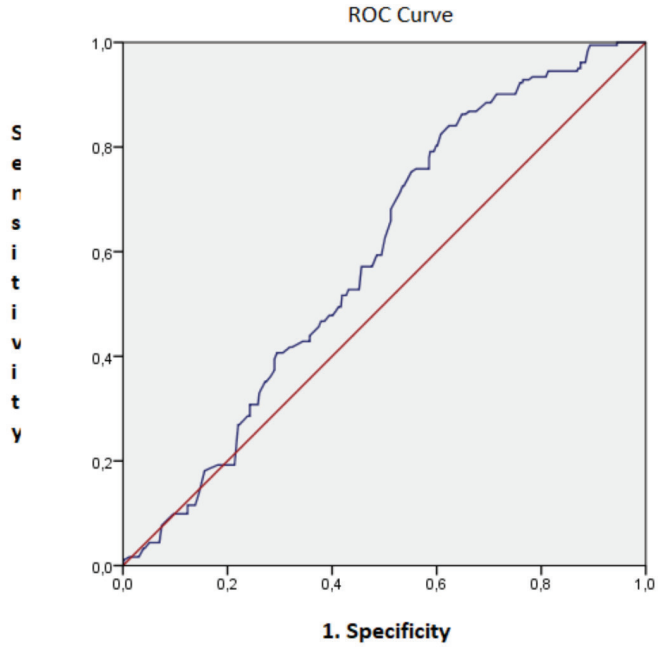

Figure 1. ROC analysis

ROC: Receiver operating characteristic

Although the requirement for NICU grew exponentially as the parity ratio increased, a statistically significant difference was also undiscovered, according to Madan et al.[17]. Similar to our investigation, the same study concluded that smoking enhanced the requirement for NICU care. Additionally, it was found in our study that male infants required more NICU care. Although it has been noted in the literature that male newborns are more likely to experience negative outcomes and require NICU care[18], we believe that the results of our study are a result of the quantitative and distributional properties of the data. The need for NICU was greater in infants whose cesarean sections were performed for fetal distress, even though cesarean section rates were similar between infants who required NICU regardless of the mode of delivery, as predicted by the subgroup analysis carried out in terms of cesarean delivery indications. However, there was no association between PAPP-A and hCG levels and cesarean section indications. According to a study looking at first trimester PAPP-A levels and the chance of developing

Table 6. Results of logistic regression analysis of variables associated with NICU

Variables	B	St. error	p	β	95% confidence interval for β	
					Bottom	Top
Still	-3.365	0.994	0.001*	0.035	-	-
Smoking (1)	2.069	0.420	0.000*	7.914	3.475	18.025
PAPP-A value	-1.227	0.336	0.000*	0.293	0.152	0.566
LBW (1)	3.198	0.557	0.000*	24.473	8.208	72.970
Cesarean indication (3)	-0.943	0.274	0.001*	0.390	0.228	0.667
Nagelkerke R2=0.269 χ^2=15.038 p=0.000*						

Reference variable: NICU (-) Cesarean indication reference variable: Fetal distress; (3): Previous uterine surgery; *: Statistical significance. PAPP-A: Pregnancy-associated plasma protein A, LBW: low birth weight. P<0.05 was considered statistically significant

intrapartum fetal distress, low PAPP-A concentration increases the likelihood of experiencing intrapartum fetal distress and, consequently, the probability of cesarean birth[19]. One thousand thirty seven pregnant women with low PAPP-A levels were included in the study by Uccella et al.[20] The umbilical artery pH was considerably lower and the incidence of emergency cesarean sections was greater in the low PAPP-A group after correcting for potential confounding factors such hypertension, small for gestational age, preterm birth, and labor induction. It was discovered the existence of a statistically significant distinction was observed between fetal weight, 5th minute Apgar scores, and gestational age was observed in a study that examined PAPP-A values in pregnancies complicated by preterm delivery, preeclampsia, and fetal growth restriction. They concluded that variations in PAPP-A levels should be considered to remember that more attentive and cautious antepartum observation may be necessary to prevent negative perinatal outcomes in a particular patient group[21]. In our study, a relationship between PAPP-A levels, gestational week, 5th minute Apgar score, and birth weight was found. With the help of this information, we think that low PAPP-A in the group of low-risk pregnancies may be able to predict low birth weight, which in this instance is evident in the Apgar score and increases the requirement for NICU. The significantly low level of PAPP-A suggests that this parameter, which is employed as a screening test, is helpful at predicting perinatal outcomes, particularly in low-risk pregnancies, even though all cases were chosen from term and low-risk pregnancies. We believe that a low PAPP-A level can be used as an indicator, although the sensitivity and specificity values are not particularly strong.

Study Limitations

The inclusion of a carefully chosen community of low-risk pregnant is the study's strength, even though the sample size and retrospective nature of the study are two of its most obvious weaknesses.

Conclusion

The ideal postpartum scenario for the family and doctor in the low-risk pregnancy group is for the mother to be able to stay with her healthy newborns. NICU care is not preferred in low-risk pregnancies, although it is more acceptable for infants in the dangerous pregnancy group. However, because the newborns of this group of expectant women may also require NICU care, a marker-like PAPP-A, which we routinely scan, can be used to foretell this potential need to inform the patient and prepare them for potential risks. On the other hand, avoiding this scenario altogether will be advantageous for both the economy and public health. As a result, necessary precautions should be taken and preparations should be made accordingly, as infants may need NICU in pregnant with low PAPP-A value, one of the first trimester screening tests.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the University of Health Sciences Turkey, Ankara City Hospital (approval no: 7, date: 25.01.2022).
Informed Consent: Retrospective study.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.E., B.L.K., D.T.E., U.Z., E.A., G.Y., E.Ü.Ö., N.H., Concept: Ö.M.T., Design: B.E., N.H., Data Collection or Processing: U.Z., E.A., Analysis or Interpretation: B.L.K., D.T.E., G.Y., Literature Search: N.H., Writing: B.E., E.Ü.Ö.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study received no financial support.

References

1. Dugoff L, Hobbins JC, Malone FD, Porter TF, Luthy D, Comstock CH, et al. First-trimester maternal serum PAPP-A and free-beta subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: a population-based screening study (the FASTER Trial). Am J Obstet Gynecol 2004;191:1446-51.
2. Yaron Y, Ochshorn Y, Heifetz S, Lehavi O, Sapir Y, Orr-Urtreger A. First trimester maternal serum free human chorionic gonadotropin as a predictor of adverse pregnancy outcome. Fetal Diagn Ther 2002;17:352-6.
3. Spencer K, Cowans NJ, Nicolaides KH. Low levels of maternal serum PAPP-A in the first trimester and the risk of pre-eclampsia. Prenat Diagn 2008;28:7-10.
4. Smith GC, Stenhouse EJ, Crossley JA, Aitken DA, Cameron AD, Connor JM. Early pregnancy levels of pregnancy-associated plasma protein a and the risk of intrauterine growth restriction, premature birth, preeclampsia, and stillbirth. J Clin Endocrinol Metab 2002;87:1762-7.
5. Ataman Yıldırım Z, Tuğrul Ersak D, Timur B, Kahyaoğlu S. The Predictive Value of First and Second Trimester Screening Test Biomarkers in Preeclampsia. Forbes J Med 2022;3:68-74.
6. Gagnon A, Wilson RD, Audibert F, Allen VM, Blight C, Brock J, et al. Archivée: Complications obstétricales associées aux analytes anormaux des marqueurs sériques maternels. J Obstet Gynaecol Can 2008;30:933-49.
7. Conover CA, Bale LK, Overgaard MT, Johnstone EW, Laursen UH, Füchtbauer EM, et al. Metalloproteinase pregnancy-associated plasma protein A is a critical growth regulatory factor during fetal development. Development 2004;131:1187-94.
8. Spencer K, Cowans NJ, Chefetz I, Tal J, Meiri H. First-trimester maternal serum PP-13, PAPP-A and second-trimester uterine artery Doppler pulsatility index as markers of pre-eclampsia. Ultrasound Obstet Gynecol 2007;29:128-34.
9. Proctor LK, Toal M, Keating S, Chitayat D, Okun N, Windrim RC, et al. Placental size and the prediction of severe early-onset intrauterine growth restriction in women with low pregnancy-associated plasma protein-A. Ultrasound Obstet Gynecol 2009;34:274-82.
10. Kirkegaard I, Uldbjerg N, Henriksen TB. PAPP-A and free β-hCG in relation to admission to neonatal intensive care unit and neonatal disease. Prenat Diagn 2011;31:1169-75.

11. Fox NS, Chasen ST. First trimester pregnancy associated plasma protein-A as a marker for poor pregnancy outcome in patients with early-onset fetal growth restriction. Prenat Diagn 2009;29:1244-8.
12. Bilagi A, Burke DL, Riley RD, Mills I, Kilby MD, Katie Morris R. Association of maternal serum PAPP-A levels, nuchal translucency and crown-rump length in first trimester with adverse pregnancy outcomes: retrospective cohort study. Prenat Diagn 2017;37:705-11.
13. Pilalis A, Souka AP, Antsaklis P, Daskalakis G, Papantoniou N, Mesogitis S, et al. Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler and PAPP-A at 11-14 weeks' gestation. Ultrasound Obstet Gynecol 2007;29:135-40.
14. Ong CY, Liao AW, Spencer K, Munim S, Nicolaides KH. First trimester maternal serum free beta human chorionic gonadotrophin and pregnancy associated plasma protein A as predictors of pregnancy complications. BJOG 2000;107:1265-70.
15. Ranta JK, Raatikainen K, Romppanen J, Pulkki K, Heinonen S. Decreased PAPP-A is associated with preeclampsia, premature delivery and small for gestational age infants but not with placental abruption. Eur J Obstet Gynecol Reprod Biol 2011;157:48-52.
16. Kirkegaard I, Henriksen TB, Uldbjerg N. Early fetal growth, PAPP-A and free beta-hCG in relation to risk of delivering a small-for-gestational age infant. Ultrasound Obstet Gynecol 2011;37:341-7.
17. Madan I, Puri I, Jain NJ, Grotegut C, Nelson D, Dandolu V. Characteristics of obstetric intensive care unit admissions in New Jersey. J Matern Fetal Neonatal Med 2009;22:785-90.
18. Tamayev L, Schreiber L, Marciano A, Bar J, Kovo M. Are there gender-specific differences in pregnancy outcome and placental abnormalities of pregnancies complicated with small for gestational age? Arch Gynecol Obstet 2020;301:1147-51.
19. Avşar AF, Seçen Eİ, Akçay GFY, Keskin HL, Taş EE, Dalgacı AF. The relationship between first-trimester pregnancy-associated plasma protein-A levels and intrapartum fetal distress development. J Turk Ger Gynecol Assoc 2016;17:139-42.
20. Uccella S, Colombo GF, Bulgheroni CM, Serati M, Bogani G, Salvatore S, et al. First-trimester maternal serum screening and the risk for fetal distress during labor. Am J Obstet Gynecol 2009;201:166.e1.6.
21. Loncar D, Varjacić M, Arsenijević S. Significance of pregnancy-associated plasma protein A (PAPP-A) concentration determination in the assessment of final outcome of pregnancy. Vojnosanit Pregl 2013;70:46-50.