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Original Research

Associations of First-Trimester Aneuploidy Markers With Neonatal Anthropometry and Small for Gestational Age/Large for Gestational Age Outcomes

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Abstract

Background: Early detection of fetal developmental abnormalities can allow for necessary precautions to be taken to reduce risks that may arise during and after birth. This study aimed to investigate the association between first-trimester aneuploidy screening markers—pregnancy-associated plasma protein A (PAPP-A), free beta-human chorionic gonadotropin (fβ-hCG), and nuchal translucency (NT)—and neonatal anthropometric measurements (weight, length, and head circumference). It also evaluated their predictive value for subsequent fetal growth abnormalities, including small for gestational age (SGA) and large for gestational age (LGA) births. **Methods**: This retrospective study included 422 singleton pregnant women and their newborns. First-trimester NT, fβ-hCG, and PAPP-A multiple of the median (MoM) values were compared among mothers who delivered SGA, appropriate for gestational age (AGA), and LGA infants. Correlations between these markers and neonatal percentiles for weight, length, and head circumference were also examined. **Results**: Mothers of SGA neonates had significantly lower PAPP-A and fβ-hCG MoM values than mothers of AGA or LGA neonates ($p < 0.05$). Receiver operating characteristic (ROC) analysis demonstrated moderate discriminatory performance for the identification of pregnancies at increased risk of SGA, with an area under the curve (AUC) of 0.687 for fβ-hCG MoM ($p < 0.001$) and 0.674 for PAPP-A MoM (p = 0.001). Spearman correlation analysis showed that PAPP-A MoM was positively correlated with neonatal birth weight (r = 0.133, p = 0.006) and length percentiles (r = 0.151, p = 0.002). fβ-hCG MoM was also positively correlated with neonatal weight (r = 0.151, p = 0.002), length (r = 0.114, p = 0.019), and head circumference percentiles (r = 0.104, p = 0.032). Correlation analysis revealed no significant association between NT MoM and neonatal anthropometric measurements. In multivariable logistic regression analysis, lower first-trimester PAPP-A MoM (adjusted odds ratio [aOR]: 2.51) and fβ-hCG MoM (aOR: 2.95) remained independently associated with SGA, whereas NT MoM did not. **Conclusions**: First-trimester PAPP-A and fβ-hCG values were significantly lower in mothers who delivered SGA infants and showed moderate discriminatory ability for the identification of pregnancies at increased risk of SGA. In addition, first-trimester PAPP-A and fβ-hCG levels were correlated with neonatal birth weight and length, and first-trimester fβ-hCG levels were also correlated with neonatal head circumference. In contrast, first-trimester NT was not associated with neonatal anthropometric outcomes.

Keywords: PAPP-A; fβ-hCG; nuchal translucency; small for gestational age; neonatal anthropometry; birth weight

1. Introduction

Nuchal translucency (NT), measured by ultrasonography, along with maternal serum levels of free beta-human chorionic gonadotropin (fβ-hCG) and pregnancy-associated plasma protein A (PAPP-A), are components of the first-trimester aneuploidy screening test. These markers are used to screen for Down syndrome, Turner syndrome, and Edwards syndrome [1].

In the literature, the terms small for gestational age (SGA) and large for gestational age (LGA) describe abnormal fetal growth. SGA is generally defined as a fetal or birth weight below the 10th percentile for a specific reference at a specific gestational age, whereas LGA refers to a weight above the 90th percentile [2]. SGA is associated with both immediate perinatal complications and an increased risk of long-term cardiometabolic and neurodevelopmental outcomes [3–5]. Conversely, LGA neonates have an increased risk of intrapartum complications, including fetal hypoxia, shoulder dystocia, and brachial plexus injury. Maternal risks include perineal trauma, postpartum hemorrhage, and operative delivery, particularly cesarean section [6]. In addition, individuals born LGA have an elevated risk of obesity, hypertension, and type 2 diabetes later in life [7].

Although often used interchangeably, SGA and fetal growth restriction (FGR) represent related but distinct clini-

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cal entities. According to the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), SGA refers to a fetus or neonate with an estimated or actual weight below the 10th percentile for gestational age and may reflect a constitutionally small fetus. In contrast, FGR is a pathological condition characterized by failure to achieve genetic growth potential and is associated with increased perinatal morbidity as well as adverse long-term outcomes [8]. Body weight, length and head circumference at birth are the primary anthropometric measurements used to assess perinatal and postnatal growth and health [9]. Early detection of fetal growth abnormalities can enable timely interventions to mitigate risks that may arise during and after birth.

This study aimed to investigate the relationship between first-trimester aneuploidy screening markers (PAPP-A, fβ-hCG, NT) and neonatal anthropometric measurements (weight, length, and head circumference). Furthermore, it also aimed to evaluate the association between these first-trimester markers and fetal growth anomalies, such as SGA and LGA, that may occur later in pregnancy.

2. Materials and Methods

The study was conducted as a retrospective chart review. Singleton pregnancies that resulted in delivery after 32 weeks of gestation at the Gynecology and Obstetrics Clinics of VM Medical Park Maltepe Hospital and Kocaeli City Hospital between April 2023 and April 2024 were included. Eligible cases underwent first-trimester aneuploidy screening between 11–14 weeks of gestation and did not develop any pregnancy complications.

Pregnant women with multiple pregnancy, fetal chromosomal abnormalities or major structural anomalies, gestational hypertension, preeclampsia, gestational diabetes, intrauterine fetal growth restriction, glucose intolerance, maternal obesity, known systemic disease, or insufficient data were excluded from the study. Fetuses diagnosed with FGR during pregnancy were excluded to allow assessment of the relationship between first-trimester aneuploidy screening markers and neonatal anthropometric outcomes in pregnancies without major complications. This approach aimed to minimize confounding effects from placental insufficiency, hypertensive disorders, and abnormal Doppler findings that typically characterize FGR and may independently affect both biochemical markers and fetal growth.

Information on eligible women and their newborns was obtained from electronic and written records. A total of 422 pregnancies were included in the study.

The study was conducted in accordance with the principles of the Declaration of Helsinki, and approval was obtained from the Kocaeli City Hospital Scientific Research Ethics Committee on September 12, 2024 (protocol number: 2024-109).

The evaluated maternal variables included maternal age, body mass index (BMI), parity, gestational age at first-trimester screening, and gestational age at delivery. Neonatal variables included birth weight, length, head circumference, and the corresponding gestational age and sex-adjusted percentiles.

In first-trimester aneuploidy screening, NT was measured by ultrasonography, and fβ-hCG and PAPP-A were measured in maternal serum. In our clinics, the corrected multiple of the median (MoM) values for these measurements are calculated according to gestational age using licensed software, and these corrected MoM values are included in the Down Syndrome screening test data.

Neonates with a birth weight below the 10th percentile for gestational age were classified as SGA, whereas those exceeding the 90th percentile were categorized as LGA. Infants with birth weights fell between the 10th and 90th percentiles were considered appropriate for gestational age (AGA). NT, fβ-hCG, and PAPP-A values, along with their corrected MoM versions, were compared among groups of pregnant women who delivered SGA, LGA, and AGA infants.

Anthropometric measurements of all newborns, including weight, length, and head circumference, were included in the study, measured immediately after birth, were recorded. These measurements were converted to gestational age and sex-adjusted percentiles based on reference data specific to the Turkish newborn population [9]. The correlation between these measurements and first-trimester NT MoM, fβ-hCG MoM and PAPP-A MoM values was evaluated.

The primary outcome of this study was SGA, defined as birth weight below the 10th percentile for gestational age. The primary exposures were first-trimester PAPP-A MoM, fβ-hCG MoM, and NT MoM values. Analyses of LGA, neonatal anthropometric percentiles, and subgroup comparisons were considered exploratory and interpreted accordingly.

All statistical analyses were performed using IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables are summarized as mean $\pm$ standard deviation (SD) and median (interquartile range, IQR), while categorical variables are expressed as frequency (percentage, %). Normality of distribution was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For comparisons among groups, one-way analysis of variance (ANOVA) was used for normally distributed variables, whereas the Kruskal-Wallis test was used for variables that did not meet normality assumptions. When overall differences were detected, post-hoc analyses were performed using Tukey's Honestly Significant Difference (HSD) test after ANOVA or Dunn's test with Bonferroni adjustment following the Kruskal-Wallis test. Discriminatory capacity for identifying SGA was evaluated using receiver operating characteristic (ROC) curve analysis, and optimal thresholds were determined by maximizing the Youden index. Multivariable logistic regression analysis was subsequently performed to examine indepen-

dent associations with SGA, with maternal age, BMI, first-trimester NT MoM, PAPP-A MoM, and fβ-hCG MoM included as covariates. Correlations between continuous variables were assessed using Spearman's rank correlation coefficient. Cases with missing key clinical or laboratory data were excluded, and a complete-case analysis approach was used. Statistical significance was defined as a two-sided p-value < 0.05.

3. Results

A total of 422 singleton pregnancies were included in the study. Of these, 36 (8.5%) resulted in SGA infants, 322 (76.3%) in AGA infants, and 64 (15.2%) in LGA infants.

Table 1 presents a comparison of groups that delivered SGA, AGA, and LGA infants with respect to demographic characteristics, first-trimester aneuploidy screening markers (fβ-hCG, PAPP-A and NT), and neonatal anthropometric measurements (weight, length, and head circumference). No significant differences were observed among the groups regarding maternal age, BMI, parity, gestational age at the time of NT ultrasonography, and gestational age at delivery. Significant differences were observed among the groups in first-trimester PAPP-A and fβ-hCG levels. Mothers who delivered SGA infants had significantly lower PAPP-A and fβ-hCG MoM values compared with those who delivered AGA and LGA infants (PAPP-A: $p = 0.002$, fβ-hCG: $p < 0.001$). No significant differences were observed in NT values across the three groups. Although not statistically significant, both PAPP-A and fβ-hCG MoM values were numerically higher in the LGA group compared to the AGA group. Neonatal anthropometric measurements (weight, length, head circumference, and their respective percentiles) differed significantly among the SGA, AGA, and LGA groups ($p < 0.001$ for all comparisons). Post-hoc analysis showed that all pairwise group comparisons (SGA-AGA, SGA-LGA, and LGA-AGA) were statistically significant.

The discriminatory performance of first-trimester PAPP-A MoM and fβ-hCG MoM values for identifying pregnancies at increased risk of SGA was evaluated using ROC analysis (Table 2). Both markers demonstrated moderate discriminatory ability, with an area under the curve (AUC) of 0.687 for fβ-hCG MoM ($p < 0.001$) and 0.674 for PAPP-A MoM ($p = 0.001$). Optimal threshold values were determined using the Youden index. Accordingly, the optimal cut-off value for first-trimester fβ-hCG MoM was 0.565, with a sensitivity of 44.4% and a specificity of 84.2%. For PAPP-A MoM, the optimal cut-off value was 1.155, yielding a sensitivity of 83.3% and a specificity of 47.4% (Table 2). The relatively high optimal cut-off value for PAPP-A MoM reflects the balance between sensitivity and specificity determined by the Youden index and should be interpreted as a statistical threshold rather than a pathological value. ROC curves for PAPP-A MoM and fβ-hCG MoM are shown in Fig. 1.

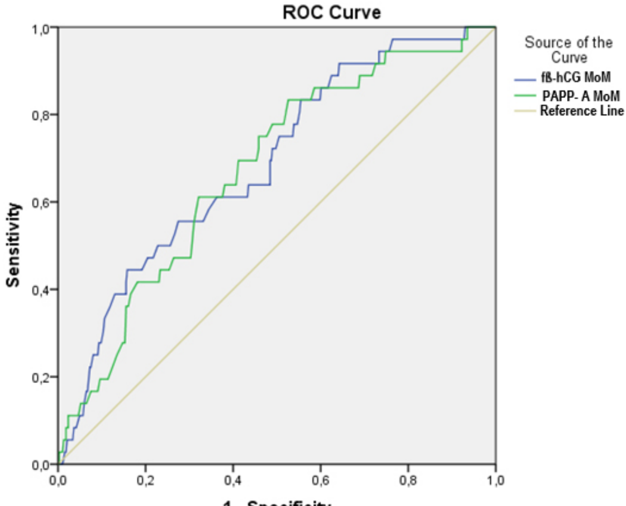

Fig. 1. ROC curves of first-trimester PAPP-A MoM and fβ-hCG MoM values for prediction of SGA birth.

The correlations between first-trimester aneuploidy screening markers (fβ-hCG, PAPP-A, and NT) and neonatal anthropometric measurements (weight, length, and head circumference) are presented in Table 3. Spearman correlation analysis showed a statistically significant positive correlation between both PAPP-A and fβ-hCG MoM values and neonatal birth weight and length percentiles. Specifically, PAPP-A MoM correlated with weight (r = 0.133, $p = 0.006$) and length (r = 0.151, $p = 0.002$), while fβ-hCG MoM showed similar correlations (weight: r = 0.151, $p = 0.002$; length: r = 0.114, $p = 0.019$). fβ-hCG MoM also showed a weaker but statistically significant correlation with head circumference percentile (r = 0.104, $p = 0.032$). NT MoM was not significantly associated with any neonatal anthropometric measurements.

In a parsimonious multivariable logistic regression model adjusted for maternal age, BMI, and first-trimester NT MoM, both lower first-trimester PAPP-A MoM (adjusted odds ratio [aOR]: 2.51, 95% confidence interval [CI]: 1.16–5.44; $p = 0.019$) and lower fβ-hCG MoM (aOR: 2.95, 95% CI: 1.35–6.45; $p = 0.007$) remained independently associated with SGA (Table 4). NT MoM was not independently associated with SGA.

4. Discussion

In this study, we investigated the relationship between first-trimester aneuploidy screening markers (PAPP-A, fβ-hCG, and NT) and neonatal anthropometric outcomes, including weight, length, and head circumference. Our findings demonstrate that PAPP-A and fβ-hCG levels are significantly associated with fetal growth patterns. PAPP-A and fβ-hCG MoM values were significantly lower in mothers who delivered SGA infants. In addition, first-trimester PAPP-A and fβ-hCG levels showed moderate correlations with neonatal birth weight and length, and first-trimester

Table 1. Comparison of that delivered SGA, AGA, and LGA groups by demographic characteristics, first-trimester screening markers (fβ-hCG, PAPP-A, and NT), and neonatal anthropometric measurements (weight, length, and head circumference).

	SGA (n = 36)	AGA (n = 322)	LGA (n = 64)	*p*-value	Post-hoc analysis *p*-values		
					SGA-AGA	SGA-LGA	LGA-AGA
Mother's age (years)	29.34 ± 5.15 29 (7.75)	30.43 ± 4.72 30 (5.13)	30.18 ± 4.94 30 (5.80)	0.420[a]	0.397	0.680	0.918
Parity (n)	0.45 ± 0.62 0 (1)	0.66 ± 0.98 0 (1)	0.71 ± 0.91 0 (1)	0.630[b]			
Gestational age at NT ultrasonography (days)	84.35 ± 4.81 85.5 (5.5)	85.93 ± 4.50 86 (7)	86.01 ± 4.90 87 (7)	0.152[a]			
Maternal BMI (kg/m^2)	25.37 ± 5.05 24.46 (6.3)	24.88 ± 4.53 24.09 (6.1)	26.21 ± 5.70 25.22 (6.40)	0.122[a]			
PAPP-A (ng/mL)	2.14 ± 1.56 1.75 (1.40)	3.39 ± 2.81 2.79 (2.38)	3.46 ± 3.39 2.71 (2.10)	***0.002***[b]	***0.001***	***0.014***	1.00
PAPP-A MoM	0.89 ± 0.48 0.83 (0.49)	1.28 ± 0.80 1.11 (0.84)	1.34 ± 1.06 1.15 (0.82)	***0.002***[b]	***0.002***	***0.007***	1.00
fβ-hCG (mIU/mL)	30.11 ± 18.45 27.5 (20.63)	47.25 ± 33.75 36.55 (35.78)	49.86 ± 31.47 40.10 (43.70)	***0.007***[a]	***0.008***	***0.010***	0.827
fβ-hCG MoM	0.79 ± 0.46 0.66 (0.63)	1.23 ± 0.83 0.96 (0.96)	1.32 ± 1.76 1.12 (1.19)	***<0.001***[b]	***0.001***	***<0.001***	0.505
NT size (mm)	1.27 ± 0.34 1.20 (0.48)	1.39 ± 0.47 1.32 (0.50)	1.38 ± 0.37 1.30 (0.60)	0.386[a]	0.352	0.555	0.977
NT MoM	0.90 ± 0.24 0.83 (0.31)	0.89 ± 0.22 0.88 (0.23)	0.89 ± 0.21 0.88 (0.28)	0.934[a]	0.942	0.931	0.991
Gestational age at birth (days)	270.58 ± 14.92 273 (14)	269.72 ± 9.27 271.50 (9)	269.01 ±12.82 273 (12.75)	0.687[b]			
Neonatal weight (g)	2588.58 ± 481 2650 (390.8)	3213.85 ± 354.6 3250 (410)	3827.95 ± 442.1 3900 (352.5)	***<0.001***[b]	***<0.001***	***<0.001***	***<0.001***
Neonatal weight (percentile)	6.01 ± 2.92 6.50 (5.98)	53.37 ± 21.58 55 (35.7)	94.5 ± 3.15 94.2 (6.75)	***<0.001***[b]	***<0.001***	***<0.001***	***<0.001***
Neonatal length (cm)	47.16 ± 4.08 48 (2.8)	49.75 ± 2.12 50 (2)	51.28 ± 2.14 52 (3)	***<0.001***[b]	***<0.001***	***<0.001***	***<0.001***
Neonatal length (percentile)	21.74 ± 17.97 17.40 (26.37)	54.70 ± 26.41 57.70 (41.60)	80.19 ± 20.87 86 (23.60)	***<0.001***[b]	***<0.001***	***<0.001***	***<0.001***
Neonatal head circumference (cm)	32.59 ± 3.01 33 (2)	34.50 ± 1.38 35 (1.5)	35.76 ± 1.54 36 (2)	***<0.001***[b]	***<0.001***	***<0.001***	***<0.001***
Neonatal head circumference (percentile)	21.63 ± 23.39 11.6 (28.38)	53.34 ± 28.25 59.37 (45.50)	80.45 ± 23.37 90 (22)	***<0.001***[b]	***<0.001***	***<0.001***	***<0.001***

Variables are given as mean ± standard deviation (SD) and median (interquartile range, IQR).

[a] ANOVA test.

[b] Kruskal-Wallis Test.

* Bold/italic value signifies statistical significance.

Abbreviations: ANOVA, analysis of variance; SGA, small for gestational age; LGA, large for gestational age; AGA, appropriate for gestational age; BMI, body mass index; PAPP-A, pregnancy associated plasma protein A; fβ-hCG, free beta-human chorionic gonadotropin; NT, nuchal translucency; MoM, multiple of the median.

Table 2. ROC analysis of first-trimester PAPP-A and fβ-hCG for prediction of SGA babies.

	AUC (95% CI)	Cut-off value	Specificity, %	Sensitivity, %	*p*-value
fβ-hCG MoM	0.687 (0.601–0.774)	≤0.565	84.2	44.4	<0.001
PAPP-A MoM	0.674 (0.587–0.761)	≤1.155	47.4	83.3	0.001

Abbreviations: AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic.

Table 3. Spearman correlation analysis of first-trimester aneuploidy screening markers (fβ-hCG, PAPP-A, and NT) and neonatal anthropometric measurements (weight, length, and head circumference).

	Neonatal weight (percentile)	Neonatal length (percentile)	Neonatal head circumference (percentile)
PAPP-A MoM	***r = 0.133, p = 0.006***	***r = 0.151, p = 0.002***	r = 0.057, *p* = 0.240
fβ-hCG MoM	***r = 0.151, p = 0.002***	***r = 0.114, p = 0.019***	***r = 0.104, p = 0.032***
NT MoM	r = 0.015, *p* = 0.759	r = 0.024, *p* = 0.630	r = 0.076, *p* = 0.117

* Bold/italic value signifies statistical significance.

Table 4. Multivariable logistic regression analysis for SGA.

Variable	aOR	95% CI	*p*-value
PAPP-A MoM	2.51	1.16–5.44	***0.019***
fβ-hCG MoM	2.95	1.35–6.45	***0.007***
NT MoM	0.69	0.15–3.13	0.629
Maternal age	1.03	0.96–1.11	0.425
Maternal BMI	1.03	0.96–1.11	0.437

Abbreviations: aOR, adjusted odds ratio.

* Bold/italic value signifies statistical significance.

fβ-hCG levels were also associated with neonatal head circumference.

PAPP-A is a metalloproteinase that mediates the proteolytic cleavage of insulin-like growth factor binding proteins (IGFBPs), particularly IGFBP-4, which increases the availability of free insulin-like growth factors (IGFs). IGFs are key regulators of fetal growth and also modulate glucose and amino acid transport in trophoblastic cells. In addition, IGFs play a crucial role in the autocrine and paracrine regulation of trophoblast invasion into the decidua. Reduced maternal serum PAPP-A levels may therefore be associated with diminished IGF activity, suboptimal trophoblast invasion, impaired placental angiogenesis, and disrupted nutrient transfer, ultimately contributing to FGR [10–12]. Previous studies have consistently reported an association between low PAPP-A concentrations and the development of SGA neonates, findings that are also supported by the results of the present study [12–17].

Some studies have shown that high PAPP-A levels lead to an increased risk of LGA and fetal macrosomia [7,17–19]. This may be due to the ability of PAPP-A to cleave IGFBPs, increasing IGF bioavailability, which is thought to mediate placental growth and nutrient transfer to the fetus [19]. In our study, although PAPP-A levels were higher in LGA pregnancies than in AGA pregnancies, this difference was not statistically significant. On the other hand maternal PAPP-A levels showed a positive correlation with neonatal birth weight. This suggests that higher PAPP-A levels may lead to an increased risk of LGA. However, Goetzinger *et al.* [20] failed to show a statistically significant association between high first-trimester PAPP-A levels and LGA birth, despite a reported reduced risk.

fβ-hCG is secreted by syncytiotrophoblasts and contributes to the maintenance of early pregnancy by promoting progesterone production. It also regulates immune tolerance and plays a role in trophoblast differentiation [21]. In addition, hCG has an indirect role in maintaining early gestational hypoxia by regulating vascular endothelial growth factor (EG-VEGF), which helps sustain physiologically low oxygen levels in early pregnancy by stimulating arterial plug formation [22,23].

In the literature, the association between first-trimester maternal fβ-hCG level and SGA infants remains unclear. While some studies [12,13] found no association between SGA and fβ-hCG levels, others [20,24] found that SGA was associated with high fβ-hCG levels. Furthermore, some studies [15,23] found that SGA was associated with low fβ-hCG levels, as observed in our study. Indeed, Barjaktarovic *et al.* [23], argued that the specific association between low hCG in the late first-trimester and reduced fetal growth could be due to suboptimal development of the trophoblast shell and arterial plugs, or earlier release of arterial plugs via lower EG-VEGF levels. This could expose the fetus to the harmful effects of O_2 free radicals. In contrast, Goetzinger *et al.* [20] found that high fβ-hCG levels above the 90th percentile in the first trimester were statistically associated with SGA. Two studies found that women with unexplained high second-trimester hCG levels were at higher risk for preterm birth, preeclampsia, and FGR, and they attributed this to the possibility that β-hCG production from placental villi may increase in the hypoxic environment [25,26]. Goetzinger *et al.* [20] reported that a similar association may apply to fβ-hCG levels in first-trimester serum screening. Similarly, Papastefanou *et al.* [24] found that the risk of SGA increased with higher first-trimester β-hCG levels. Specifically, they observed that a 0.1 increase in fβ-hCG MoM resulted in a 4.02% increase in the risk of SGA.

The relationship between fβ-hCG and LGA has been examined in several studies. Poon *et al.* [19] found that first-trimester fβ-hCG levels were significantly higher in pregnancies with macrosomic fetuses than in controls. In our study, first-trimester fβ-hCG levels, similar to PAPP-A, were higher in LGA pregnancies than in AGA pregnancies, although the difference did not reach statistical significance. We also observed a statistically significant positive correlation between first-trimester maternal fβ-hCG levels and infant birth weight. Plasencia *et al.* [18], reported findings similar to those of our study: first-trimester fβ-hCG levels were higher in the LGA group, but did not differ significantly from the control group. They attributed this

result to the small number of LGA infants included in the study. In the study by Kantomaa *et al*. [14], a fβ-hCG MoM level above the 90th percentile was associated with LGA only in gestational diabetes mellitus (GDM) pregnancies. Monari *et al*. [7] observed no significant difference in first-trimester fβ-hCG between pregnancies delivering LGA and non-LGA fetuses. As shown, the literature reports inconsistent findings on the relationship between first-trimester fβ-hCG levels and the development of SGA and LGA. Multicenter prospective studies and meta-analyses are needed to clarify the association between first-trimester fβ-hCG levels and birth weight.

Importantly, the independent associations of PAPP-A and fβ-hCG with SGA persisted after adjustment for key maternal factors, supporting a potential placental contribution beyond maternal characteristics alone. Correlation analysis in our study revealed a positive and statistically significant relationship between neonatal weight and length percentile and both PAPP-A MoM and fβ-hCG MoM values in the first trimester. First-trimester fβ-hCG MoM values were also associated with neonatal head circumference. These findings may indicate that these biomarkers provide early information related to subsequent fetal growth. Notably, a recent study published in 2025 further supports the link between first-trimester PAPP-A and fβ-hCG levels and impaired fetal growth, with significant associations with intrauterine growth restriction (IUGR). These findings suggest that alterations in early pregnancy biochemical markers may reflect a continuum of placental dysfunction, ranging from milder growth restriction such as SGA to more severe phenotypes, including IUGR [27].

ROC curve analysis in our study showed that PAPP-A MoM and fβ-hCG MoM values exhibited moderate discriminatory power for the identification of pregnancies at increased risk of SGA, with AUC values of 0.674 and 0.687, respectively. Although the ROC analyses demonstrated discriminatory ability beyond chance, the observed AUC values indicate only moderate predictive performance, with notable trade-offs between sensitivity and specificity at the proposed cut-off values. Therefore, first-trimester PAPP-A and fβ-hCG levels alone are unlikely to serve as reliable standalone screening tools for SGA. However, as supported by the multivariable analysis in the present study, these markers may provide incremental prognostic value when incorporated into multifactorial predictive models that include maternal characteristics and ultrasound parameters. Interestingly, the optimal cut-off value for PAPP-A MoM identified in this study ($\leq$1.155) was higher than the conventional threshold commonly associated with placental dysfunction. This finding likely reflects the exclusion of pregnancies complicated by overt placental pathology and FGR, resulting in a relatively narrow distribution of PAPP-A values. Therefore, the cut-off should be interpreted as a discriminatory value within a low-risk population rather than a clinically abnormal level. These findings suggest that biochemical markers obtained in early pregnancy may provide clinical insight not only for aneuploidy screening but also for potential fetal growth abnormalities. In clinical practice, low PAPP-A and fβ-hCG levels may be considered early indicators of increased risk of SGA, and closer monitoring with more frequent follow-up may be warranted throughout pregnancy. Furthermore, these findings are consistent with recent recommendations on risk-adapted timing of third-trimester ultrasound evaluation. Current guideline reviews indicate that, in low-risk pregnancies, a routine growth scan around 36 weeks may be appropriate, whereas in pregnancies identified as higher risk, based on pre-existing maternal factors or early screening results, earlier and serial growth assessments should be considered to improve the detection of FG [28]. In this context, the association observed in our study between first-trimester biochemical markers and neonatal growth outcomes may support more individualized risk stratification and tailored third-trimester surveillance strategies.

In this study, no differences in NT were observed among the SGA, AGA, and LGA groups, and no association was found between NT and neonatal anthropometric measurements (weight, length, head circumference). These results suggest that NT measurement is primarily intended for the detection of chromosomal abnormalities and may not directly reflect placental or fetal growth dynamics. In a study published in 2004, Krantz *et al*. [29] reported no association between NT and IUGR, consistent with our study. Subsequent studies have suggested a relationship between NT and SGA or LGA. A study published in 2011 reported a positive association between NT thickness and birth weight, indicating that greater NT measurements were correlated with higher neonatal weight, whereas lower NT values were linked to an increased likelihood of delivering a small infant [16]. Some studies have found an association between increased NT and LGA [19,30,31]. Kelekci *et al*. [31] reported that markedly elevated NT measurements were linked to a higher frequency of impaired glucose tolerance and macrosomia. In their cohort, pregnancies with NT values exceeding the 95th percentile were compared with those within the normal range. The authors stated that the increased rate of macrosomia in the group with increased NT may be due to the higher prevalence of impaired glucose tolerance. They proposed that microcirculatory disorders and increased capillary permeability in patients with hyperglycemia may cause an increase in NT. The absence of a relationship between NT and neonatal growth parameters in our study may be explained by the exclusion of patients with diabetic conditions, including those with diagnosed glucose intolerance.

Limitations

Several limitations should be considered when interpreting these findings. First, the retrospective design and the relatively small number of SGA cases may result in

limited statistical power and generalizability. The exclusion of fetuses with FGR, although allowing evaluation of an uncomplicated population, may have led to an underestimation of the strength of the associations between first-trimester biochemical markers and impaired fetal growth. Therefore, the results may not be directly generalizable to pregnancies complicated by FGR. Although a multivariable logistic regression analysis was performed adjusting for available maternal factors, including maternal age and BMI, information on smoking status and race or ethnicity was not consistently available and could not be included, representing an additional limitation. The lack of longitudinal fetal growth assessment during pregnancy also precluded evaluation of dynamic growth trajectories.

5. Conclusions

In conclusion, first-trimester PAPP-A and fβ-hCG MoM values were significantly lower in mothers who delivered SGA infants and show moderate predictive value for SGA. In addition, first-trimester PAPP-A and fβ-hCG levels were associated with neonatal birth weight and birth length, and first-trimester fβ-hCG levels are also correlated with neonatal head circumference. Our findings support the hypothesis that certain parameters measured during first-trimester aneuploidy screening, particularly PAPP-A and fβ-hCG, may be associated with fetal growth outcomes at birth. These markers may hold clinical value not only for detection of chromosomal anomalies but also for early prediction of impaired fetal growth. Further prospective studies with larger cohorts are warranted to develop robust predictive models for identification of neonatal growth anomalies.

Availability of Data and Materials

Raw data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

MD: Conceptualization, methodology, data collection, data analysis, literature review, original draft writing, review and editing, project management. ES: Methodology, data collection, formal analysis, original draft writing, review and editing. ÇY: Methodology, formal analysis, literature review, original draft writing, review and editing. SZ: Concept and design, data collection, review and editing. DEA: Concept and design, data collection, review and editing. All authors contributed to editorial changes in the manuscript. All authors have read and approved the final manuscript. All authors have been sufficiently involved in the work and agree to be responsible for all aspects of the work.

Ethics Approval and Consent to Participate

The design of this study was carried out in accordance with the guidelines of the Helsinki Declaration and was approved by the Kocaeli City Hospital Scientific Research Ethics Committee on September 12, 2024 (protocol number: 2024-109). All patients or their families/guardians gave their informed consent before participating in the study.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG49735.

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