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Original Research

Fetomaternal Outcome among Pregnant women with Low Level of Pregnancy-Associated Plasma Protein A during First Trimester: A hospital-based study

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ABSTRACT:

Background: Pregnancy involves significant physiological changes to support fetal growth and development. Pregnancy-Associated Plasma Protein A (PAPP-A), produced primarily by the placenta, plays a crucial role in regulating fetal growth and placental function. Adverse pregnancy outcomes, such as preeclampsia, intrauterine growth restriction (IUGR), and preterm birth, continue to pose challenges in maternal-fetal medicine. Low PAPP-A levels during the first trimester have been associated with adverse outcomes, but evidence remains inconclusive. This study aimed to investigate the relationship between low PAPP-A levels and fetomaternal outcomes to aid in risk stratification and intervention for improved maternal and fetal health. **Methods:** This retrospective cohort study investigated fetomaternal outcomes in pregnant women with low Pregnancy-Associated Plasma Protein A (PAPP-A) levels during the first trimester. Ethical approval was obtained from the institutional review board. Participants were pregnant women who received antenatal care and delivered at the Maheswara Medical College, a suburban tertiary care centre of South India between November 2017 and November 2021. Data, including demographic, clinical, and outcome variables, were collected from electronic medical records and antenatal care databases. PAPP-A levels were measured using an electrochemiluminescence assay. Low PAPP-A was defined as concentration below the 5th percentile for gestational age. Statistical analysis was performed using SPSS 20.0. **Results:** Among 1876 pregnant women, 14.0% (n=262) had PAPP-A levels below 0.5 MoM, while 86.0% (n=1614) had levels above 0.5 MoM. Demographic and clinical characteristics were comparable between Group A and Group B. Group A had a higher incidence of preterm deliveries (20.2% vs. 12.4%) and lower mean gestational age (37.3±1.42 weeks vs. 38.6±1.38 weeks) and higher rates of PIH (16.8% vs. 4.3%), abortions (6.9% vs. 2.0%), PROM (30.2% vs. 13.2%), LSCS (53.8% vs. 38.0%), and instrumental deliveries (11.1% vs. 4.0%) compared to group B. Group A had a higher proportion of infants with intrauterine demise (2.9% vs. 0.9%) and percentage of infants with a birth weight ≥2500 grams (76.8% vs. 88.0%) compared to Group B. **Conclusion:** The results showed that women with PAPP-A levels below 0.5 MoM (Group A) had a higher risk of adverse outcomes, including preterm delivery, low birth weight, and an increased likelihood of cesarean section deliveries, as well as higher rates of pregnancy complications such as Pregnancy-Induced Hypertension (PIH) and premature rupture of membranes (PROM).

Keywords: Pregnancy-Associated Plasma Protein A (PAPP-A), First trimester, Adverse pregnancy outcomes, Preterm delivery, Low birth weight

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INTRODUCTION

Pregnancy is a transformative phase in a woman's life, characterized by significant physiological and biochemical changes to support the growth and development of the fetus [1]. Pregnancy-Associated Plasma Protein A (PAPP-A), a glycoprotein primarily produced by the syncytiotrophoblasts of the placenta, plays a crucial role in regulating fetal growth and placental function [2,3]. During early pregnancy, PAPP-A levels serve as a valuable biomarker, aiding in the assessment of placental health and predicting adverse pregnancy outcomes [4].

Despite the remarkable progress in maternal-fetal medicine and perinatal care, adverse pregnancy outcomes still pose a considerable challenge worldwide. Pregnancy complications, such as

preeclampsia, intrauterine growth restriction (IUGR), preterm birth, and fetal abnormalities, continue to contribute to maternal and neonatal morbidity and mortality [5]. Identifying potential risk factors and implementing appropriate interventions is crucial to improving maternal and fetal health outcomes [6,7].

In recent years, researchers have explored the association between low levels of Pregnancy-Associated Plasma Protein A during the first trimester and adverse fetomaternal outcomes [8,9]. Although some studies have suggested a significant correlation, the evidence remains inconclusive and requires further investigation. Understanding the impact of low PAPP-A levels during early pregnancy on fetal development and maternal well-being is vital for early risk stratification and timely intervention [9].

The groundbreaking randomized clinical trial FASTER discovered that having Pregnancy-Associated Plasma Protein A (PAPP-A) levels below the 5th percentile was linked to various adverse pregnancy outcomes. These outcomes included fetal growth restriction (FGR) with an odds ratio (OR) of 3.2, small for gestational age (SGA) with an OR of 2.5, preterm delivery (PTD) with an OR of 1.9, birthweight below the 5th percentile with an OR of 2.8, preeclampsia (PE) with an OR of 1.5, and placental abruption with an OR of 1.8 [10].

This hospital-based study aimed to elucidate the relationship between low PAPP-A levels during the first trimester and fetomaternal outcomes. By conducting a comprehensive analysis of a diverse and sizeable cohort, we endeavor to provide insights into the potential implications of low PAPP-A levels and its predictive value for adverse pregnancy outcomes. Additionally, this study seeks to identify specific adverse outcomes associated with low PAPP-A levels, contributing valuable information to the existing body of knowledge in obstetrics and perinatal care.

MATERIALS and METHODS

Study Design and Participants

This hospital-based study followed a retrospective cohort design to investigate the fetomaternal outcomes among pregnant women with low levels of Pregnancy-Associated Plasma Protein A (PAPP-A) during the first trimester. Ethical approval was obtained from the institutional review board before the commencement of data collection.The study included pregnant women who received antenatal care and delivered at the Maheswara Medical College, a suburban tertiary care centre of South India between November 2017 and November 2021. Eligible participants were identified from electronic medical records using predefined inclusion criteria, which consisted of Pregnant women with confirmed gestational age based on early ultrasound assessment (6-12 weeks), available PAPP-A measurements during the first-trimester screening, obtained between 10-14 weeks of gestation, singleton pregnancies to eliminate potential confounding effects. Patients with multiple pregnancies, renal diseases, chronic hypertension, insulin-dependent diabetes mellitus, cardiac disorders, and chromosomal abnormalities were excluded from the study.

Data Collection

Relevant data for this research were obtained from the hospital's electronic medical records and antenatal care databases. Trained medical personnel collected the following demographic and clinical information for each participant: maternal age, education, religion, socioeconomic status, body mass index (BMI), obstetric history (gravida), and gestational age at the time of PAPP-A measurement. Additionally, data related to pregnancy outcomes, and neonatal complications were recorded.

Measurement of Pregnancy-Associated Plasma Protein A (PAPP-A)

PAPP-A levels were measured during the first-trimester prenatal screening, which is routinely conducted for all pregnant women seeking antenatal care at tertiary care hospital. The PAPP-A assay was conducted using an electrochemiluminescence assay on a Cobase601 analyzer, which automatically provided marker concentration.The results were reported in multiples of the median (MoM) to adjust for gestational age variations and other influencing factors.

Definition of Low PAPP-A Level

For the purposes of this study, a low PAPP-A level was defined as a concentration below the 5th percentile of the expected normal range for the gestational age at the time of screening, based on the laboratory's reference values [11].

Outcome Variables

The primary outcome variables assessed in this study were fetomaternal complications associated with low PAPP-A levels during the first trimester. These included but were not limited to mean gestational age, preterm delivery, mode of delivery, pregnancy induced hypertension (PIH), abortion, pre-rupture of membrane (PROM), placental abruption, intrauterine death (IUD), small for gestational age (SGA), and low birth weight (LBW).

Data Analysis

Data analysis was performed using SPSS 20.0 statistical software. Descriptive statistics were employed to summarize demographic and clinical characteristics of the study population. Continuous variables were expressed as mean ± standard deviation or median (interquartile range), depending on their distribution. Categorical variables were presented as frequencies and percentages.To assess the association between low PAPP-A levels and fetomaternal outcomes, appropriate statistical tests,

such as chi-square test, Fisher's exact test, or Student's t-test, were employed as applicable.

RESULTS

The distribution of PAPP-A levels revealed that 262 participants (14.0%) had PAPP-A levels below 0.5 MoM (Multiple of the Median), indicating a lower-than-expected value. Conversely, 1614 participants (86.0%) demonstrated PAPP-A levels above 0.5 MoM, indicating a higher-than-expected value (Figure 1).

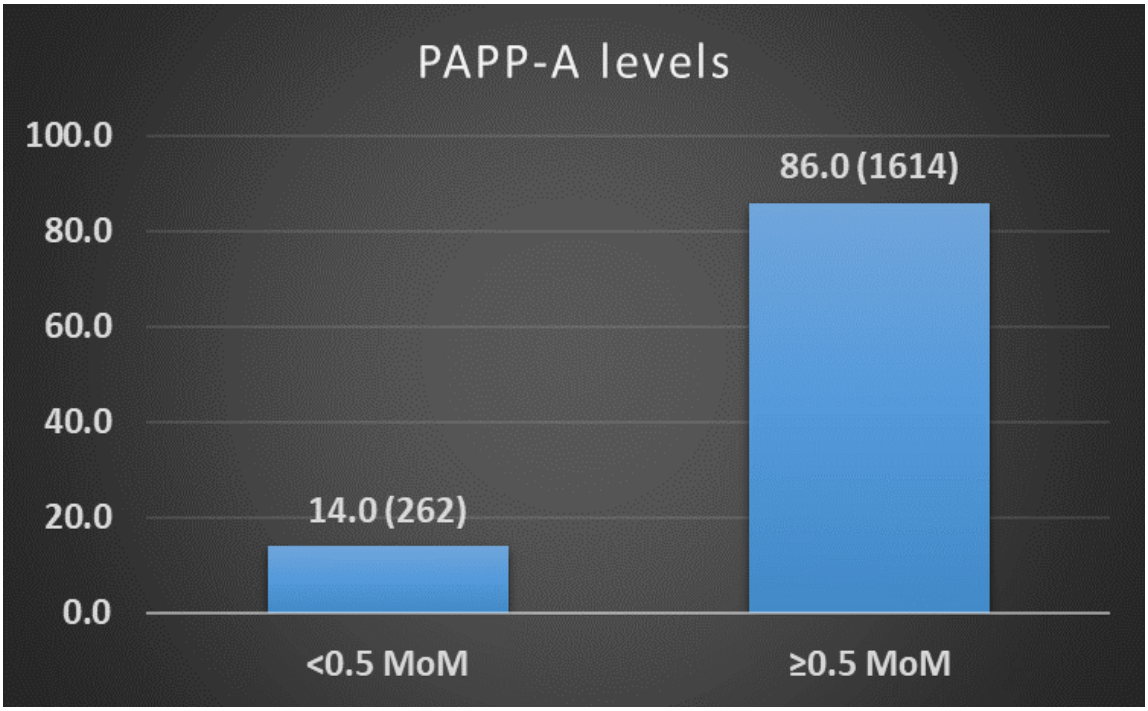

Figure 1. Distribution of PAPP-A levels among pregnant women (N=1876).

The comparison of demographic and clinical characteristics between Group A (PAPP-A levels <0.5 MoM) and Group B (PAPP-A levels >0.5 MoM) revealed no significant differences in age distribution, education level, socioeconomic status, religion, and BMI. The two groups exhibited similar age distributions, with most participants falling within the age groups of <25 and 25-30 years. The mean age in Group A was 27.6±3.9 years, while it was 27.9±4.1 years in Group B, showing no statistically significant difference (p=0.268). Similarly, there were no significant differences in education level, socioeconomic status, religion, and BMI between the two groups. These findings indicate that the maternal demographics and baseline characteristics were comparable between women with low PAPP-A levels and those with higher PAPP-A levels during the first trimester of pregnancy (Table 2).

Table 1. Comparison of baseline characteristics among two groups.

Variables	Frequency	%	Frequency	%	Pvalue
	Group A (n=262)		Group B (n=1614)		
Age group (in years)					
<25	153	58.4	973	60.3	0.740
25-30	92	35.1	546	33.8	
>30	18	6.9	95	5.9	
Mean age (in years)	27.6±3.9		27.9±4.1		0.268
Education					
Illiterate	61	23.3	413	25.6	0.721
Primary or middle school	90	34.4	544	33.7	
High school or above	111	42.4	657	40.7	
Socioeconomic status					
Upper class	35	13.4	236	14.6	0.382
Upper and Lower middle	113	43.1	681	42.2	
Upper lower and Lower	114	43.5	594	36.8	
BMI (in Kg/m^2)					
<25	149	56.9	872	54.0	0.421

25-29.9	102	38.9	694	43.0	
≥30	10	3.8	48	3.0	
Mean BMI (in Kg/m^2)	26.3±3.7		26.7±3.2		0.088
Gravida					
Primiparous	122	46.6	715	44.3	0.493
Multiparous	140	53.4	899	55.7	
Mean Gravida	1.45±0.63		1.43±0.72		0.671

The comparison of maternal outcomes revealed that Group A had a higher incidence of preterm deliveries (20.2%) compared to Group B (12.4%). Additionally, Group A showed a lower mean gestational age (37.3±1.42 weeks) compared to Group B (38.6±1.38 weeks). Group A also had a significantly lower rate of normal vaginal deliveries (35.1%) compared to Group B (58.0%). Also, Group A had a higher incidence of pregnancies with Pregnancy-Induced Hypertension (PIH) (16.8% vs. 4.3%), abortions (6.9% vs. 2.0%), and premature rupture of membranes (PROM) (30.2% vs. 13.2%), as well as a higher incidence of cesarean section deliveries (LSCS) (53.8% vs 38.0%) and instrumental deliveries (4.0% vs. 11.1%) as compared to Group B.Regarding fetal outcomes, Group A had a higher proportion of infants with intrauterine demise (IUD) (2.9% vs. 0.9%). Furthermore, the mean birth weight in Group A was significantly lower (2723.2±523.3 grams) than that in Group B (2995.4±493.2 grams). The percentage of infants with a birth weight ≥2500 grams was lower in Group A (76.8%) compared to Group B (88.0%) (Table 2).These findings suggest that Group A, with low PAPP-A levels during the first trimester, is associated with a higher risk of adverse maternal and fetal outcomes, including preterm delivery, low birth weight, and an increased likelihood of cesarean section deliveries and pregnancy complications like PIH and PROM.

Table 2. Comparison of fetomaternal outcomes among two groups.

Fetomaternal outcome	Frequency	%	Frequency	%	P value
	Group A (n=262)		Group B (n=1614)		
Maternal outcome					
Delivery period					
Preterm	53	20.2	200	12.4	0.0005
Term	209	79.8	1414	87.6	
Mean gestation age (in weeks)	37.3±1.42		38.6±1.38		<0.0001
Mode of Delivery					
Normal VD	92	35.1	936	58.0	<0.0001
LSCS	141	53.8	613	38.0	
Instrumental delivery	29	11.1	65	4.0	
PIH					
Yes	44	16.8	69	4.3	<0.0001
No	218	83.2	1545	95.7	
Abortion					
Yes	18	6.9	32	2.0	<0.0001
No	244	93.1	1582	98.0	
PROM					
Yes	79	30.2	213	13.2	<0.0001
No	183	69.8	1562	96.8	
Placental Abruption					
Yes	8	3.1	19	1.2	0.018
No	254	96.9	1595	98.8	
Fetal outcome					
Fetal birth	**(n=244)**		**(n=1582)**		
Live	237	97.1	1441	91.1	0.012
IUD	7	2.9	14	0.9	
Birth weight (in grams)	**(n=237)**		**(n=1441)**		
≥2500	182	76.8	1268	88.0	<0.0001
<2500	55	23.2	173	12.0	
Mean Birth weight (in grams)	2723.2±523.3		2995.4±493.2		<0.0001

DISCUSSION

In our study, we classified the participants into two groups based on their PAPP-A levels during the first trimester of pregnancy. Group A comprised participants with PAPP-A levels below 0.5 MoM, indicating a lower-than-expected value, while Group B consisted of participants with PAPP-A levels above 0.5 MoM, indicating a higher-than-expected value. In our study, the cut-off value for low Pregnancy-Associated Plasma Protein A (PAPP-A) was set at 0.49 MoM, which aligns with a study conducted by Patil et al., [11]. The definition of low PAPP-A varies across studies by Saruhan et al., Malik et al., Barrett et al., and Yaron et al., with values between 0.3-0.5 MoM considered as indicative of low levels [12,13,14,15].In our study, the incidence of low PAPP-A (<5th percentile) was observed in 14% of cases, which is similar to study by Yaron et al., which reported an incidence of 15.4% [15]. Another study by Cooper et al., reported an incidence of 5.4% using an absolute cut-off of PAPP-A <0.4 MoM [16].

The comparison of demographic and clinical characteristics between Group A and Group B revealed no significant differences in age distribution, education level, socioeconomic status, religion, and BMI. These findings indicate that the maternal demographics and baseline characteristics were comparable between women with low PAPP-A levels (Group A) and those with higher PAPP-A levels (Group B) during early pregnancy.

Furthermore, we found that Group B had a lower incidence of abortions (2.0% vs. 6.9%)compared to Group A. Studies by Krantz et al., Barrett et al., Hanita et al., and Tul et al., demonstrated an association between low PAPP-A and increased pregnancy loss [2,14,17,18].

Kaijomaa et al., Dugoff et al., Morris et al., and Barrett et al., reported a strong risk factor for small for gestational age (SGA) in the low PAPP-A group, suggesting a potential link to suboptimal placental growth and function, leading to insufficiency [10,14,19,20].

Moving on to maternal outcomes, we observed notable differences between the two groups. Group A, with PAPP-A levels below 0.5 MoM, had a higher incidence of preterm deliveries (20.2%) compared to Group B (12.4%). Additionally, the mean gestational age in Group A was significantly lower (37.3±1.42 weeks) than that in Group B (38.6±1.38 weeks). These findings suggest that pregnant women with low PAPP-A levels may be at increased risk of preterm delivery and have shorter gestational ages.Studies by Hughes et al., Pummara et al., Patil et al., and Gupta et al., proposed that PAPP-A levels below the 10th percentile are associated with idiopathic preterm delivery, suggesting a high-risk label for such pregnancies [11,21,22,23].

The incidence of pregnancy-induced hypertension (PIH) was higher in the study group (16.8%) as compared to control group (4.3%), but the difference was statistically significant. Similar positive but strong correlations were found in studies Van Ravenswaaij et al., Malik et al., and Ong et al., [13,24,25].

Furthermore, we found that Group B had a lower incidence of premature rupture of membranes (PROM) (13.2% vs. 30.2%) compared to Group A. Turning to fetal outcomes, Group A had a higher proportion of infants with intrauterine demise (IUD) (2.9% vs. 0.9%) compared to Group B. Additionally, the mean birth weight in Group A was significantly lower (2723.2±523.3 grams) than that in Group B (2995.4±493.2 grams). The percentage of infants with a birth weight ≥2500 grams was lower in Group A (76.8%) compared to Group B (88.0%), suggesting that low PAPP-A levels may be associated with an increased risk of low birth weight and intrauterine demise.These findings are consistent with the findings of previous studies by Barrett et al., Dugoff et al., Cohen et al., and Krantz et al.,[2,10,14,26].

LIMITATIONS

Our study has some limitations that should be considered when interpreting the results. First, it was conducted at a single healthcare center, which may limit the generalizability of the findings to a broader population. Additionally, the retrospective design introduces potential selection bias and limitations in data collection. The sample size was relatively small, which could impact the statistical power to detect significant differences. Unmeasured confounding factors and the potential for outcome misclassification are other important limitations. As an observational study, causality cannot be inferred, and variability in PAPP-A measurements may also influence the results. Despite these limitations, our findings provide valuable insights into the association between PAPP-A levels and adverse maternal and fetal outcomes. Further prospective, multicenter studies are needed to confirm and strengthen these findings.

CONCLUSION

In conclusion, our study investigated the association between PAPP-A levels during the first trimester of pregnancy and maternal and fetal outcomes. The results showed that women with PAPP-A levels below 0.5 MoM (Group A) had a higher risk of adverse outcomes, including preterm delivery, low birth weight, and an increased likelihood of cesarean section deliveries, as well as higher rates of pregnancy complications such as Pregnancy-Induced Hypertension (PIH) and premature rupture of membranes (PROM). Additionally, infants born to mothers in Group A had a higher incidence of intrauterine demise (IUD).Despite comparable baseline characteristics between the two groups, Group A exhibited a significantly different pattern of maternal and fetal outcomes. These findings indicate that PAPP-A levels below 0.5 MoM in the first trimester may serve as a potential marker for

identifying pregnant women at higher risk of adverse outcomes.

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