International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Virdi S et al. Int J Reprod Contracept Obstet Gynecol. 2026 Oct;15(10):3925-3930
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20263426

Original Research Article

Variation of pregnancy-associated plasma protein-A: a level in the first trimester of pregnancy and its clinical outcomes

Simran Virdi, Aditi*, Satwant Kaur

Adesh Medical College and Hospital, Kurukshetra, Haryana, India

Received: 03 August 2026
Revised: 13 September 2026
Accepted: 16 September 2026

***Correspondence:**
Dr. Aditi,
E-mail: dhiman87aditi@gmail.com

ABSTRACT

Background: Pregnancy-associated plasma protein-A (PAPP-A) is a placental glycoprotein used in first-trimester screening and is involved in placental development through the insulin-like growth factor pathway. Low PAPP-A has been associated with placental dysfunction and adverse pregnancy outcomes. This study evaluated the association between first-trimester maternal serum PAPP-A and subsequent maternal and fetal outcomes in singleton pregnancies.
Methods: This hospital-based prospective study was conducted in the Department of Obstetrics and Gynaecology, Adesh Medical College and Hospital, Shahabad, Kurukshetra, from March 2024 to February 2025. A total of 134 low-risk singleton pregnant women aged 18–35 years, attending antenatal care and undergoing first-trimester screening at 11-13 weeks, were enrolled. Serum PAPP-A was measured by chemiluminescence and expressed as multiples of the median (MoM). Participants were followed until delivery, and outcomes were analysed using a <0.4 MoM cut-off.
Results: Mean maternal age was 28.46±3.33 years. Mean PAPP-A was 0.695±0.324 mIU/ml and 0.278±0.130 MoM. Gestational hypertension occurred in 26.9%, preterm labour in 35.8%, PROM in 11.9%, and oligohydramnios in 5.2%. Fetal growth restriction occurred in 24.6% and stillbirth in 2.2%. PAPP-A<0.4 MoM was significantly associated with gestational hypertension (p=0.002), preterm labour (p=0.013), and FGR (p=0.002). Mean PAPP-A was significantly lower in gestational hypertension and oligohydramnios.
Conclusions: Low first-trimester PAPP-A was associated with selected adverse maternal and fetal outcomes, particularly gestational hypertension and FGR. PAPP-A may support early risk stratification and closer antenatal surveillance, but should not be used as a stand-alone diagnostic or predictive test. in routine practice.

Keywords: PAPP-A, First trimester, Pregnancy outcome, Fetal growth restriction, Gestational hypertension, Preterm labour, Placental dysfunction

INTRODUCTION

Pregnancy-associated plasma protein-A (PAPP-A) is a glycoprotein produced mainly by the placental syncytiotrophoblast and can be detected in maternal blood from early pregnancy. It is a zinc-dependent metalloproteinase in the insulin-like growth factor (IGF) system and increases local IGF activity by cleaving IGF-binding proteins. Through this pathway, PAPP-A contributes to trophoblastic invasion, placental development and fetal growth.[1,2]

The role of PAPP-A is not limited to aneuploidy screening. Experimental and placental studies have linked the PAPP-A/IGF pathway with trophoblastic growth and placental development, and altered placental PAPP-A expression has been reported in pregnancies complicated by fetal growth restriction (FGR).[3-5] Disturbances in early placentation may later present as hypertensive disorders, impaired fetal growth, preterm birth and other placenta-mediated complications.[6,7]

Several clinical studies have found an association between low first-trimester PAPP-A and FGR, small-for-

gestational-age birth, hypertensive disorders, preterm delivery, miscarriage and stillbirth. The strength of these associations, however, differs between populations and according to the cut-off used.[7-10] PAPP-A alone also has limited sensitivity and positive predictive value, so it is more appropriately considered a marker of increased risk rather than a stand-alone screening test.[8-11]

Studies from India have reported similar findings, including higher rates of hypertensive disorders, preterm birth and FGR among women with low PAPP-A, although not all outcomes have shown consistent statistical associations.[9,12,13] More recent work suggests that very low PAPP-A may identify pregnancies at particularly high risk, while combining PAPP-A with other placental markers, such as placental growth factor (PlGF), may improve risk assessment.[14,15] Recent studies have also continued to report an association between lower PAPP-A and impaired fetal growth.[16,17]

The present study was undertaken to assess the relationship between first-trimester maternal serum PAPP-A and maternal and fetal outcomes in low-risk singleton pregnancies at a tertiary-care hospital in Haryana. It also examined the clinical significance of a PAPP-A level below 0.4 MoM.

METHODS

Study type

It was a hospital-based prospective study.

Study place and period

The study was carried out in the Department of Obstetrics and Gynaecology, Adesh Medical College and Hospital, Mohri, Shahabad, Kurukshetra, Haryana, India, from March 2024 to February 2025.

Selection criteria of the patients

The study included 134 low-risk singleton pregnant women aged 18-35 years who attended the antenatal outpatient department and agreed to first-trimester PAPP-A testing. Women with liver or renal disease, essential hypertension, overt diabetes mellitus, multiple pregnancy, severe anaemia (haemoglobin <7 g/dL), smoking or tobacco chewing were excluded.

Procedure

Following institutional ethical approval, women presenting at 11-13 weeks of gestation were counselled about first-trimester screening and enrolled after written informed consent. A detailed clinical history was recorded on a pre-designed proforma, including age, parity, previous obstetric history and body mass index. Serum PAPP-A was measured as part of first-trimester screening using a chemiluminescence assay and reported as MoM. PAPP-A was analysed both as a continuous measure and using the predefined cut-off of<0.4 MoM. Participants were followed until delivery, and maternal and fetal outcomes were recorded. Maternal outcomes included gestational hypertension, placental abruption, spontaneous miscarriage, preterm delivery, preterm rupture of membranes, preterm labour requiring tocolytic therapy and oligohydramnios. Fetal outcomes included FGR, stillbirth, congenital malformations and intrauterine fetal demise. Mode of delivery, indications for intervention, gestational age at delivery and neonatal sex were also recorded.

Ethical approval

The study was approved by institutional ethics committee for Biomedical and Health Research (IEC-BHR), Adesh Medical College and Hospital (approval reference AMCH/IEC-BHR/2024/04/02, dated 10 April 2024). Written informed consent was obtained from all participants, and participant confidentiality was maintained.

Statistical analysis

Data were recorded on a pre-designed and pre-tested proforma and entered into Microsoft excel. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 26.0. Microsoft excel 2021 was used for data entry and graphical representation. Categorical variables were summarized as frequencies and percentages. Associations between categorical variables were assessed using the chi-square test, with continuity correction for 2×2 tables where appropriate; Fisher's exact test was used when expected cell counts were <5. Quantitative variables were summarized as mean±standard deviation for normally distributed data and as median with interquartile range for non-normally distributed data.

Normality was assessed using appropriate tests. The unpaired Student's t test or Mann-Whitney U test was used to compare two independent groups according to data distribution. PAPP-A MoM was analysed both continuously and categorically using the <0.4 MoM cut-off. All tests were two-tailed, and $p<0.05$ was considered statistically significant.

RESULTS

A total of 134 low-risk singleton pregnancies were included. The mean maternal age was 28.46±3.33 years and the mean duration of marriage was 3.91±1.44 years. All participants were in non-consanguineous marriages. Gravida 2 the most common category (38.8%), followed by gravida 3 (24.6%); 16.4% of women were primigravida.

Para 1 accounted for 41.8% of participants while 32.8% nulliparous. One living child was reported by 44.8% of

women and 35.8% had no living child. Most participants (59.7%) had no history of abortion.

Normal vaginal delivery was the most common mode of delivery (58.2%), followed by lower-segment caesarean section (38.8%) and instrumental delivery (3.0%). More than half of the women (53.7%) had no recorded antenatal complication. Gestational hypertension was the most frequent antenatal complication (26.9%), followed by preterm labour (11.2%), oligohydramnios (5.2%) and PROM (3.0%). In the maternal-outcome analysis, preterm labour was recorded in 35.8%, gestational hypertension in 26.9%, PROM in 11.9% and oligohydramnios in 5.2%.

Term deliveries accounted for 65.7% and preterm deliveries for 34.3%. Male and female neonates accounted for 50.7% and 49.3%, respectively.

The mean first-trimester PAPP-A concentration was 0.695±0.324 mIU/ml, with values ranging from 0.130 to 1.215 mIU/ml. The mean PAPP-A value expressed as MoM was 0.278±0.130, with a range of 0.052-0.486.

Women with gestational hypertension had a lower mean PAPP-A MoM than those without gestational hypertension (0.228±0.123 vs 0.296±0.128; p=0.0071).

Mean PAPP-A was also lower among women with oligohydramnios (0.180±0.093 vs 0.283±0.129; p=0.0362). The difference in mean PAPP-A for PROM was not statistically significant (p=0.3419).

In contrast, women with recorded preterm labour had a higher mean PAPP-A MoM than those without preterm labour (0.319±0.131 vs 0.255±0.124; p=0.0044).

FGR occurred in 33 pregnancies (24.6%), while 3 pregnancies (2.2%) ended in stillbirth. A normal fetal outcome was recorded in 98 pregnancies (73.2%). Of the 33 FGR cases, 32 (97.0%) had PAPP-A <0.4 MoM and 1 (3.0%) had PAPP-A ≥0.4 MoM (p=0.002).

All three stillbirths occurred in the <0.4 MoM group, although this association was not statistically significant (p=1.000).

Table 1: Demographic and obstetric profile of the study participants, (n=134).

Characteristics	Category	N	Percentages (%)
Age (in years)	Mean±SD	28.46±3.33	-
Years since marriage	Mean±SD	3.91±1.44	-
Consanguinity	Non-consanguineous	134	100.0
Gravida	G1	22	16.4
	G2	52	38.8
	G3	33	24.6
	G4	17	12.7
	G5	10	7.5
Para	P0	44	32.8
	P1	56	41.8
	P2	31	23.1
	P3	3	2.2
Living children	0	48	35.8
	1	60	44.8
	2	25	18.7
	3	1	0.7
Previous abortions	0	80	59.7
	1	34	25.4
	2	12	9.0
	3	8	6.0

Table 2: Delivery characteristics, maternal complications and selected perinatal characteristics, (n=134).

Variables	Category	N	Percentages (%)
Mode of delivery	NVD	78	58.2
	LSCS	52	38.8
	Instrumental	4	3.0
Antenatal complication	None	72	53.7
	Gestational hypertension	36	26.9
	Preterm labour	15	11.2
	Oligohydramnios	7	5.2
	PROM	4	3.0
Indication for intervention	No intervention	56	41.7

Continued.

Variables	Category	N	Percentages (%)
	Fetal distress	28	20.9
	Previous LSCS	17	12.7
	Failed induction	12	9.0
	Non-progress of labour	10	7.5
	Malpresentation	6	4.5
	Hypertensive disorder	5	3.7
Gestational age at delivery	Term	88	65.7
	Preterm	46	34.3
Neonatal sex	Male	68	50.7
	Female	66	49.3
Maternal outcome	Preterm labour	48	35.8
	Gestational hypertension	36	26.9
	Normal	27	20.1
	PROM	16	11.9
	Oligohydramnios	7	5.2

Table 3: Distribution of first-trimester PAPP-A values.

PAPP-A measure	Mean±SD	Minimum	Maximum	Range
PAPP-A (mIU/ml)	0.695±0.324	0.130	1.215	1.085
PAPP-A (MoM)	0.278±0.130	0.052	0.486	0.434

Table 4: Comparison of mean PAPP-A MoM across maternal outcome categories.

Outcomes	Yes, N	PAPP-A MoM, Yes	No, N	PAPP-A MoM, No	P value
Gestational hypertension	36	0.228±0.123	98	0.296±0.128	0.0071
PROM	16	0.249±0.119	118	0.282±0.131	0.3419
Preterm labour	48	0.319±0.131	86	0.255±0.124	0.0044
Oligohydramnios	7	0.180±0.093	127	0.283±0.129	0.0362
Normal maternal outcome	27	0.314±0.116	107	0.269±0.132	0.1314

Table 5: Association between categorized PAPP-A and fetal outcomes, (n=134).

Fetal outcomes	PAPP-A <0.4 MoM	PAPP-A ≥0.4 MoM	P value
FGR	32 (97.0%)	1 (3.0%)	0.002
Stillbirth	3 (100.0%)	0 (0.0%)	1.000
Normal fetal outcome	69 (70.4%)	29 (29.6%)	0.001

DISCUSSION

In this cohort of 134 low-risk singleton pregnancies, first-trimester PAPP-A was associated with some adverse pregnancy outcomes, most clearly gestational hypertension and FGR. This finding is biologically plausible given the role of PAPP-A in the IGF system and in early trophoblastic and placental development. Reduced PAPP-A may reflect impaired placental development before clinical complications become apparent.[1-5]

FGR was the clearest fetal finding in this study. Nearly all FGR cases (97.0%) had PAPP-A<0.4 MoM, and the association was statistically significant (p=0.002). This is in keeping with earlier reports linking low first-trimester PAPP-A with impaired fetal growth.[3,8,13] The recent study by Ceballos Medina et al also found that lower PAPP-A was associated with IUGR, both when PAPP-A was analysed as a continuous measure and when threshold-based analyses were used.[16] These findings support the value of low PAPP-A as an early marker of pregnancies that may need closer assessment of fetal growth.

Gestational hypertension was also associated with lower PAPP-A in the present study. The mean MoM was 0.228 in women with gestational hypertension compared with 0.296 in those without the condition (p=0.0071), and 97.2% of affected women had PAPP-A<0.4 MoM. This association is consistent with the proposed role of abnormal trophoblastic invasion and placental vascular development in hypertensive pregnancy. Earlier studies have reported similar associations, although the findings have not been uniform across populations.[7,9,12] Uriel et al reported that PAPP-A levels differed between gestational hypertension and preeclampsia, suggesting that the marker may not behave in the same way across all hypertensive disorders.[19] The present results should therefore be interpreted specifically in relation to gestational

hypertension rather than extended to all hypertensive disease.

Women with oligohydramnios also had lower mean PAPP-A MoM (0.180 vs 0.283; p=0.0362), and all seven cases were in the <0.4 MoM group. The categorical comparison was not statistically significant (p=0.348), however, and only seven cases were available for analysis. The finding is of interest but should be interpreted cautiously because the small number of cases does not allow a firm conclusion.

The findings for preterm labour are less straightforward. When PAPP-A was categorized at <0.4 MoM, preterm labour was significantly associated with the low-PAPP-A group (p=0.013), which is in line with previous reports of an association between low PAPP-A and preterm birth.[7,10,13,17] In the continuous analysis, however, women with recorded preterm labour had a higher mean PAPP-A than those without preterm labour (0.319 vs 0.255 MoM; p=0.0044). Because these two analyses point in opposite directions, the result should be treated with caution. The original case-level data and the definition used for preterm labour should be checked before drawing a definite conclusion about this outcome.

All three stillbirths occurred among women with PAPP-A<0.4 MoM, but the association was not statistically significant (p=1.000). Although this direction is similar to reports linking markedly low PAPP-A with stillbirth and placental dysfunction, the number of stillbirths in the present study was too small to support a reliable statistical inference.[7,14]

The mean PAPP-A MoM in the study population was 0.278±0.130. This relatively low value may partly reflect the characteristics of the study population, which consisted of low-risk singleton pregnancies attending a single tertiary-care centre and undergoing first-trimester screening. The observed distribution should therefore not be assumed to represent the wider obstetric population.

A useful feature of this study is that PAPP-A was assessed both as a continuous variable and at the predefined <0.4 MoM threshold. The threshold-based analysis showed clear associations with gestational hypertension and FGR. At the same time, these findings do not establish that 0.4 MoM is the best cut-off for every population. Recent studies have suggested that very low PAPP-A may identify a subgroup at greater risk, and that combining PAPP-A with PlGF may improve risk assessment compared with PAPP-A alone.[14,15]

Taken together, the results suggest that low first-trimester PAPP-A may be a useful marker of early placental dysfunction, rather than a test that can diagnose a particular pregnancy complication. Previous work has also shown that PAPP-A alone has limited predictive performance and is more useful when considered with maternal characteristics, ultrasound findings and other placental markers.[11,15,20] In practice, women with markedly low PAPP-A may merit closer surveillance, especially for fetal growth and hypertensive disease, but management should not be based on PAPP-A alone.

Limitations

This study was conducted at a single centre and included 134 women, which limits the generalizability of the findings and reduces the power to assess uncommon outcomes such as stillbirth. Because the study was restricted to low-risk singleton pregnancies and excluded several major maternal conditions, the results may not apply to higher-risk populations. No multivariable analysis was reported, so the effect of potential confounding factors cannot be excluded. Although the assay was described as chemiluminescence, the analyser or manufacturer and details of MoM calibration were not provided. The most important issue is the opposite direction of the categorical and continuous preterm-labour analyses; these findings should be checked against the original case-level data before the results are used for publication. Several outcomes listed in the study protocol, including placental abruption, spontaneous miscarriage, congenital malformations and intrauterine fetal demise, were not accompanied by numerical results in the presented Results tables and have not been interpreted here.

CONCLUSION

In this prospective study of 134 low-risk singleton pregnancies, PAPP-A <0.4 MoM was significantly associated with gestational hypertension and FGR, and mean PAPP-A was lower among women with oligohydramnios. The findings for preterm labour were inconsistent between the categorical and continuous analyses and should be verified. PAPP-A may help identify pregnancies that warrant closer surveillance, particularly for fetal growth and hypertensive disease, but it should be interpreted together with clinical and ultrasound findings and not used as a stand-alone predictive test.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Virdi S, Aditi, Kaur S. Variation of pregnancy-associated plasma protein-A: a level in the first trimester of pregnancy and its clinical outcomes. Int J Reprod Contracept Obstet Gynecol 2026;15:3925-30.