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Original Research Article

Comparison of low level of pregnancy-associated plasma protein - A between first and early second trimester of pregnancy in intrauterine growth restriction

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ABSTRACT

Background: Intrauterine growth restriction (IUGR) is the failure of the fetus to reach its growth potential due to pathological factors, most commonly placental dysfunction and is a major contributor to perinatal morbidity and mortality worldwide. This study compares low maternal serum PAPP-A levels in the first and early second trimesters to predict IUGR risk. The aim of the study was to compare low levels of Pregnancy-Associated Plasma Protein-A (PAPP-A) between the first and early second trimesters of pregnancy in relation IUGR.
Methods: This prospective cohort study was conducted at the Department of Obstetrics and Gynecology, Dhaka Medical College Hospital in 2020, including 186 pregnant women (6–12 and 13–20 weeks gestation) to assess PAPP-A's predictive value for IUGR. Eligible healthy singleton pregnancies underwent blood PAPP-A testing and serial ultrasounds with Doppler. IUGR was diagnosed by fetal measurements and Doppler, with low PAPP-A defined as <0.5 MoM. Data analysis used SPSS with ROC curves.
Results: Most participants were aged 26–29 years. IUGR occurred in 17 (Group A) and 19 (Group B), with low PAPP-A in 12 and 13 cases, respectively. Low PAPP-A significantly predicted IUGR (RR: 10.73 and 9.03, $p<0.001$). Diagnostic performance was high in both trimesters (AUC>0.85, sensitivity>89%, specificity>69%). Serum PAPP-A is a reliable early predictor of IUGR.
Conclusions: Low maternal serum PAPP-A levels in early pregnancy moderately predict IUGR, with comparable accuracy in both first and early second trimesters.

Keywords: Intrauterine growth restriction, Pregnancy associated plasma protein-A, Trimester comparison

INTRODUCTION

IUGR, also known as fetal growth restriction, is defined as the failure of the fetus to meet its growth potential due to pathological factors, most commonly placental dysfunction.[1] It differs from the term small for gestational age (SGA) because while growth-restricted fetuses are generally SGA, 50–70% of SGA fetuses are constitutionally small and exhibit normal growth patterns consistent with maternal factors.[2] The most widely accepted definition of IUGR is a fetus with estimated weight below the 10th percentile and abdominal circumference (AC) below the 2.5th percentile for gestational age.[2,3] AC measurement has high specificity and sensitivity for IUGR diagnosis and a fetus is considered 'at risk' when AC is less than the 2.5th

percentile alongside low estimated fetal weight.[3,4] IUGR is a major contributor to perinatal morbidity and mortality worldwide, particularly in developing countries like Bangladesh, where low birth weight affects approximately 22.6% of infants.[5] Risk factors include early maternal age, poor socioeconomic status, anemia and nutritional deficiencies.[6] Accurate gestational dating, ideally by ultrasound between 8–13 weeks, is essential for IUGR diagnosis.[2] Fetal growth involves early cell hyperplasia followed by hypertrophy, processes influenced by placental function.[7] Impaired placental synthesis of nitric oxide and polyamines can contribute to IUGR, reflecting nutritional extremes.[8] Placental growth follows a sigmoid pattern with key maternal and vascular adaptations to sustain fetal nutrient delivery.[9] Early insults during the hyperplasia phase cause symmetrical IUGR, whereas later insults lead to asymmetrical growth restriction.[10] IUGR etiologies include maternal factors (hypertension, diabetes, malnutrition), fetal anomalies and placental insufficiency.[2]

PAPP-A, a placental and fetal protease, increases throughout pregnancy with a normal range≥0.5 MoM.[11] Low PAPP-A levels are associated with abnormal placentation and adverse perinatal outcomes including IUGR.[12,13] PAPP-A, produced by syncytiotrophoblasts, regulates insulin-like growth factors critical for placental growth and fetal development.[12] Early measurement of maternal serum PAPP-A in the first or early second trimester predicts risks such as fetal growth restriction, fetal demise, preterm birth and preeclampsia.[13] Several studies recommend including serum PAPP-A in early pregnancy screening for IUGR risk.[14,15] Malik et al found that PAPP-A levels<0.5 MoM significantly increase risks for preterm delivery, stillbirth and fetal growth restriction.[15] Similarly, low PAPP-A in early pregnancy correlates with elevated IUGR risk, with low birth weights reported in 24.1% of cases when PAPP-A<0.29 MoM.[15] Normal or elevated PAPP-A levels do not show this association.[3]

Given the high prevalence of IUGR and low birth weight infants in Bangladesh and similar settings, early prediction is critical.

This study aims to compare the predictive value of low maternal serum PAPP-A levels in the first and early second trimesters for identifying fetuses at risk of growth restriction, evaluating sensitivity, specificity, positive and negative predictive values and relative risk.

Objective

To compare low levels of PAPP-A between the first and early second trimesters of pregnancy in relation to IUGR.

METHODS

This prospective cohort study was conducted at the Department of Obstetrics and Gynecology, Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh, from January to December 2020. A total of 186 pregnant women were enrolled to evaluate the predictive value of PAPP-A levels for IUGR. Participants were divided into two groups based on gestational age at sampling Group A comprised 93 women in the first trimester (6-12 weeks) and Group B included 93 women in the early second trimester (13-20 weeks). Both groups were selected according to specific inclusion and exclusion criteria.

Inclusion criteria

Pregnant women in the first or early second trimester (6–20 weeks). Singleton pregnancies. Otherwise, healthy individuals. Provided informed consent

Exclusion criteria

Known fetal anomalies (structural or chromosomal). Multiple pregnancies. Pregnancies complicated by hypertension, anemia, endocrine disorders (e.g., diabetes, thyroid disease), malnutrition or other systemic illnesses. Maternal age <18 or >35 years.

After informed consent, participants underwent clinical assessments at booking and during follow-up visits. Blood samples (3 cc) were collected by venipuncture, processed and stored at –20°C until PAPP-A analysis, which was performed using the DRG PAPP-A ELISA kit. Results were expressed in mIU/l and converted to multiples of the median (MoM). Serial ultrasound examinations were conducted at 6–12 weeks (confirmation and dating), 18–22 weeks (anomaly scan, fetal growth, uterine artery Doppler), 26–28 weeks (fetal biometry, umbilical artery Doppler) and 30–32 weeks (IUGR confirmation, middle cerebral artery Doppler) at DMCH's Nuclear Medicine Department or certified private centers. IUGR was defined as fetal weight below the 10th percentile and abdominal circumference below the 2.5th percentile for gestational age, confirmed by ultrasound biometry and Doppler studies. Low PAPP-A was defined as <0.5 MoM and normal as ≥0.5 MoM. Key study variables included PAPP-A levels, gestational age and confounders such as maternal age, education and occupation.

Data were entered and analyzed using SPSS version 25. Categorical variables were compared using Chi-square or Fisher's exact tests and continuous variables with t-tests. Receiver operating characteristic (ROC) curve analysis assessed the predictive value of PAPP-A for IUGR, with calculations of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and relative risk (RR). Statistical significance was set at $p<0.05$.

Ethical approval was obtained from the Ethical Review Committee of Dhaka Medical College Hospital. The study complied with the Declaration of Helsinki and written informed consent was obtained from all participants.

RESULTS

Table 1 presents the socio-demographic characteristics of the respondents in Group A (6–12 weeks of gestation) and Group B (13–20 weeks). The mean age was similar between the groups (Group A: 25.51±4.36 years, Group B: 25.18±3.75 years), with no statistically significant difference (t = 0.541, p=0.589). Most participants in both groups were aged 26–29 years. The majority of respondents belonged to the middle socio-economic class in both groups (82.8% in Group A vs. 76.3% in Group B), with no significant difference (p=0.523). Educational status showed a significant variation (p=0.015), with more primary-level educated respondents in Group A and more secondary or higher-educated respondents in Group B. Occupational status also differed significantly (p=0.007), with a higher proportion of working women in Group B (41.9%) compared to Group A (22.6%). Table 2 displays the distribution of BMI categories in relation to PAPP-A levels among respondents in Group A (6–12 weeks) and Group B (13–20 weeks). In Group A, 35.3% of participants with normal BMI had low PAPP-A levels compared to 27.6% with normal PAPP-A. The proportion of overweight individuals was similar across low (64.7%) and normal (65.8%) PAPP-A categories. In Group B, a higher percentage of those with normal BMI had low PAPP-A levels (55.6%) than those with normal PAPP-A levels (32.0%). Overweight participants showed distributions of 38.9% (low PAPP-A) and 58.7% (normal PAPP-A). However, none of these associations were statistically significant (Group A: p=0.655, Group B: p=0.599).

Table 3 illustrates the association between PAPP-A levels and the occurrence of intrauterine growth restriction (IUGR) in Group A. Among participants with normal PAPP-A levels, 93.4% showed no evidence of IUGR, whereas 70.6% of those with low PAPP-A levels had IUGR. This difference was statistically highly significant (χ^2=38.104, p<0.001), indicating a strong association between low PAPP-A levels in early pregnancy and the development of IUGR. Table 4 presents the association between PAPP-A levels and intrauterine growth restriction (IUGR) in Group B. The majority of participants with normal PAPP-A levels (92.0%) did not develop IUGR. Conversely, 72.2% of those with low PAPP-A levels had IUGR. This association mirrors the findings from Group A and was statistically highly significant (χ^2=36.83, p<0.001), suggesting a strong link between low PAPP-A levels and IUGR in the second trimester as well.

Figure 1 illustrates the ROC curve analysis assessing the predictive value of serum PAPP-A levels for intrauterine growth restriction (IUGR) in Group A. The area under the curve (AUC) was 0.856 (p<0.001), indicating strong diagnostic accuracy during the first trimester. A PAPP-A cutoff value of 0.51 MoM provided a sensitivity of 93% and specificity of 71% for identifying IUGR. Table 5 summarizes the predictive value of low PAPP-A levels for detecting intrauterine growth restriction (IUGR) in both study groups. In Group A, the Positive Predictive Value (PPV) was 70.59%, indicating that approximately 71% of those with low PAPP-A developed IUGR. The Negative Predictive Value (NPV) was 93.42%, showing that over 93% with normal PAPP-A experienced normal fetal growth. In Group B, the PPV was 72.22% and the NPV was 92%, demonstrating comparable predictive accuracy for detecting IUGR in the second trimester.

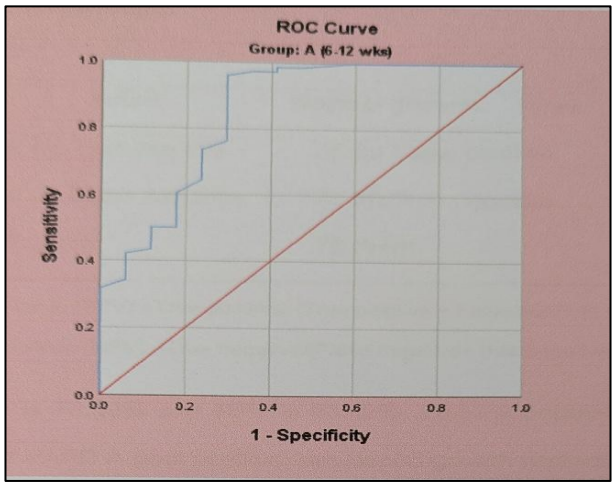

Figure 1: ROC curve analysis of PAPP-A for predicting IUGR in Group A (6–12 weeks gestation).

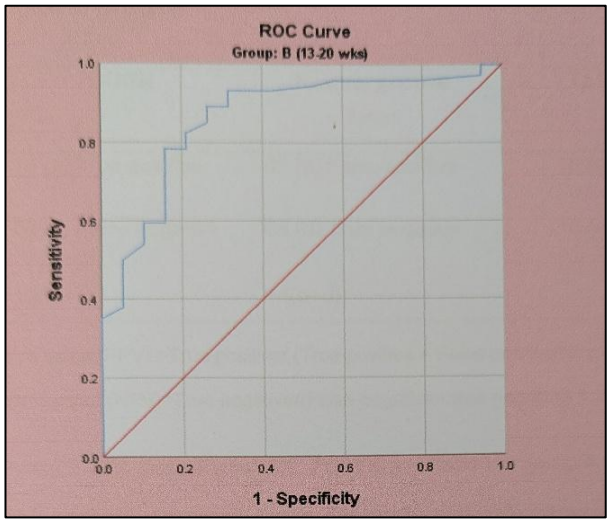

Figure 2: ROC curve analysis for PAPP-A in predicting IUGR in Group B (13–20 weeks).

Figure 2 illustrates the receiver operating characteristic (ROC) curve assessing the diagnostic value of serum PAPP-A levels for predicting intrauterine growth restriction (IUGR) in Group B (early second trimester) participants. The analysis revealed that PAPP-A is a significant predictor of IUGR, with an Area Under the Curve (AUC) of 0.865 and a p-value<0.001, indicating high diagnostic accuracy. The optimal cut off value for PAPP-A was determined to be 0.56, which provided a sensitivity of 89% and a specificity of 69% in

distinguishing IUGR cases from normal fetal growth. Table 6 presents the relative risk (RR) of intrauterine growth restriction (IUGR) in relation to low PAPP-A levels (<0.5 MoM) across two pregnancy intervals. In Group A (6–12 weeks), the risk of developing IUGR was 10.73 times higher in women with low PAPP-A compared to those with normal levels. Similarly, in Group B (13–20 weeks), the risk was 9.03 times higher in the low PAPP-A group, indicating a strong association between decreased PAPP-A and IUGR in both trimesters. Comparison of the diagnostic accuracy of low PAPP-A levels for predicting IUGR in early pregnancy between Group A (first trimester) and Group B (early second trimester). Group A showed a cut-off value of 0.51 MoM with sensitivity 93%, specificity 71%, PPV 70.59%, NPV 93.42% and relative risk (RR) of 10.73 (p<0.001). Group B demonstrated similar performance with a cut-off value of 0.56 MoM, sensitivity 89%, specificity 69%, PPV 72.22%, NPV 92% and RR of 9.03 (p<0.001).

A strong correlation between raised pulsatility index (PI) of the umbilical artery and low serum PAPP-A levels measured at 26–28 weeks of gestation. Women with low PAPP-A (<0.5 MoM) were 12.02 times more likely to have a raised PI compared to those with normal PAPP-A levels, indicating a significant association with compromised fetal blood flow.

Table 1: Distribution of the respondents by socio-demographic variables.

Variable		Group A (6–12 weeks)	Group B (13–20 weeks)	χ^2 / t-test	P value
Age distribution (in years)	Mean±SD	25.51±4.36	25.18±3.75	t=0.541	0.589
Socio-economic status	Lower	11 (11.8%)	14 (15.1%)	1.296	0.523
	Middle	77 (82.8%)	71 (76.3%)		
	Upper	5 (5.4%)	8 (8.6%)		
Educational status	Illiterate	2 (2.2%)	2 (2.2%)	9.673	0.015
	Can sign only	7 (7.5%)	15 (16.1%)		
	Primary	68 (73.1%)	48 (51.6%)		
	Secondary and above	16 (17.2%)	28 (30.1%)		
Occupation	Housewife	72 (77.4%)	54 (58.1%)	7.971	0.007
	Working	21 (22.6%)	39 (41.9%)		

Table 2: Distribution of BMI category by PAPP-A level in both groups.

Group	BMI category	Low PAPP-A (<0.5 MoM)	Normal PAPP-A (≥0.5 MoM)	χ^2 Test	P value
Group A (6–12 weeks gestation)	Normal	6 (35.3%)	21 (27.6%)	0.912	0.655
	Overweight	11 (64.7%)	50 (65.8%)		
	Obese	0 (0.0%)	5 (6.6%)		
Group B (13–20 weeks gestation)	Normal	10 (55.6%)	24 (32.0%)	3.479	0.599
	Overweight	7 (38.9%)	44 (58.7%)		
	Obese	1 (5.6%)	7 (9.3%)		

Table 3: Association between PAPP-A level and IUGR in Group A (6–12 weeks gestation).

IUGR status	Low PAPP-A (<0.5 MoM)	Normal PAPP-A (≥0.5 MoM)	χ^2 Test	P value
Absent	5 (29.4%)	71 (93.4%)	38.104	<0.001
Present	12 (70.6%)	5 (6.6%)		
Total	17 (100.0%)	76 (100.0%)		

Table 4: Association between PAPP-A level and IUGR in Group B (13–20 weeks gestation).

IUGR status	Low PAPP-A (<0.5 MoM)	Normal PAPP-A (≥0.5 MoM)	χ^2 Test	P value
Absent	5 (27.8%)	69 (92.0%)	36.83	<0.001
Present	13 (72.2%)	6 (8.0%)		
Total	18 (100.0%)	75 (100.0%)		

Table 5: Predictive performance of low PAPP-A levels for IUGR in Group A and Group B.

Group	PAPP-A Level	IUGR *(TP / FN)*	Normal Growth *(FP / TN)*	Total (a+b / c+d)
Group A (6–12 weeks)	Low	12 (a)–True positive	05 (b)–False positive	17 (a+b)
	Normal	05 (c)–False negative	71 (d)–True negative	76 (c+d)
	Total	17 (a+c)	76 (b+d)	
Group B (13–20 weeks)	Low	13 (a)–True positive	05 (b)–False positive	18 (a+b)
	Normal	06 (c)–False negative	69 (d)–True negative	75 (c+d)
	Total	19 (a+c)	74 (False positive+True negative)	

Table 6: Relative risk of developing IUGR in low PAPP-A levels during early pregnancy (Group A: 6–12 weeks, Group B: 13–20 weeks).

Pregnancy group	PAPP-A level	IUGR	Normal fetal growth	Total	RR=a/(a+b)/ c/(c+d)
Group A (8-12 weeks)	Low (<0.5 MoM)	12 (a)–True positive	05 (b)–False positive	17 (a+b)	10.73
	Normal (≥0.5 MoM)	05 (c)–False negative	71 (d)–True negative	76 (c+d)	
Group B (13-20 weeks)	Low (<0.5 MoM)	13 (a)–True positive	05 (b)–False positive	18 (a+b)	9.03
	Normal (≥0.5 MoM)	06 (c)–False negative	69 (d)–True negative	75 (False negative+True negative)	

Table 7: Comparison of diagnostic performance of PAPP-A for predicting IUGR between group A (6–12 weeks) and Group B (13–20 Weeks).

Group	Cut-off value (MoM)	Sensitivity	Specificity	PPV	NPV	Relative risk (RR)	P value
Group A (6–12 weeks)	0.51	93%	71%	70.59%	93.42%	10.73	<0.001
Group B (13–20 weeks)	0.56	89%	69%	72.22%	92.00%	9.03	<0.001

Table 8: Correlation between raised pulsatility index (PI) of umbilical artery and low serum PAPP-A levels at 26–28 weeks gestation.

Pulsatility index	Low PAPP-A (<0.5MoM)	Normal PAPP-A (≥0.5MoM)	RR=a/(a+b) / c/(c+d)
Raised PI	25 (13.4%) (True positive)	07 (3.76%) (False positive)	
Normal PI	10 (5.38%) (False negative)	144 (77.4%) (True negative)	12.02
Total	36 (18.78%)	150 (81.2%)	

DISCUSSION

This prospective cohort study aimed to evaluate the predictive value of pregnancy-associated plasma protein-A (PAPP-A) measured during the first and early second trimesters for the development of intrauterine growth restriction (IUGR). A total of 186 pregnant women attending the obstetrics and fetomaternal medicine outpatient department of Dhaka Medical College Hospital were included, divided equally into Group A (first trimester, 6–12 weeks) and Group B (early second trimester, 13–20 weeks). The mean ages of Group A and Group B were 25.51 (±4.36) and 25.18 (±3.75) years, respectively, with most patients aged 26–29 years (Group A: 36.6%, Group B: 43%). There was no statistically significant difference in age between the groups (p=0.589)

In follow-up, 18.3% of Group A and 20.4% of Group B developed IUGR. These findings align with Strobino et al who reported no association between maternal age and low birth weight, although extreme maternal age remains a recognized risk factor for IUGR.[16,17] Most participants were from the middle socioeconomic class. While earlier studies have linked lower socioeconomic status, maternal race and living in developing countries to increased risk of IUGR, this study did not observe a significant association, possibly due to the relatively small sample size.[6] Regarding body mass index (BMI), a notable proportion of women with low PAPP-A levels were overweight 64.7% in Group A and 58.7% in Group B while normal

BMI was observed in 35.3% and 55.6% respectively. This concurs with Radulescu et al who reported a higher incidence of IUGR among obese patients.[19] In both groups, most patients who developed IUGR had low PAPP-A levels, with some false positives and false negatives noted. Specifically, 12 patients in Group A and 13 in Group B had low PAPP-A, meanwhile, five patients in each group with low PAPP-A showed normal fetal growth (false positives) and five (Group A) and six (Group B) patients with normal PAPP-A developed IUGR (false negatives). The predictive power of serum PAPP-A for IUGR was highly significant ($p<0.001$), with relative risks of 10.73 in the first trimester and 9.03 in the early second trimester. Receiver operating characteristic (ROC) curve analysis showed PAPP-A as a strong predictor in both trimesters (AUC=0.856 and 0.865, respectively, $p<0.001$). The optimal PAPP-A cutoff in the first trimester was 0.51 MoM, yielding 93% sensitivity, 71% specificity, 70.59% positive predictive value (PPV) and 93.42% negative predictive value (NPV). This corresponds with findings by Patil et al who reported increased IUGR risk with PAPP-A<0.5 MoM (PPV 14%, OR 2.7).

In the early second trimester, the cutoff was 0.56 MoM, with 89% sensitivity, 69% specificity, 72.22% PPV and 92% NPV. Bersinger et al similarly identified low PAPP-A (13–17 weeks) as significantly associated with fetal growth restriction ($p<0.001$).[19] Gupta et al also reported an odds ratio of 7.83 for fetal growth restriction with PAPP-A<0.4 MoM.[20] These results are in line with Agarwal et al who reported a cutoff of 0.45 MoM for PAPP-A predicting IUGR with 92.6% specificity and 56.2% PPV.[21] Fox et al documented birth weights <10th centile in 47.8% of cases with PAPP-A <5th centile, supporting the association between low PAPP-A and growth restriction.[22]

False-negative rates in this study (5.38% in Group A and 6.45% in Group B) were consistent with Patil et al who observed 4.8% IUGR in patients with normal PAPP-A (>0.5 MoM).[23] Cooper et al noted that low PAPP-A (<0.4 MoM) combined with elevated uterine artery Doppler pulsatility index (PI > 1.45) increased FGR risk in 36–64% of patients.[24] The Genetics Committee of the Society of Obstetrics and Gynaecologists of Canada similarly linked unexplained low PAPP-A (<0.4 MoM) to higher adverse outcome rates, including IUGR.[25] Ekin et al reported that PAPP-A levels in the lowest 5th percentile at 8–14 weeks gestation increased IUGR risk (OR 2.9).[26]

Mader et al demonstrated a correlation between fetal growth rate from the first to second trimester and PAPP-A levels, with values below 0.3 MoM associated with growth rates below the 10th percentile (adjusted OR 2.05).[27] Smith et al, also reported that PAPP-A levels below the 5th centile at 8–14 weeks were associated with IUGR (OR 2.9).[28] Hoseini et al found low PAPP-A at 11–14 weeks correlated with fetal growth restriction ($r=0.442$, $p<0.001$) with 80.9% sensitivity and 85% specificity at a cutoff of 0.75 MoM.[29]

Sonographic biometric fetal measurements, including Doppler studies of uterine, umbilical and middle cerebral arteries, were used to diagnose IUGR alongside clinical examination. Raised pulsatility indices in the uterine artery (relative risk (RR) 3.92) and umbilical artery (RR 12.02) and low pulsatility index in the middle cerebral artery (RR 5.85), were strongly associated with low maternal serum PAPP-A levels (>0.5 MoM). Fetal biometric parameters such as head circumference to abdominal circumference ratio (HC/AC), femoral length to abdominal circumference ratio (FL/AC), amniotic fluid index (AFI), placental grading and estimated fetal weight (EFW) also showed significant relationships with low maternal PAPP-A, reinforcing the role of this biomarker in predicting fetal growth restriction.

The study had several limitations like sample size was a major constraint. Data were collected from a single center (DMCH), limiting the generalizability of the findings. The study was conducted during the COVID-19 pandemic, which restricted the scope and exploration of additional variables. Opportunities for broader data collection and extended analysis were missed due to pandemic-related disruptions.

CONCLUSION

In the current study, maternal serum PAPP-A levels were measured during the first and early second trimesters among OPD patients at Dhaka Medical College Hospital. During follow-up, 18.3% and 20.4% of fetuses developed IUGR in the two groups, respectively. Most IUGR cases had low PAPP-A levels in early pregnancy, with positive predictive values of 70.59% and 72.22%, respectively. The sensitivity and specificity of this biomarker were approximately 90% and 70% in both groups. Thus, low serum PAPP-A levels in early pregnancy have a moderate predictive value for IUGR, which was similar across both groups.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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