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Efficacy of combined screening tests used in the first trimester in predicting adverse pregnancy outcomes

Ruken Dayanan [a,*], Gizem Aktemur [a], Betul Tokgoz Cakir [a], Gulsan Karabay [a], Ahmet Arif Filiz [a], Nazan Vanli Tonyali [a], Merve Ayas Ozkan [a], Dilara Duygulu Bulan [a], Mevlut Bucak [a], Hatice Ayhan [b], Ali Turhan Caglar [a]

[a] *Ankara Etlik City Hospital, Clinic of Obstetrics and Gynecology, Division of Perinatology, Ankara, Türkiye*
[b] *Ankara Etlik City Hospital, Clinic of Obstetrics and Gynecology, Ankara, Türkiye*
**Corresponding author: rukendayanan@gmail.com (Ruken Dayanan)*

MAIN POINTS

- First-trimester screening test parameters (PAPP-A, β-hCG, NT) show potential in predicting adverse pregnancy outcomes. Low PAPP-A levels were significantly associated with gestational diabetes mellitus, fetal growth restriction, and preeclampsia.
- NT values were significantly elevated in pregnancies complicated by gestational diabetes mellitus.
- Elevated β-hCG levels were significantly associated with preterm birth and placenta accreta spectrum or placenta previa.
- ROC analysis revealed predictive thresholds: PAPP-A <0.64 for preeclampsia (AUC=0.760), β-hCG >1.01 for PAS/PP (AUC=0.814), and NT >0.75 for GDM (AUC=0.588).
- PAPP-A emerged as the most consistent biomarker across multiple adverse pregnancy outcomes.

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ABSTRACT

Aim: This study aims to evaluate the predictive efficacy of first-trimester screening test parameters, including free β-human chorionic gonadotropin (β-hCG), pregnancy-associated plasma protein-A (PAPP-A), and nuchal translucency (NT), in identifying adverse pregnancy outcomes such as gestational diabetes mellitus (GDM), fetal growth restriction (FGR), preeclampsia, preterm birth, and placenta accreta spectrum (PAS) or placenta previa (PP).

Materials and Methods: A retrospective cohort analysis involved 776 pregnant women who underwent first-trimester screening tests between January 2023 and August 2024. Patients were categorized into two groups based on the presence or absence of pregnancy complications.

Results: Pregnancy complications were identified in 36.6% of participants, with GDM, FGR, and preterm birth being the most common. PAPP-A levels were significantly reduced in pregnancies complicated by GDM (p=0.033), FGR (p=0.048), and preeclampsia (p=0.001). NT values were notably elevated in GDM cases (p=0.016). Free β-hCG levels were significantly higher in preterm birth (p=0.040) and PAS/PP cases (p=0.016). ROC analysis revealed notable predictive thresholds: PAPP-A <0.64 for preeclampsia (AUC=0.760, p=0.001) and β-hCG >1.01 for PAS/PP (AUC=0.814, p=0.016).

Conclusion: First-trimester screening test parameters, particularly PAPP-A, NT, and β-hCG, exhibit potential in predicting adverse pregnancy outcomes. Reduced PAPP-A levels correlate with GDM, FGR, and preeclampsia, while elevated NT and β-hCG levels are associated with GDM and PAS/PP, respectively. Although these markers demonstrate promise, larger-scale prospective studies are needed to confirm their clinical utility and reliability in predicting pregnancy complications.

Keywords: First trimester screening, Pregnancy complications, Gestational diabetes mellitus, Preeclampsia, Fetal growth restriction, Placenta accreta spectrum

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INTRODUCTION

Pregnancy induces substantial physiological and biochemical alterations in the female body commencing with conception. The physiological pressure and stress induced by pregnancy may precipitate the early onset of chronic diseases in predisposed individuals. Increasing evidence indicates that pregnancy complications, including GHT, PE, GDM, preterm labor, and FGR, can adversely influence maternal and fetal outcomes and may have enduring detrimental effects on maternal and fetal health post-pregnancy. Notwithstanding several studies, there remains inadequate data to anticipate and avert poor pregnancy outcomes [1,2].

First-trimester examination Aneuploidy screening tests are

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the most prevalent assessments for predicting the delivery of a child with chromosomal abnormalities during early pregnancy and for forecasting potential adverse pregnancy outcomes. The procedure utilizes the characteristics of PAPP-A, free β-hCG, and fetal NT [3]. The application of multi-parameter tests to forecast adverse pregnancy outcomes relies on biomarkers and ultrasound results. Predicting problems during pregnancy is important for taking precautionary measures to reduce adverse outcomes, planning effective pregnancy follow-up, and managing care. It also involves referring high-risk pregnant women to specialized centers or experts.

While adverse pregnancy outcomes are classified as distinct clinical processes, it is a fact that they share common pathophysiological mechanisms. Aberrant placenta implantation is the common cause of FGR, preeclampsia, and placental diseases, including placenta previa and the accreta spectrum. GDM or maternal hyperglycemia is related with spontaneous abortion, macrosomia, congenital abnormalities, stillbirth, and maternal preeclampsia, similar to other adverse pregnancy outcomes [4]. PAPP-A, a component of this screening test, has been demonstrated in numerous studies to positively regulate insulin-like growth factors (IGF) and may be linked to GDM. Likewise, diminished levels of 1st Trimester PAPP-A have been correlated with abortion and low birth weight [5,6]. Similarly, data indicates that elevated free β-hCG levels in both the 1st and 2nd trimesters are correlated with preeclampsia, gestational hypertension, and fetal growth restriction [7,8].

Our study sought to examine the predictive efficacy of parameters utilized in the first trimester prenatal screening tests advised for all pregnant women concerning the spectrum of gestational hypertension, preeclampsia, gestational diabetes mellitus, fetal growth restriction, and placenta previa or accreta. We assert that our findings will assist doctors in forecasting these adverse pregnancy outcomes, which bear significant implications for both maternal and newborn health, and may enhance patient management.

MATERIALS AND METHODS

Study design

This retrospective cohort research encompassed patients who received first-trimester combined tests at Etlik City Hospital from January 2023 to August 2024. This study followed the Declaration of Helsinki on Research Involving Human Subjects and received approval from the hospital's Ethics Committee (approval number: AESH-EK1–2024-913). Due to the retrospective nature of the study data, informed consent was not acquired from the patients.

Study participants

The study included 776 participants who performed first-trimester combined tests. Patients who did not deliver at our facility were excluded from the study. Subsequently, patients were categorized into a control group comprising individuals without pregnancy complications, based on diagnoses of GDM, FGR, preterm labor, polyhydramnios, oligohydramnios, GHT, threatened preterm labor, imminent abortion, fetal anomaly, abortion, preeclampsia, intrauterine fetal demise, and placenta accreta spectrum or placenta previa.

The first-trimester combined test, which includes PAPP-A, f-βhCG, and nuchal translucency (NT), is performed around 11–14 weeks of gestation in our clinic. Demographic, clinical, laboratory, and ultrasonographic data from the cases were retrospectively obtained using the hospital data management system.

Definition of pregnancy complications

Gestational diabetes mellitus

In our clinic, two different methods are used to diagnose GDM during pregnancy: a single-stage 75-gram oral glucose tolerance test (OGTT) or a two-stage process. In the single-stage method, the fasting plasma glucose value should be below 92 mg/dL, the 1st hour value should be below 180 mg/dL, and the 2nd hour value should be below 153 mg/dL in the 75-gram OGTT performed between 24-28 weeks of pregnancy. If any of these values are high, GDM is diagnosed.

The two-stage approach commences with the administration of a 50-gram OGTT. Consequently, patients exhibiting plasma glucose levels of 130 mg/dL or higher undergo a 100-gram OGTT. The reference values for this test are established as 95 mg/dL for fasting, 180 mg/dL for the first hour, 155 mg/dL for the second hour, and 140 mg/dL for the third hour. GDM is diagnosed if a minimum of two out of these four values exceed the designated threshold values. These methods seek to guarantee the precise and reliable diagnosis of gestational diabetes [9].

Gestational hypertension

Gestational hypertension is defined by the International Society for the Study of Hypertension in Pregnancy (ISSHP) as hypertension that manifests after the 20th week of gestation, lacking the distinctive features of preeclampsia. This diagnosis defines hypertension as a systolic blood pressure (SBP) of 140 mmHg or greater, or a diastolic blood pressure (DBP) of 90 mmHg or greater. The differentiating characteristic of preeclampsia is the lack of symptoms unique to the condition, such proteinuria or organ dysfunction. Gestational hypertension is regarded as a significant issue impacting maternal health during pregnancy and necessitates vigilant monitoring [10].

Pre-eclampsia

Preeclampsia is a multifaceted condition that arises throughout gestation and is characterized by the emergence of novel symptoms. This syndrome is marked by hypertension, typically arising after the 20th week of gestation, accompanied by

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different indicators of organ malfunction. Indicators of organ dysfunction encompass proteinuria, compromised renal or hepatic function, coagulopathy, or fetal growth limitation. Preeclampsia is a significant pregnancy problem that requires vigilant monitoring and management post-diagnosis, since it may result in serious health issues for both the mother and the infant [11,12].

Preterm birth

Preterm birth is described as the delivery of an infant prior to the conclusion of the 37th week of gestation. The precise process causing spontaneous preterm birth remains mostly unclear in many instances. This syndrome is believed to possess a complex composition. Factors contributing to preterm birth encompass inflammation, uteroplacental ischemia or bleeding, uteroplacental infections, uterine overdistension, stress, and various immune system-mediated mechanisms. This syndrome is regarded as a significant obstetric issue necessitating thorough assessment and a multidisciplinary strategy due to its intricate etiology [13].

Fethal growth restiriction

The diagnosis of late-onset fetal growth restriction (FGR) was evaluated according to the Delphi Consensus Criteria. Accordingly, the diagnosis of fetal growth restriction was made when the abdominal circumference (AC) or estimated fetal weight (EFW) fell below the 3rd percentile. At least two additional criteria were required to make this diagnosis definitive. These criteria were as follows: (1) AC or EFW below the 10th percentile, (2) AC or EFW decreased by more than two quartiles, (3) Abnormalities were detected in Doppler ultrasound results. Among the Doppler abnormalities, the umbilical artery Doppler pulsatility index (PI) exceeding the 95% percentile or the cerebro-placental ratio (CPR) falling below the 5% percentile. The evaluation of these criteria together was applied to increase the accuracy of the FGR diagnosis [14].

Placenta accreta spectrum or placenta previa

Placenta previa refers to the presence of placental tissue that obstructs the internal cervical os. An unusual placental location may result in considerable antepartum, intrapartum, and/or postoperative uterine bleeding. Further sequelae include the requirement for cesarean delivery and an increased risk of preterm birth.

PAS denotes the abnormal infiltration of trophoblasts into the myometrium, sometimes reaching or surpassing the serosa. The clinical relevance is in the placenta's inability to detach spontaneously during delivery, with manual extraction efforts resulting in hemorrhage, which may be life-threatening and frequently necessitates hysterectomy. The pathogenesis of most cases of PAS is thought to include placental implantation at a location of compromised decidualization resulting from previous damage to the endometrial-myometrial interface. The principal risk factor for PAS is the existence of placenta previa subsequent to a prior surgical section [15].

Statistical analysis

Statistical analyses were conducted utilizing IBM SPSS version 22.0 (IBM Corporation, Armonk, NY, USA). Normality of the distribution was assessed separately for each group. The Shapiro–Wilk test was applied for subgroups with n<50, while the Kolmogorov–Smirnov test was used for larger groups ($n \geq 50$). Given that several adverse outcome subgroups had small sample sizes, primary comparisons were conducted using non-parametric tests (Mann–Whitney U), which are robust to non-normality. In addition, because no prospective sample size calculation was performed at study initiation, a post-hoc power analysis was performed using G*Power software (version xx, Universität Düsseldorf, Germany). Based on the observed effect sizes of our strongest associations (e.g., PAPP-A predicting preeclampsia, AUC=0.760; β-hCG predicting PAS/PP, AUC=0.814), the achieved power was calculated as 94.5% and 80.2%, respectively, at α=0.05. Endpoints with smaller AUCs (~0.58–0.59) yielded more limited power (≈53–70%). Descriptive statistics for continuous variables are presented as "mean ± standard deviation" for normally distributed data, and as "median (interquartile range)" for non-normally distributed data. Categorical variables were analyzed using the chi-squared test or Fisher's exact test. Continuous variables, both normally and non-normally distributed, were analyzed using the independent sample t-test and the Mann-Whitney U test, respectively. The receiver operating characteristic (ROC) curve was utilized to compute and compare the areas under the curve (AUC) and establish the optimal cutoff values. Statistical significance for all tests was established as a P-value of less than 0.05.

RESULTS

The research examined the correlation between first-trimester screening metrics and adverse pregnancy outcomes. A total of 776 pregnancies were assessed, of which 492 (63.4%) were uncomplicated, whereas 284 (36.6%) experienced at least one problem. The prevalence of adverse pregnancy outcomes are summarized in Table 1 and depicted in Figure 1. Common problems comprised gestational diabetes mellitus (9.3%), fetal growth restriction (6.3%), and premature delivery (5.9%). Significantly, certain patients encountered multiple problems concurrently.

A comparison of first-trimester screening parameters β-hCG, PAPP-A, and NT between pregnancies with problems and those without showed no significant difference in the total group analysis (Table 2). Nonetheless, subgroup studies revealed significant results for some problems. β-hCG levels were markedly elevated in instances of preterm birth (p=0.040) and placenta accreta spectrum (PAS) or placenta

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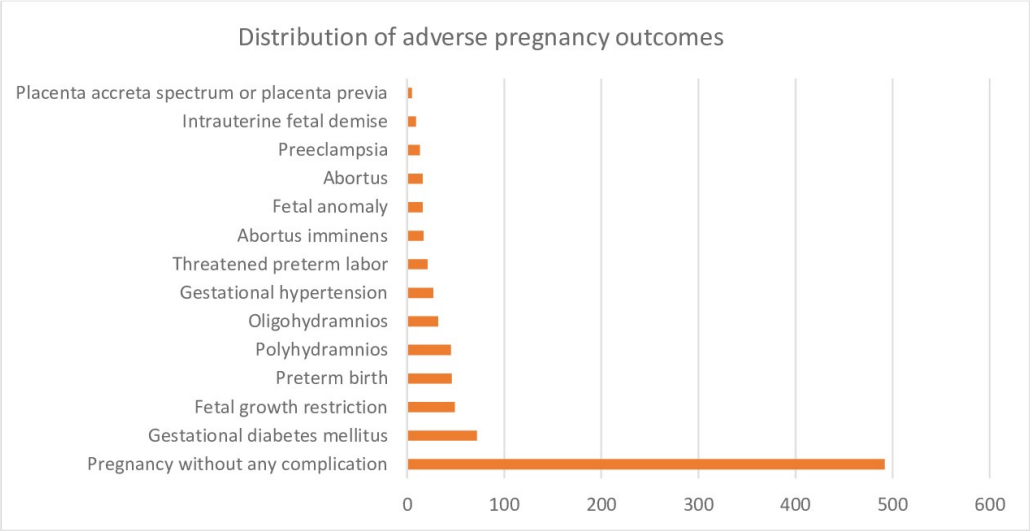

Figure 1. Distribution of adverse pregnancy outcomes.

previa (p=0.016) (Table 3). PAPP-A levels were markedly reduced in pregnancies affected by GDM (p=0.033), FGR (p=0.048), and preeclampsia (p=0.001) (Table 4). NT values were markedly elevated in pregnancies with gestational diabetes mellitus (p=0.016) (Table 5).

ROC analysis was conducted to evaluate the predictive significance of these indicators for specific problems (Table 6). Among the findings, NT with a cut-off value exceeding 0.75 predicted GDM with an area under the curve (AUC) of 0.588 (p=0.016). PAPP-A <0.79 correlated with gestational diabetes mellitus (AUC=0.578, p=0.033), while PAPP-A <0.82 forecasted fetal growth restriction (AUC=0.585, p=0.048). β-hCG >1.01 showed a moderate predictive value for PAS or placenta previa (AUC=0.814, p=0.016), but PAPP-A <0.64 exhibited significant predictive power for preeclampsia (AUC=0.760, p=0.001).

Table 1. Rate of adverse pregnancy outcomes observed.

Pregnancy without adverse outcomes	492 (63.4%)
Gestational diabetes mellitus	72 (9.3%)
Fetal growth restriction	49 (6.3%)
Preterm birth	46 (5.9%)
Polyhydramnios	45 (5.8%)
Oligohydramnios	32 (4.1%)
Gestational hypertension	27 (3.5%)
Threatened preterm labor	21 (2.7%)
Abortus imminens	17 (2.2%)
Fetal anomaly	16 (2%)
Abortus	16 (2%)
Preeclampsia	13 (1.6%)
Intrauterine fetal demise	9 (1.1%)
Placenta accreta spectrum or placenta previa	5 (0.6%)

*More than one pregnancy complication can occur simultaneously in the same patient. When calculating the rates associated with adverse pregnancy outcomes, each adverse outcome was calculated separately.

DISCUSSION

This study assessed the correlation between maternal free β-hCG, maternal PAPP-A, and NT values—parameters analyzed in the first trimester combined test —and various conditions including GDM, FGR, preterm labor, threatened preterm labor, GHT, preeclampsia, threatened miscarriage, intrauterine fetal demise, and placenta accreta spectrum or placenta previa. Maternal serum PAPP-A levels were dramatically reduced in individuals with GDM, FGR, and preeclampsia. We have found that NT MoM levels were markedly elevated solely in patients with GDM. We determined that free β-hCG maternal levels were markedly elevated in the cohort experiencing preterm labor and in patients with placenta accreta spectrum or placenta previa. These metrics are universally relevant across all centers, particularly those in poor countries, due to their simplicity and practicality.

The association between GDM, a prevalent perinatal complication, and PAPP-A, a parameter in the double test, has been extensively studied. PAPP-A levels have been demonstrated to be markedly reduced in GDM. Nonetheless, some research indicate that there is no correlation between dual test values and GDM [16,17]. A recent study by Yildiz et al. indicated that PAPP-A and Free β-hCG levels were markedly lower in the GDM group, but no significant change was observed for NT [3]. PAPP-A is a protease of insulin-like growth factor binding protein (IGFBP) that contributes to embryonic growth and development. Decreased PAPP-A levels are regarded as a marker of placental dysfunction and are correlated with FGR, preeclampsia, and chromosomal anomalies [18,19]. Simultaneously, research has corroborated the association between PAPP-A and metabolic disorders. Nonetheless, its association with GDM remains ambiguous. Kantomaa et al. conducted a study involving 4,697 pregnant women with GDM and discovered that levels of PAPP-A and

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Table 2. Comparison of parameters used for first trimester screening in groups with and without adverse pregnancy outcomes.

	Pregnancy with complication n=284 (36.6%)	Pregnancy without complication n= 492 (63.4%)	p-value
β-hcg mom	0.83 (0.87)	0.81 (0.76)	0.982[a]
PAPP-A mom	0.87 (0.69)	0.95 (0.71)	0.054[a]
NT mom	0.76 (0.26)	0.72 (0.27)	0.102[a]

[a]: Mann-Whitney U, β-hcg: Beta-human chorionic gonadotropin, PAPP-A: Pregnancy associated plasma protein A, NT: Nuchal translucency, mom: A multiple of the median.

Table 3. Comparison of β-hCG used for first trimester anomaly screening in groups with adverse pregnancy outcomes and those without adverse pregnancy outcomes.

	β-hcg mom	p-value*
Pregnancy without adverse outcomes	0.81 (0.76)	
Gestational diabetes mellitus	0.78 (0.75)	0.158[a]
Fetal growth restriction	0.79 (1.03)	0.991[a]
Preterm birth	0.99 (1.1)	**0.040[a]**
Polyhydramnios	0.87 (0.89)	0.288[a]
Oligohydramnios	0.70 (0.88)	0.144[a]
Gestational hypertension	0.85 (0.91)	0.529[a]
Threatened preterm labor	0.89 (0.62)	0.713[a]
Abortus imminens	0.82 (0.79)	0.787[a]
Fetal anomaly	0.70 (0.64)	0.091[a]
Abortus	0.71 (0.83)	0.078[a]
Preeclampsia	0.82 (1.31)	0.729[a]
Intrauterine fetal demise	0.84 (1.65)	0.724[a]
Placenta accreta spectrum or placenta previa	1.68 (1.07)	**0.016[a]**

* The given p values were found by comparing with the group that pregnancy without any adverse outcomes. β-hcg: Beta-human chorionic gonadotropin, mom: A multiple of the median.

Table 4. Comparison of PAPP-A used for first trimester anomaly screening in groups with adverse pregnancy outcomes and those without adverse pregnancy outcomes.

	PAPP-A mom	p-value*
Pregnancy without adverse outcomes	0.95 (0.71)	
Gestational diabetes mellitus	0.79 (0.58)	**0.033[a]**
Fetal growth restriction	0.77 (0.67)	**0.048[a]**
Preterm birth	0.88 (0.61)	0.713[a]
Polyhydramnios	1.08 (0.67)	0.352[a]
Oligohydramnios	0.85 (0.52)	0.134[a]
Gestational hypertension	0.89 (0.69)	0.928[b]
Threatened preterm labor	1.14 (1.11)	0.061[a]
Abortus imminens	1.18 (1.07)	0.427[a]
Fetal anomaly	0.89 (0.50)	0.284[a]
Abortus	0.77 (1.83)	0.348[a]
Preeclampsia	0.53 (0.35)	**0.001[a]**
Intrauterine fetal demise	0.85 (0.95)	0.473[a]
Placenta accreta spectrum or placenta previa	0.79 (0.38)	0.521[a]

* The given p values were found by comparing with the group that pregnancy without any adverse outcomes. PAPP-A: Pregnancy associated plasma protein A, mom: A multiple of the median.

free β-hCG were dramatically decreased, while NT MoM levels were markedly elevated in the GDM cohort [20]. Conflicting data exist regarding the relationship between NT and GDM. One study examined NT between insulin-dependent and insulin-free GDM pregnant women, revealing no statistically significant difference [21]. A study comparing normal pregnant women and those with GDM revealed no statistically significant change in NT [17]. Our investigation found no statistically significant difference in β-hCG levels between the GDM group and the control group. Nonetheless, PAPP-A levels were statistically considerably lower, while NT mom values were significantly greater exclusively in the GDM group among all adverse pregnancy outcomes.

Gestational hypertension and preeclampsia are significant contributors to maternal and neonatal morbidity and mortality, impacting 2-8% of pregnancies. Given the parallels in placental pathophysiology between FGR and the onset of GHT and preeclampsia, it is anticipated that analogous biomarkers will forecast both conditions [22]. A study revealed that PAPP-A and Free β-hCG levels were markedly reduced in pa-

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Table 5. Comparison of NT used for first trimester anomaly screening in groups with adverse pregnancy outcomes and those without adverse pregnancy outcomes.

	NT mom	p-value
Pregnancy without adverse outcomes	0.72 (0.27)	
Gestational diabetes mellitus	0.78 (0.28)	**0.016**[a]
Fetal growth restriction	0.74 (0.19)	0.999[a]
Preterm birth	0.76 (0.35)	0.121[a]
Polyhydramnios	0.75 (0.23)	0.266[a]
Oligohydramnios	0.70 (0.22)	0.444[a]
Gestational hypertension	0.78 (0.33)	0.546[a]
Threatened preterm labor	0.68 (0.14)	0.388[a]
Abortus imminens	0.80 (0.29)	0.114[a]
Fetal anomaly	0.67 (0.21)	0.207[a]
Abortus	0.66 (0.61)	0.795[a]
Preeclampsia	0.78 (0.23)	0.247[a]
Intrauterine fetal demise	0.81 (0.33)	0.267[a]
Placenta accreta spectrum or placenta previa	0.76 (0.19)	0.631[a]

* The given p values were found by comparing with the group that without adverse pregnancy outcomes. NT: Nuchal translucency, mom: A multiple of the median.

Table 6. Evaluation of first trimester screening parameters in predicting adverse pregnancy outcomes using ROC analysis.

	LR+	Cut-off*	Sensitivity	Specificity	AUC	%95 CI	P-value
NT mom (for GDM)	1.37	>0.75	58.3%	57.4%	0.588	0.52 -- 0.66	**0.016**
PAPP-A mom (for GDM)	1.28	<0.79	62.3%	51.4%	0.578	0.51 -- 0.65	**0.033**
PAPP-A mom (for FGR)	1.44	<0.82	60.1%	58.3%	0.585	0.50 -- 0.67	**0.048**
β-hcg mom (for PAS or Placenta previa)	2.13	>1.01	80%	62.6%	0.814	0.70 -- 0.93	**0.016**
β-hcg mom (for preterm birth)	1.35	>0.94	80%	62.6%	0.592	0.50 -- 0.68	**0.040**
PAPP-A mom (preeclampsia)	2.54	<0.64	78.4%	69.2%	0.760	0.62 -- 0.90	**0.001**

*Cut-off values were found according to Youden index. LR: Likelihood ratio, AUC: Area under the curve, CI: Confidence Interval, β-hcg: Beta-human chorionic gonadotropin, PAPP-A: Pregnancy associated plasma protein A, NT: Nuchal translucency, mom: A multiple of the median, GDM: Gestational hypertension, FGR: Fetal growth restriction, PAS: Placenta accreta spectrum

tients with proteinuric GHT and FGR [23]. Tul et al. discovered that only low levels of PAPP-A were linked to FGR. Nevertheless, they asserted that all other indicators were ineffective in predicting GHT [16]. In a separate investigation, PAPP-A and Free β-hCG levels were dramatically decreased in patients with preeclampsia, FGR, and placental abruption [24]. D'Antonio et al. also identified markedly reduced PAPP-A levels in pregnancies complicated by preeclampsia, FGR and preterm birth [25]. PAPP-A is a metric utilized in the first trimester preeclampsia risk assessment approach employed by the Fetal Medicine Foundation (FMF) [26]. A guideline issued by the Royal College of Obstetricians and Gynaecologists in 2024 advised that patients with PAPP-A values below 0.415 mom should get closer monitoring and ultrasound follow-up for FGR [27]. In our investigation, consistent with the existing literature, only PAPP-A levels were significantly decreased in the FGR and preeclampsia cohorts. The disparity in free β-hCG and NT maternal levels was not statistically significant in these conditions The PAPP-A level, a parameter of the second trimester screening test, may serve as an additional finding or supportive data for selecting patients to initiate low-dose aspirin [28] which is utilized for preeclampsia prophylaxis and has recently received strong evidence-based recommendations.

Preterm delivery is a prevalent pregnancy condition associated with negative mother and newborn outcomes. The incidence ranges from 7.8% to 12%, contingent upon the country, and results in several complications impacting around 15 million infants globally each year [29]. Numerous research has been undertaken to forecast preterm birth; however, no highly substantiated predictor has been identified to yet. The parameters of first-trimester combined tests have been extensively examined for predictive purposes, although the findings remain contentious. In a study, pregnant women who delivered at or before 34 weeks were compared with those who delivered at or after 37 weeks. Despite elevated levels of PAPP-A and Free β-hCG in the preterm birth cohort, this disparity was not statistically significant [16]. One study indicated that PAPP-A levels below 0.40 mom may be utilized for identifying FGR, preterm birth, and GHT [30]. Yildiz et al. discovered that only low PAPP-A levels were correlated with preterm labor [31]. Swiercz et al. demonstrated a link between Free β-hCG in the first trimester and low PAPP-A, as well as preterm birth [32]. In our investigation, preterm birth was statistically significant alone with elevated maternal β-hCG levels. The inconsistent results indicate that the use of these markers, whether individually or in combination, remains insufficiently accurate for predicting premature birth. More comprehensive research are required for this purpose.

Currently, the rising incidence of cesarean sections, coupled

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with the escalation of placenta previa and accreta spectrum instances, remain a significant worry for obstetricians. Despite numerous studies indicating that ultrasound may diagnose these placental diseases in the first and early second trimesters, the inability to identify a substantial proportion of them during these gestational periods is seen as a considerable issue [33–35]. Our investigation did not identify a link between PAPP-A and the placenta accreta spectrum (PAS) or placenta previa (PP) as reported in prior research [36,37]. A 2019 study revealed a strong link between PAPP-A levels and the extent of bleeding in patients with PAS; however, it also demonstrated no correlation between β-hCG levels and PAS compared to the control group [38]. Büke et al. discovered that elevated PAPP-A and β-hCG levels in the first trimester correlated with PAS [39]. In another investigation, a difference in β-hCG levels was noted between the control group and the PP group; however, this difference was not statistically significant. When comparing the PAS group to the control group, the disparity in both biochemical parameters was statistically significant, with the mean values being elevated for the PP and PAS groups [40]. In our investigation, the elevation of β-hCG in mothers of PP and PAS patients was substantially different from that of the control group. Nonetheless, similar to other studies, the limited sample size in our research is a challenge, necessitating larger investigations with further meta-analyses to enhance the reliability of these data.

Limitations

This study has several limitations. Although the overall sample size was relatively large, the number of cases with some rare outcomes (such as preeclampsia and PAS/PP) was limited, which may have affected the statistical power of these subgroup analyses. Furthermore, since no prospective sample size calculation was performed at the beginning of the study, we conducted a post-hoc power analysis. This revealed adequate power for the strongest associations (94.5% for PAPP-A and preeclampsia; 80.2% for β-hCG and PAS/PP), while outcomes with modest AUC values had limited power (~53–70%). This limitation may explain why some results were not statistically significant and highlights the importance of larger, prospective studies. In addition, as this was a retrospective design, prospective power analysis could not be performed. Finally, only univariable ROC analyses were conducted; multivariable models could not be applied due to case distribution. Future larger, prospective studies with multivariable approaches are needed to validate and strengthen these findings.

CONCLUSION

This study investigated the possible implications of biochemical indicators (free β-hCG, PAPP-A) and NT values obtained in the first-trimester combined test in predicting adverse pregnancy outcomes .Our findings indicated that PAPP-A levels were markedly reduced in problems such as GDM, FGR, and preeclampsia, whereas NT exhibited a considerable elevation correlated with GDM. Moreover, free β-hCG levels were considerably elevated in instances of preterm labor and PAS/PP cases. Consequently, the significance of forthcoming large-scale and high-evidence investigations is underscored to enhance the efficacy of these biochemical parameters in clinical applications. Screening test characteristics such as PAPP-A may be associated with certain adverse outcomes, but their incorporation into routine clinical practice requires confirmation in larger, prospective studies.

Ethics Committee Approval: This study followed the Declaration of Helsinki on Research Involving Human Subjects and received approval from the Etlik City Hospital's Ethics Committee (approval number: AESH-EK1–2024-913).

Informed Consent: Since the study was designed retrospectively, no written informed consent form was obtained from patients.

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