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Original Article

Low Pregnancy-Associated Plasma Protein A as a Predictor of Delivery Timing in Intrauterine Growth Restriction and Fetal Growth Variations: A Prospective Study

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ABSTRACT

Background: Low pregnancy-associated plasma protein-A (PAPP-A) reflects impaired placental function and has been associated with fetal growth abnormalities and adverse pregnancy outcomes. However, its relationship with delivery timing among pregnancies complicated by intrauterine growth restriction (IUGR) and fetal growth variations remains insufficiently characterized. **Aim of the study:** To determine the association of low PAPP-A with delivery timing in pregnancies complicated by IUGR and fetal growth variations. **Methods & Materials:** A prospective observational study was conducted among 96 pregnant women with suspected or confirmed IUGR or fetal growth variation at a tertiary-level hospital in Bangladesh. Maternal, obstetric, fetal, biochemical, and delivery data were collected prospectively until delivery. Serum PAPP-A was expressed as multiples of the median (MoM), with <0.4 MoM categorized as low. Delivery timing was classified as <34, 34–36, and ≥37 weeks, and multivariable logistic regression was performed to identify factors independently associated with preterm delivery. **Results:** The mean maternal age was 27.1±4.6 years, and the mean gestational age at enrollment was 32.5±2.7 weeks. IUGR was present in 60.4% of participants, while 38.5% had abnormal umbilical artery Doppler findings. Low PAPP-A was identified in 40.6% of participants, with a mean PAPP-A level of 0.58±0.31 MoM. Overall, 58.3% delivered preterm, including 27.1% before 34 weeks. Delivery timing differed significantly by PAPP-A status (p=0.003), with delivery before 34 weeks occurring in 43.6% of women with low PAPP-A compared with 15.8% with normal PAPP-A. Low PAPP-A was independently associated with preterm delivery (aOR 4.36, 95% CI 1.65–11.54; p=0.003), alongside abnormal umbilical artery Doppler and IUGR. **Conclusion:** Low PAPP-A was independently associated with earlier delivery and preterm birth among pregnancies complicated by IUGR and fetal growth variations. Pregnancy-associated plasma protein-A; PAPP-A; intrauterine growth restriction; fetal growth restriction; preterm delivery

Keywords: *Pregnancy-associated plasma protein-A; PAPP-A; intrauterine growth restriction; fetal growth restriction; preterm delivery.*

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INTRODUCTION

Fetal growth restriction (FGR), also termed intrauterine growth restriction (IUGR), is a condition in which a fetus fails to achieve its genetically determined growth potential because of maternal, fetal, or placental factors. It is distinct from a constitutionally small fetus because pathological growth restriction is associated with increased perinatal morbidity and mortality [1,2]. Globally, up to 10% of pregnancies are affected by fetal growth restriction, which is a major contributor to perinatal morbidity and mortality [1]. In Bangladesh, 39.2% of term infants were classified as small for gestational age below the 10th percentile [3]. Normal fetal growth requires adequate maternal perfusion, placental development, and efficient transfer of oxygen and nutrients across the placenta. Abnormal maternal vascular adaptation can impair placental perfusion and produce placental insufficiency. Reduced placental function limits fetal oxygen and nutrient supply and can lead to progressive growth restriction [2,4]. Placental dysfunction can also alter the maternal biochemical profile and contribute to abnormal fetal growth through impaired trophoblast function and vascular development [4,5]. Pregnancy-associated plasma protein-A (PAPP-A) is a placental protein released into the maternal circulation during pregnancy [5]. It acts as an insulin-like growth factor binding protein-4 protease and increases local insulin-like growth factor activity at the maternal-fetal interface [5,6]. Altered PAPP-A concentration therefore reflects aspects of placental function and has been associated with impaired fetal growth and adverse pregnancy outcomes [7,8]. FGR is associated with preterm birth, low birth weight, fetal compromise, neonatal intensive care admission, and perinatal death [1,2,7]. The clinical course can vary from mild growth deviation to progressive placental insufficiency with abnormal fetal Doppler findings and hypoxic deterioration. Management requires serial assessment of fetal growth and fetal well-being. Umbilical artery Doppler and cardiotocography are important components of surveillance after FGR is diagnosed [1]. The timing of delivery is particularly important because continued intrauterine exposure to placental insufficiency can increase fetal risk, while early delivery can increase complications related to prematurity. This balance is challenging with placental dysfunction or deteriorating fetal status in FGR [1,9]. Low PAPP-A has the advantage of being measurable during routine first-trimester biochemical screening and can provide an early indication of abnormal placental function before clinically apparent fetal growth restriction [5,7]. Low PAPP-A is associated with SGA, FGR, preterm birth, and earlier gestational age at delivery [7,8,10]. However, PAPP-A alone has limited screening performance and cannot determine delivery timing independently [8]. Its clinical relevance is therefore greater when considered in relation to fetal growth and subsequent obstetric outcomes. Despite the established association between low PAPP-A and impaired fetal growth, the relationship between PAPP-A concentration and the actual timing of delivery among pregnancies with IUGR and fetal growth variations remains insufficiently characterized. Data from Bangladesh are also limited regarding whether low maternal PAPP-A is associated with gestational age at delivery in pregnancies with abnormal fetal growth. The present study aimed to determine the association of low pregnancy-associated plasma protein A with delivery timing in pregnancies complicated by intrauterine growth restriction and fetal growth variations.

METHODS & MATERIALS

This prospective observational study was conducted in Department of Clinical Pathology, Mugda Medical College, Dhaka, Bangladesh during the study period from July 2024 to June 2025. A total of 96 eligible pregnant women were enrolled

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consecutively and followed prospectively until delivery.

Inclusion Criteria

- Pregnant women aged 18–40 years with a viable singleton pregnancy.
- Women with suspected or confirmed IUGR or fetal growth variation based on clinical assessment and obstetric ultrasonography.
- Women at ≥28 weeks of gestation at enrolment.
- Women who underwent PAPP-A assessment during the study period.

Exclusion Criteria

- Women with multiple pregnancy.
- Women with known major fetal congenital or chromosomal anomalies.
- Women with incomplete PAPP-A or relevant obstetric records.
- Women unwilling to provide informed consent.

Ethical Considerations

The study protocol was reviewed and approved by the appropriate institutional ethics committee before commencement. Written informed consent was obtained from all participants after explaining the study objectives, procedures, potential benefits, and confidentiality measures. Participation was voluntary, and participants were informed of their right to withdraw at any stage without affecting their medical care. Personal identifiers were excluded from the analytical dataset, and confidentiality of all collected information was maintained throughout the study.

Data Collection

Data were collected prospectively using a structured data collection form. Sociodemographic and maternal variables included age, residence, parity, and antenatal care status. Obstetric and fetal variables included gestational age at enrolment, pregnancy type, IUGR status, estimated fetal weight, umbilical artery Doppler findings, oligohydramnios, and fetal growth variation. Participants were followed until delivery, and gestational age at delivery and mode of delivery were recorded. Neonatal outcome data, including NICU admission, were also documented.

Assessment of PAPP-A and Fetal Growth

Maternal serum PAPP-A was assessed using the available standardized laboratory assay and expressed as multiples of the median (MoM), adjusted according to gestational age and relevant maternal characteristics where applicable. A PAPP-A level <0.4 MoM was considered low, while a level ≥0.4 MoM was considered normal. Fetal growth was assessed using obstetric ultrasonography, including estimated fetal weight and gestational-age-specific growth parameters. IUGR was identified according to predefined obstetric criteria. Estimated fetal weight below the 10th percentile, abnormal umbilical artery Doppler, and oligohydramnios were recorded as fetal growth-related findings.

Assessment of Delivery Timing

Delivery timing was categorized as <34 weeks, 34–36 weeks, and ≥37 weeks of gestation. Overall preterm delivery was defined as delivery before 37 completed weeks of gestation. The primary outcome was timing of delivery, particularly preterm delivery, while secondary outcomes included delivery before 34 weeks, IUGR, birth weight below the 10th percentile, abnormal umbilical artery Doppler, oligohydramnios, and NICU admission.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 26.0. Continuous variables were expressed as mean ± standard deviation, while categorical variables were summarized as frequencies and percentages. Associations between PAPP-A status and categorical obstetric or fetal outcomes were assessed using the chi-square test or Fisher's exact test where appropriate. Logistic regression analysis was performed to estimate crude and adjusted odds ratios (aORs) with 95% confidence intervals (CIs) for factors associated with preterm delivery. Variables considered clinically relevant were included in the multivariable model. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

The mean maternal age was 27.1±4.6 years, with 39.6 aged 25–29 years, while 0.2% each were aged <25 and ≥30 years. Rural residence was reported in 56.2% participants and urban residence in 43.8%. Most participants were primigravida (59.4%), and 70.8% received regular antenatal care. Multigravida women accounted for 40.6%, while 29.2% had irregular antenatal care (*Table I*).

Table I

Sociodemographic and maternal characteristics of the participants (*n*=96).

Variables	Frequency (n)	Percentage (%)
Age (years)		
<25	29	30.2
25–29	38	39.6
≥30	29	30.2
Residence		
Urban	42	43.8
Rural	54	56.2
Parity		
Primigravida	57	59.4
Multigravida	39	40.6
Antenatal care		
Regular	68	70.8
Irregular	28	29.2
Maternal age (years)		
Mean ± SD	27.1 ± 4.6	

The mean gestational age at enrolment was 32.5±2.7 weeks; 44.8% participants were enrolled at 32–34 weeks, 32.3% at 28–31 weeks, and 22.9% at ≥35 weeks. IUGR was present in 60.4% participants, while 39.6% had no IUGR. Estimated fetal weight below the 10th percentile was observed in 56.3%, abnormal umbilical artery Doppler in 38.5%, and oligohydramnios in 30.2%. Fetal growth variation without IUGR was identified in 39.6% participants. All pregnancies were singleton (100.0%) (*Table II*).

Table II
Obstetric and fetal characteristics of the participants (*n*=96).

Variables	Frequency (n)	Percentage (%)
Gestational age at enrolment (weeks)		
Mean ± SD	32.5 ± 2.7	
28–31	31	32.3
32–34	43	44.8
≥35	22	22.9
IUGR		
Yes	58	60.4
No	38	39.6
Estimated fetal weight <10th percentile		
Yes	54	56.3
No	42	43.7
Abnormal umbilical artery Doppler		
Yes	37	38.5
No	59	61.5
Oligohydramnios		
Yes	29	30.2
No	67	69.8
Fetal growth variation without IUGR		
Yes	38	39.6
No	58	60.4
Pregnancy type		
Singleton	96	100.0
Multiple	0	0.0

Low PAPP-A (<0.4 MoM) was identified in 40.6% participants, whereas 59.4% had PAPP-A ≥0.4 MoM. The mean PAPP-A level was 0.58±0.31 MoM (*Table III*).

Table III
Distribution of PAPP-A levels among the study participants (*n*=96).

PAPP-A status	Frequency (n)	Percentage (%)
Low PAPP-A (<0.4 MoM)	39	40.6
Normal PAPP-A (≥0.4 MoM)	57	59.4
Mean ± SD (MoM)	0.58 ± 0.31	

The mean gestational age at delivery was 34.8±2.6 weeks. Delivery occurred before 34 weeks in 26 (27.1%), at 34–36 weeks in 31.2%, and at ≥37 weeks in 41.7%. Overall, 58.3% had preterm delivery and 41.7% delivered at term. Caesarean section was performed in 70.8% and vaginal delivery in 29.2% participants (*Table IV*).

Table IV
Delivery characteristics of the study participants (*n*=96).

Variables	Frequency (n)	Percentage (%)
Delivery timing		
<34 weeks	26	27.1
34–36 weeks	30	31.2
≥37 weeks	40	41.7
Overall delivery status		
Preterm delivery (<37 weeks)	56	58.3
Term delivery (≥37 weeks)	40	41.7
Mode of delivery		
Caesarean section	68	70.8
Vaginal delivery	28	29.2
Gestational age at delivery (weeks)		
Mean ± SD	34.8 ± 2.6	

Delivery timing differed significantly according to PAPP-A status (p=0.003). Among women with low PAPP-A, delivery occurred at <34 weeks in 43.6%, at 34–36 weeks in 35.9%, and at ≥37 weeks in 20.5%. Corresponding values among women with normal PAPP-A were 15.8%, 28.1%, and 56.1%, respectively (*Table V*).

Table V
Delivery timing according to PAPP-A status (*n*=96).

Variables	Low PAPP-A (n=39)		Normal PAPP-A (n=57)		p-value
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)	
<34 weeks	17	43.6	9	15.8	0.003
34–36 weeks	14	35.9	16	28.1	
≥37 weeks	8	20.5	32	56.1	

Low PAPP-A was associated with IUGR (aOR 3.44, 95% CI 1.39–8.50; p=0.007), birth weight <10th percentile (aOR 3.03, 95% CI 1.25–7.35; p=0.013), abnormal UA Doppler (aOR 2.48, 95% CI 1.04–5.90; p=0.040), and NICU admission (aOR 2.66, 95% CI 1.13–6.27; p=0.025). The association with oligohydramnios was not statistically significant (aOR 2.36, 95% CI 0.95–5.84; p=0.064). Delivery before 34 weeks was also associated with low PAPP-A (aOR 4.12, 95% CI 1.60–10.60; p=0.003), whereas delivery at 34–36 weeks was not (aOR 1.43, 95% CI 0.57–3.55; p=0.446) (*Table VI*).

Table VI
Association of maternal, fetal characteristics and low PAPP-A with preterm delivery (*n*=96).

Outcome	Low PAPP-A (n=39)		Normal PAPP-A (n=57)		aOR	95% CI	p-value
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)			
IUGR	30	76.9	28	49.1	3.44	1.39–8.50	0.007
Birth weight <10th percentile	28	71.8	26	45.6	3.03	1.25–7.35	0.013
Abnormal UA Doppler	20	51.3	17	29.8	2.48	1.04–5.90	0.04
Oligohydramnios	16	41.0	13	22.8	2.36	0.95–5.84	0.064
NICU admission	23	59.0	20	35.1	2.66	1.13–6.27	0.025
Delivery <34 weeks	17	43.6	9	15.8	4.12	1.60–10.60	0.003
Delivery 34–36 weeks	14	35.9	16	28.1	1.43	0.57–3.55	0.446

In multivariable analysis, low PAPP-A remained independently associated with preterm delivery (aOR 4.36, p=0.003). Abnormal UA Doppler (aOR 2.87, p=0.028) and IUGR (aOR 3.21, p=0.014) were also independently associated with preterm delivery, whereas maternal age ≥30 years, primigravida status, and oligohydramnios were not statistically significant (*Table VII*).

Table VII
Multivariable logistic regression analysis of factors associated with preterm delivery (*n*=96).

Predictor	aOR	95% CI	p-value
Low PAPP-A (<0.4 MoM)	4.36	1.65–11.54	0.003
Maternal age ≥30 years	1.42	0.59–3.44	0.432
Primigravida	1.31	0.55–3.12	0.543
Abnormal UA Doppler	2.87	1.12–7.35	0.028
IUGR	3.21	1.27–8.13	0.014
Oligohydramnios	1.76	0.68–4.57	0.245

DISCUSSION

Low maternal PAPP-A is associated with earlier delivery among pregnancies complicated by IUGR and fetal growth variation, consistent with evidence linking reduced PAPP-A to impaired placental function, fetal growth restriction, and preterm birth [11]. The maternal profile showed a mean age of 27.1±4.6 years, with 59.4% of women being primigravida and 56.2% residing in rural areas. Similar study was reported by Dane et al. reported a mean maternal age of approximately 27 years in women evaluated for subsequent preterm delivery, while low-PAPP-A and normal-PAPP-A groups had comparable demographic characteristics [12]. Gupta et al also reported a relatively young population, with mean ages of 25.42 years among women with low PAPP-A and 24.33 years among controls [13]. IUGR was present in 60.4%, estimated fetal weight below the 10th percentile in 56.3%, abnormal umbilical artery Doppler in 38.5%, and oligohydramnios in 30.2%. These findings are consistent with Cignini et al., in a prospective study of 3332 pregnancies, found that very low PAPP-A concentrations were significantly associated with SGA, supporting the relationship between placental biochemical abnormalities and impaired fetal growth [14]. Similarly, Baer et al., using data from more than 134,000 pregnancies, demonstrated that decreasing PAPP-A percentiles were progressively associated with increased risk of SGA, particularly among births occurring after 32 weeks [15]. A South Indian study by Bhat et al. likewise reported associations between low PAPP-A and adverse obstetric outcomes, including fetal growth restriction and preterm birth [16]. 40.6% of women had PAPP-A <0.4 MoM, while the mean PAPP-A concentration was 0.58±0.31 MoM. Gupta et al. reported low PAPP-A <0.4 MoM in 7.92% of screened pregnancies, and these women subsequently demonstrated significantly higher rates of IUGR and preterm birth [13]. A similar study by Honarjoo et al. showed that, a PAPP-A concentration <0.4 MoM was associated with approximately threefold higher odds of SGA [17]. The mean gestational age at delivery was 34.8±2.6 weeks, with 58.3% delivering before 37 weeks and 27.1% before 34 weeks. Pummara et al., in a population-based screening study of 3160 pregnancies, found that low PAPP-A was associated with progressively greater risks of preterm delivery at ≤36, ≤34 and ≤32 weeks, with relative risks of 2.37, 3.79 and 5.41, respectively [18]. Dane et al. similarly found that women with PAPP-A ≤0.35 MoM had significantly lower gestational age at delivery and an increased risk of early preterm birth [12]. Among women with low PAPP-A, 43.6% delivered before 34 weeks compared with only 15.8% of those with normal PAPP-A, whereas delivery at ≥37 weeks occurred in 20.5% and 56.1%, respectively (p=0.003). She et al. reported a positive relationship between first-trimester

PAPP-A and gestational age at delivery, with lower PAPP-A concentrations associated with a greater likelihood of preterm delivery [19]. Kirkegaard et al. also demonstrated that low PAPP-A, particularly when accompanied by abnormal early fetal growth, was associated with preterm delivery, supporting the concept of a shared placental pathway linking impaired early placentation, restricted growth and earlier birth [20]. IUGR occurred in 76.9% of women with low PAPP-A compared with 49.1% with normal PAPP-A (aOR 3.44, 95% CI 1.39–8.50; p=0.007), while birth weight below the 10th percentile was observed in 71.8% versus 45.6% (aOR 3.03, 95% CI 1.25–7.35; p=0.013). These findings are consistent with evidence from large observational study demonstrating a graded relationship between lower PAPP-A and reduced fetal size [15,21]. The association with abnormal UA Doppler was also significant (aOR 2.48, 95% CI 1.04–5.90; p=0.040), suggesting that low PAPP-A may identify pregnancies in which biochemical evidence of placental dysfunction coexists with increased fetal vascular resistance. Conversely, oligohydramnios did not reach statistical significance (p=0.064). This is consistent with Baer et al. indicating that PAPP-A does not necessarily predict all individual manifestations of placental insufficiency; in a study of preterm isolated oligohydramnios, PAPP-A was not associated with NICU admission, fetal distress or mode of delivery [15]. Low PAPP-A remained independently associated with preterm delivery (aOR 4.36, 95% CI 1.65–11.54; p=0.003), after adjustment for maternal age, parity, abnormal UA Doppler, IUGR and oligohydramnios. Abnormal UA Doppler (aOR 2.87) and IUGR (aOR 3.21) also remained independently associated with preterm delivery, whereas maternal age, primigravida status and oligohydramnios did not. This finding is consistent with D'Antonio et al., in 12,355 pregnancies, found that maternal PAPP-A was significantly lower among women who subsequently developed SGA or delivered preterm, although they emphasized that PAPP-A alone had limited screening performance [22]. Similarly, Krantz et al. found that very low first-trimester PAPP-A was associated with IUGR and particularly early preterm delivery [23].

LIMITATIONS

PAPP-A was assessed at ≥28 weeks of gestation, limiting evaluation of its potential value as an early pregnancy biomarker. The study did not assess longitudinal changes in PAPP-A or incorporate other placental biomarkers. Delivery timing may also have been influenced by clinical indications related to fetal growth and Doppler abnormalities, which could introduce confounding in the observed association between PAPP-A and gestational age at delivery.

CONCLUSION & RECOMMENDATIONS

Low PAPP-A (<0.4 MoM) was significantly associated with earlier delivery, particularly delivery before 34 weeks, and remained independently associated with preterm delivery after multivariable adjustment. Abnormal umbilical artery Doppler and IUGR were also independently associated with preterm birth. PAPP-A may complement established fetal surveillance parameters in pregnancies affected by abnormal fetal growth. Serial assessment of fetal growth and Doppler indices should remain central to clinical monitoring, with low PAPP-A considered as an additional risk-stratification marker. Larger prospective studies should evaluate its incremental predictive value for delivery timing and neonatal outcomes.

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CONFLICT OF INTEREST

None declared.

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee.

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