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Original Article

Obstetrics and Gynaecology Section

Role of First Trimester Screening Test Results (Beta-hCG, PAPP-A, Nuchal Translucency) in Predicting Fetal Growth Restriction: A Retrospective Study

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ABSTRACT

Introduction: Foetal Growth Restriction (FGR) is defined as the rate of foetal weight that is smaller compared to the week of gestation below 10 percentile. The increased prenatal mortality and morbidity associated with FGR make its detection all the more important. It can lead to serious perinatal complications, including prematurity, cerebral palsy, intrauterine foetal death, and neonatal mortality. Given the burden of FGR and the lack of reliable early screening tools, further studies are warranted to evaluate the predictive value of these widely used biomarkers.

Aim: The present study aimed to investigate the effectiveness of first trimester screening test results {Pregnancy-Associated Plasma Protein A (PAPP-A) and free β Human Chorionic Gonadotropin (free β-hCG), and foetal Nuchal Translucency thickness (NT)} in predicting patients with FGR.

Materials and Methods: The present retrospective study was carried out to assess 659 pregnant women diagnosed with FGR and an equal number of women with normal foetal development, all of whom delivered at the Health Sciences University Ankara Etlik Zübeyde Hanım Gynaecology Training and Research Hospital between February 2016 and June 2020. The investigation focused on comparing first trimester serum levels of PAPP-A, free β-hCG, and NT measurements to explore their potential link with FGR. Statistical analysis involved the use of an independent samples t-test or Mann-Whitney U test for continuous variables, based on their distribution, and the Chi-square test for categorical data. To determine the predictive value of PAPP-A, free β-hCG, and NT, Receiver Operating Characteristic (ROC) curve analysis was utilised. A p-value of less than 0.05 was considered indicative of statistical significance.

Results: The median age of pregnant women in the FGR group was 26 (18-43) years, and in the control group was 26 (18-42) years (p=0.206). Demographic data of both groups were similar. The mean free βhCG value was 46.53±36.28 ng/mL in the FGR group and 41.24±34.26 ng/mL in the control group (p=0.006). The mean PAPP-A value was 2.89±2.47 mIU/mL in the FGR group and 3.38±2.57 in the control group (p<0.001). In the FGR group, the mean value of Nuchal Translusens was 1.16±0.38 mm, the mean value of NT (MoM) was 0.75±0.24, and in the control group, the mean value of nuchal translusens was 1.23±0.36 mm, NT (MoM) mean value was 0.78±0.21 (p<0.001). Low PAPP-A (AUC=0.576, p<0,001) and NT values (AUC=0.570, p<0,001) and high free βhCG (AUC 0,576, p<0,001) levels were found to be associated with FGR.

Conclusion: The present study shows that FGR is associated with low PAPP-A, high free β-hCG, and low NT values in the first trimester. However, none of these parameters alone demonstrated sufficient predictive value for the early detection of FGR. These findings suggest that while early screening markers may reflect placental dysfunction, they should not be solely relied upon for FGR prediction in clinical practice.

Keywords: Beta-Human Chorionic Gonadotropin, Foetal Growth Retardation, Pregnancy-Associated Plasma Protein A, Placental insufficiency, Prenatal screening, Trophoblastic biomarkers, Ultrasound imaging

INTRODUCTION

The FGR is the inability of a foetus to reach its developmental and genetic potential in line with its gestational age [1,2]. The pathogenesis and prediction of FGR remain controversial. Among the several causes of FGR are preeclampsia, genetic abnormalities, environmental elements, and placental insufficiency [1,3,4]. Malperfusion, enhanced reactive oxygen species, cellular apoptosis, and endothelial dysfunction are all caused by increased vascular resistance in the placenta. These factors can lead to utero placental circulation being impaired, which in turn can result in FGR [5,6]. The diagnosis is typically made based on foetal measurement, which is determined by an Estimated foetal Weight (EFW) or abdominal circumference that is below the 10th percentile for gestational age, following established reference standards [7].

The increased prenatal mortality and morbidity associated with FGR make its detection all the more important. It can lead to serious perinatal complications, including prematurity, cerebral palsy, intrauterine foetal death, and neonatal mortality. Moreover, FGR affects long-term health issues, including a higher incidence of type 2 diabetes, obesity, and hypertension in adulthood [8,9]. Early biomarkers that could act as predictors of negative pregnancy outcomes, including FGR, have drawn increasing focus in recent years. Originally intended to estimate the risk of aneuploidies such as trisomy 21 and 18, the first trimester combined screening test consists of measuring foetal NT and maternal serum levels of PAPP-A and free β-hCG. Placental function indirectly affects these markers, which might reflect early abnormalities in placental development and trophoblast invasion [10-12].

Adverse pregnancy outcomes, including low birth weight, stillbirth, preterm birth, and FGR, have been linked to low levels of fetoplacental-derived PAPP-A and modified levels of trophoblast-derived free β-hCG [13-15]. Although increased NT has also been linked to structural malformations and chromosomal abnormalities, its possible function in reflecting placental haemodynamics is yet unknown. Moreover, abnormal NT values in fetuses with normal karyotype have also been associated with foetal growth disturbances and adverse perinatal outcomes [16].

Despite these associations, the clinical value of these first trimester markers in forecasting FGR is still unknown, and the results of earlier studies can vary. Variabilities in results arise from differences in study populations, gestational age at diagnosis, inclusion criteria, and FGR definition. While some studies show only modest or non-significant associations, others favour the use of low PAPP-A levels as a predictive marker for FGR [17,18]. Similarly, the role of free β-hCG and NT in FGR prediction remains debatable [19,20]. Identifying significant early predictors may contribute to risk stratification and closer surveillance of high-risk pregnancies in clinical practice.

Given the burden of FGR and the lack of reliable early screening tools, further studies are warranted to evaluate the predictive value of these widely used biomarkers. The present study aimed to compare pregnancies diagnosed with FGR to those with normal foetal growth to examine the relationship between first trimester screening markers (PAPP-A, free β-hCG, and NT) and FGR.

MATERIALS AND METHODS

The present retrospective case-control study was conducted between February 2016 and June 2020 at the Health Sciences University Ankara Etlik Zübeyde Hanım Gynaecology Training and Research Hospital (Ankara, Turkey). The study protocol was approved by the Institutional Ethics Committee (Protocol ID: 05/06/2020-08). The study was conducted in accordance with the universal ethical standards of the Declaration of Helsinki.

Inclusion and Exclusion criteria: Pregnant women aged 18-45 years with singleton pregnancies who applied for first trimester anomaly screening and delivered at the respected hospital were included. Those with FGR were assigned to the study group, while those without FGR were assigned to the control group. Exclusion criteria were multiple pregnancies, fetuses with aneuploidy or foetal anomaly, pre-existing diabetes mellitus, chronic kidney disease, endocrine disorders (hypothyroidism, hyperthyroidism, adrenal insufficiency), autoimmune or vascular diseases (systemic lupus erythematosus, Behçet's disease, vasculitis), cyanotic heart disease, chronic lung disease, sickle cell anaemia, and antiphospholipid antibody syndrome. Pregnancies with gestational hypertension, gestational diabetes mellitus, or preeclampsia, as well as those with missing first trimester screening test results, were also excluded from the study.

Sample size calculation The study included 659 pregnant women diagnosed with FGR as the study group and 659 pregnant women with normal foetal growth as the control group. The required sample size was determined using G*Power 3.1 software based on the adverse outcome rates reported by Kirkegaard I et al., which were 13.3% in the low PAPP-A group and 4.9% in the normal PAPP-A group [21]. To detect this difference with a two-tailed significance level of $\alpha = 0.05$ and a statistical power of $1-\beta = 0.95$, a z-test for difference between two independent proportions was used. Based on this effect size ($h \approx 0.29$), G*Power calculated that a minimum of 302 participants per group (total n = 604) would be required to achieve 95% power. The sample size in the current study (n = 659 per group) exceeded this requirement, ensuring sufficient power to detect the expected effect [21].

Study Procedure

The FGR was defined according to American College of Obstetricians and Gynecologists (ACOG) criteria as an EFW and/or abdominal circumference below the 10th percentile for gestational age [7]. Gestational age was determined based on the Crown-Rump Length (CRL) measured by early pregnancy ultrasonography. Patients with a CRL between 45 and 84 mm who agreed to undergo first trimester screening were evaluated by an Obstetrician, and concurrent blood samples were collected. NT was measured in millimetres with the foetus in a neutral longitudinal CRL position. Maternal blood samples collected on the same day were analysed for PAPP-A and free β-hCG levels. These values were converted to MoM values adjusted for maternal age, weight, and gestational age using the automated Siemens Immulite 2000xpi Prisca program.

Demographic information, including age, Body Mass Index (BMI) (kg/m²), gravidity, parity, number of abortions, number of living children, infant gender, mode of delivery, birth weight, and gestational age at delivery, was obtained from the hospital records system.

STATISTICAL ANALYSIS

Data analysis was performed using SPSS version 22.0 (Chicago, IL, USA). Descriptive statistics were presented as mean±standard deviation and median (25th-75th percentile) for continuous variables and as numbers and percentages for categorical variables. The normality of continuous variables was evaluated using the Shapiro-Wilk test. Continuous variables that did not meet the assumptions of parametric tests were compared between two groups using the Mann-Whitney U test. Logistic regression analysis was conducted to examine the relationship between first trimester screening markers and FGR. ROC analysis was used to assess the diagnostic value of these markers for FGR and to determine cut-off points. A p-value of <0.05 was considered statistically significant.

RESULTS

Significant differences were noted between the EFW <10th percentile group and controls in terms of gestational age at birth {37 weeks (29-41) vs. 38 weeks (37-41)}, mode of delivery (caesarean: 54.2% vs. 38.2%), and birth weight {median 2420 g (800-2990) vs. 3552 g (3040-4420)} (all p<0.001). A higher rate of female neonates was observed in the FGR group (55.7%, p<0.001) [Table/Fig-1].

Variables	EFW <10th Centile group (n=659)	Control group (n=659)	p-value
Maternal age in years, median (min-max)	26.0 (18.0 - 43.0)	26.0 (18.0 - 42.0)	0.206
BMI (kg/m²), Mean±SD	27.7±3,6	28.1±3.7	0.047
Gravida, median (min-max)	2 (1-6)	2.0 (1-7)	0.575
Parity, median (min-max)	1 (0-5)	1 (0-6)	0.520
Abort, median (min-max)	1 (0-5)	1 (0-4)	0.821
Gestational age at birth in weeks, median (min-max)	37 (29-41)	38 (37-41)	<0.001
Mode of delivery, n (%)			
SVD	302 (45.8%)	407 (61.8%)	<0.001
C-Section	357 (54.2%)	252 (38.2%)	
Birth weight (gr), median (min-max)	2420 (800-2990)	3552 (3040-4420)	<0.001
Neonatal gender, n (%)			
Male	292 (44.3%)	357 (54.2%)	<0.001
Female	367 (55.7%)	302 (45.8%)	

[Table/Fig-1]: Comparison of maternal and neonatal outcomes in Estimated Foetal Weight (EFW) below 10th percentile and control groups.
P<0.05 was considered statistically significant. Variables presented as median (25th–75th percentile) were compared using the Mann-Whitney U test; variables presented as mean±standard deviation were compared using the Student's t-test; and categorical variables presented as n (%) were analysed using the chi-square test.
EFW: Estimated Foetal weight; SD: Standard deviations; BMI: Body mass index; SVD: Spontaneous vaginal delivery; C-section: Caesarean section

Free β-hCG levels and MoM values were significantly higher in the FGR group (35.60 ng/mL vs. 33.40 ng/mL, p=0.006; MoM 1.00 vs. 0.91, p=0.004). PAPP-A levels and MoM values were significantly lower in the FGR group (2.17 vs. 2.65 mIU/mL; MoM 0.80 vs. 1.00; both p<0.001). NT and NT MoM values were also lower in the FGR group (NT: 1.10 mm vs. 1.20 mm; MoM: 0.71 vs. 0.75, p<0.001 for both) [Table/Fig-2].

Univariate logistic regression analysis [Table/Fig-3] showed significant associations between FGR and free β-hCG (OR: 1.004,

p=0.008), free β-hCG MoM (OR: 1.215, p=0.002), PAPP-A (OR: 0.922, p=0.001), PAPP-A MoM (OR: 0.770, p=0.001), NT (OR: 0.577, p=0.001), and NT MoM (OR: 0.538, p=0.019).

Biomarkers	Control Group (n:659)		FGR Group (n:659)		p-value
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	
Free β hCG (ng/mL)	41.24± 34.26	33.40 (21.50, 50.40)	46.53± 36.28	35.60 (23.80, 5.10)	0.006
Free β hCG (MoM)	1.13±0.85	0.91 (0.62, 1.40)	1.28±0.97	1.00 (0.66, 1.57)	0.004
PAPP-A (mIU/mL)	3.38±2.57	2.65 (1.69, 4.32)	2.89±2.47	2.17 (1.41, 3.76)	<0.001
PAPP-A (MoM)	1.17±0.69	1.00 (0.70, 1.47)	1.02±0.90	0.80 (0.56, 1.24)	<0.001
NT (mm)	1.23±0.36	1.20 (1.00, 1.40)	1.16±0.38	1.10 (0.90, 1.30)	<0.001
NT (MoM)	0.78±0.21	0.75 (0.64, 0.88)	0.75±0.24	0.71 (0.60, 0.84)	<0.001

[Table/Fig-2]: Comparison of first trimester biomarkers between FGR group and control group.
P<0.05 was considered statistically significant. Variables were compared using the Student's t-test.
IQR: Interquartile range; SD: Standard deviation; β hCG: Beta Human Chorionic Gonadotropin; PAPP-A: Pregnancy-Associated Plasma Protein A; NT: Nuchal translucency

Biomarkers	OR	%95 CI	p-value
Free β hCG (ng/mL)	1.004	1.001-1.008	0.008
Free β hCG (MoM)	1.215	1.071-1.378	0.002
PAPP-A (mIU/mL)	0.922	0.881-0.966	0.001
PAPP-A (MoM)	0.770	0.658-0.901	0.001
NT (mm)	0.577	0.423-0.787	0.001
NT (MoM)	0.538	0.327-0.886	0.019

[Table/Fig-3]: Univariate logistic regression analysis of first trimester biomarkers for FGR prediction.
P<0.05 was considered statistically significant.
OR: Odds ratio; CI: Confidence interval; β hCG: Beta human chorionic gonadotropin; PAPP-A: Pregnancy-associated plasma protein A; NT: Nuchal translucency

In ROC analysis [Table/Fig-4], PAPP-A MoM <0.81 had the highest predictive value with an AUC of 0.597 (95% CI: 0.567–0.628), 51.5% sensitivity, and 65.7% specificity (p<0.001). Other biomarkers showed modest performance, with AUCs ranging from 0.544 to 0.576.

Biomarkers	Cut-off value	AUC (% 95 CI)	Sensitivity	Specificity	p-value
Serbest β hCG (ng/mL)	>57.8	0.544 (0.513, 0.575)	24.1 %	83.0%	0.006
Serbest β hCG (MoM)	>1.15	0.546 (0.515, 0.577)	42.8%	65.3%	0.004
PAPP-A (mIU/mL)	<2.43	0.576 (0.545, 0.607)	57.1%	56.6%	<0.001
PAPP-A (MoM)	<0.81	0.597 (0.567, 0.628)	51.5%	65.7%	<0.001
NT (mm)	<1.15	0.570 (0.539, 0.601)	53.7%	58.4%	<0.001
NT (MoM)	<0.72	0.562 (0.531, 0.593)	54.0%	57.2%	<0.001

[Table/Fig-4]: Diagnostic performance of first trimester biomarkers for FGR prediction.
AUC significance was assessed using the DeLong test. P<0.05 was considered statistically significant.
AUC: Area under curve; CI: Confidence interval; β hCG: Beta Human Chorionic gonadotropin; PAPP-A: Pregnancy-associated plasma protein A; NT: Nuchal translucency

DISCUSSION

In the first trimester of pregnancy, the combination of foetal NT thickness, maternal serum PAPP-A, and free β-hCG levels is widely used for screening chromosomal abnormalities [12]. With in conflict with findings published in the literature, the use of these biomarkers in predicting FGR and pregnancy complications remains debatable [12,13,15].

The association between first trimester biomarkers and unfavorable pregnancy outcomes has been the subject of numerous studies. Morssink LP et al., found no association between first trimester PAPP-A and free β-hCG levels and adverse pregnancy outcomes in infants with birth weights below the 5th percentile [22]. On the other hand, Smith GCS et al., found a significant correlation between low PAPP-A levels and intrauterine foetal death, preterm birth, preeclampsia, and FGR [23]. In a similar vein, Pedersen JF et al., found a positive correlation between low PAPP-A and lower birth weight, suggesting that it is linked to unfavourable perinatal outcomes [24]. This was supported by Spencer K et al., who demonstrated that low maternal serum PAPP-A levels increased the risk of low birth weight and preeclampsia [12], and Pihl K et al., who found that lower PAPP-A and free β-hCG MoM values were associated with low birth weight and preterm birth in a large cohort [25].

In the present study, pregnancies complicated by FGR were found to have significantly lower PAPP-A levels. However, ROC curve analysis demonstrated that PAPP-A has limited diagnostic value (AUC: 0.576; 95% CI: 0.545-0.607), suggesting that PAPP-A alone is insufficient as a screening tool for FGR.

One of the most important markers of placental function during pregnancy is free β-hCG, a biomarker generated by the trophoblast. Numerous studies have connected low birth weight and FGR to elevated levels of free β-hCG [14,26]. According to Krantz D et al., free β-hCG levels below the first percentile predict FGR with a high specificity (99.2%) and a low sensitivity (2%) [14]. NT thickness is a well-established marker for chromosomal abnormalities, but it is also associated with other adverse pregnancy outcomes, such as foetal loss, structural anomalies, and preeclampsia [27,28]. Tsai MS et al., found a positive correlation between increased NT and gestational hypertension and preeclampsia [29]. NT measurements were significantly lower in the FGR group (OR: 0.577, p=0.001). Nevertheless, the ROC analysis showed that its sensitivity and specificity were inadequate to qualify it as a reliable diagnostic tool (AUC: 0.570). PAPP-A, free β-hCG, and NT are associated with FGR, despite their limited diagnostic capabilities. Combining these markers may help identify FGR in the early stages of pregnancy, particularly when considering known risk factors. To determine their applicability in clinical settings, more research is necessary.

The study has several strengths. The homogeneous patient group and large sample size help to improve the validity of the results. Using consistent ACOG criteria for FGR diagnosis, all data were collected from a single centre, providing methodological consistency.

Limitation(s)

As it was a retrospective study the potential to involve all possible confounders was restricted. Important variables such as maternal smoking, socioeconomic status, and nutrition were not included in the analysis. Prospective, multicenter studies are needed to more clearly establish the diagnostic value of first trimester markers. Incorporating molecular and genetic biomarkers into screening protocols may improve early detection. Combining biochemical and ultrasound parameters could support earlier identification of FGR and reduce pregnancy-related complications.

CONCLUSION(S)

First trimester biomarkers such as PAPP-A, free β-hCG, and NT have demonstrated a correlation with FGR. However, their effectiveness as independent screening tests continues to be limited in diagnostic performance. Although low levels of PAPP-A and elevated levels of free β-hCG have been associated with FGR, their sensitivity and specificity are insufficient for reliable early prediction. Additionally, while the diagnostic accuracy of NT remains suboptimal, it has been observed that NT readings are also lower in cases of FGR. The integration of these biomarkers with established clinical risk

factors may facilitate the early identification of FGR in light of these limitations. Early detection could potentially be enhanced through a comprehensive strategy that incorporates multiple biochemical and ultrasound markers, thereby diminishing pregnancy-related complications and improving neonatal outcomes.

Declarations

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. This manuscript is based on the thesis study of Aziz Kından and was conducted under the supervision of Prof. Dr. Salim Erkaya. It has not been previously published or submitted elsewhere for consideration.

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AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

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