Pregnancy-Associated Plasma Protein-A: Its Significance as a Single Biomarker for Adverse Obstetric Outcomes

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ABSTRACT

OBJECTIVES: Low levels of pregnancy-associated plasma protein-A in pregnant women linked to unhealthy placentation and a spectrum of maternal and fetal complications. Its assessment as a single biomarker has the potential to identify high-risk pregnancies. This prospective observational study was conducted to find a correlation between low pregnancy-associated plasma protein-A levels in the first trimester of pregnancy with various obstetric outcomes to establish if it can be used as a single biomarker for counseling couples.

STUDY DESIGN: The study was conducted at Base Hospital, Delhi Cantt. Maternal serum pregnancy-associated plasma protein-A levels were assessed at 11 to 13+6 weeks of gestation, converted in multiples of the median and patients were followed till delivery. Maternal outcomes were recorded in terms of abortions, development of gestational hypertension, gestational diabetes, preeclampsia, placental abruption, fetal growth restriction, fetal demise, neonatal intensive care unit admission, etc., and analyzed to find an association with levels first trimester of pregnancy-associated plasma protein-A.

RESULTS: Low pregnancy-associated plasma protein-A levels showed a statistically significant association with gestational hypertension, preeclampsia, abortion, fetal demise, and also for adverse neonatal outcomes like APGAR <5 at 1 min, fetal growth restriction, neonatal intensive care unit admission, and perinatal deaths. No significant association was observed for preterm delivery, gestational diabetes, and placental abruption.

CONCLUSION: Serum pregnancy-associated plasma protein-A levels in the first trimester of pregnancy have the potential of being utilized as a validated marker for adverse pregnancy outcomes. Early identification of such pregnancies can help in optimizing feto-maternal outcomes through closer surveillance, timely intervention, and referral to tertiary care centers. Further research would help the fraternity in developing a prediction model.

Keywords: Biomarker, Fetal growth restriction, Neonatal intensive care unit, Pregnancy-associated plasma protein-A, Preeclampsia

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Introduction

Adverse outcomes such as stillbirth, preterm birth, intrauterine fetal demise (IUFD), low birth weight, small for gestational age (SGA), threatened abortion, and preeclampsia are commonly associated with pregnancy. These complications impose a significant burden on healthcare and have profound psychological effects on families. Identifying biomarkers for early prediction of these complications would greatly benefit both clinicians and patients. The discovery of glycoprotein PAPP-A in the plasma of pregnant women by Lin et al. in 1974 has enabled its inclusion in first-trimester aneuploidy screening and opened doors to investigating new associations between biomarkers and adverse pregnancy outcomes/complications (1,2).

The human placenta produces many proteins. Some of these proteins include hormones like human chorionic gonadotrophin (HCG) and human placental lactogen (HPL), pregnancy-associated plasma protein A (PAPP-A). During pregnancy, the concentrations of these proteins in the maternal blood increase and can be used as biomarkers to identify high-risk pregnancies (3). Placental dysfunction can cause alteration in the levels of these hormones in maternal serum (4). Early prediction of placental dysfunction before its establishment has the potential to improve pregnancy outcomes through timely intervention, close monitoring, or referral to higher-level healthcare facilities as necessary. Additionally, it would aid clinicians in counseling patients about the prognosis and probable outcome of their pregnancy.

PAPP-A is a large metalloproteinase that plays a role in placental development by cleaving insulin-like growth factor (IGF) binding proteins. This cleavage leads to increased availability of IGF, which is crucial for the multiplication, differentiation, and invasion of trophoblastic cells. Additionally, IGF regulates the uptake of glucose and amino acids, thereby influencing fetal growth. Thus, PAPP-A is involved in the regulation of IGF activity (5-7). Emerging evidence suggests that low PAPP-A levels are associated with fetal rejection, compromised placentation, and a range of complications including spontaneous abortion, preterm delivery, fetal growth restriction, preeclampsia, and stillbirth. The influential FASTER trial found that PAPP-A levels below the 5th percentile were linked to an increased risk of fetal growth restriction, spontaneous abortions, preterm delivery, low birth weight, preeclampsia, and placental abruption, and these results were consistent with findings from other studies (6,8).

PAPP-A has been studied as a potential predictor for IUFD and fetal growth restriction (FGR) (9-11). It has also shown value as a single predictor for adverse perinatal outcomes, but combining it with other maternal serum markers improves detection rates (8,12-14). Lower levels of PAPP-A are associated with an increased risk of adverse pregnancy outcomes, although its positive predictive value varies across populations, leading to debate over its use as a standalone screening tool (15,16).

To validate PAPP-A as a single maternal serum marker for predicting pregnancy outcomes, more studies are needed to fully understand and exploit its full potential. Since, despite a vast amount of research, studies could not verify the high sensitivity of PAPP-A as a single biomarker in detecting low or high-risk pregnancies, we, at our center planned to study the correlation between low levels of PAPP-A in the first trimester of pregnancy with various obstetric outcomes and establish if it can be used as a single biomarker for counseling the couples.

Material and Method

This hospital-based observational prospective cohort study was conducted in the Department of Obstetrics and Gynaecology at Base Hospital, Delhi Cantt from 01 Aug 2020 to 30 Dec 2021. The institutional ethical committee of Base Hospital & Army College of Medical Sciences, Delhi Cantt, New Delhi India approved the study protocol on 24 Aug 2020 vide IEC No IEC/08/2020/02. Informed consent of the study participants was taken and the study was conducted in accordance with the Declaration of Helsinki.

The sample size of 600 the study was based on a study by Singh & Singh (2019) (14), who reported the prevalence of low PAPP-A as 10% in pregnant women. The sample size was calculated according to the formula: $N = \frac{(Z_{1-\alpha/2})^2 * p * (1-p)}{\delta^2}$

Where, *p* (prevalence of Target Condition) =0.1,δ (Precision) =0.025 (2.5%), α (Type I error)=5%, $Z_{1-\alpha/2}$= 1.96 and Confidence interval - 95%

Convenience sampling, a type of non-probability sampling was adapted for the study. Six hundred and eighty women were enrolled considering attrition due to peculiar service conditions and transfers in the armed forces population. Six hundred and eighty consecutive cases with first-trimester pregnancies reported in the outpatient department (OPD) during the study period and fulfilling the inclusion and exclusion criteria were enrolled.

Inclusion criteria: All women with spontaneous singleton pregnancies who were willing to participate in the study.

Exclusion criteria: Patients with multifetal gestation

Patients conceived with assisted reproductive technology

Patients consuming tobacco in any form

Patients with fetal aneuploidies and anomalies

Patients with comorbidities such as a history of diabetes, chronic hypertension, renal and liver diseases, autoimmune or metabolic disease, and other chronic medical diseases.

The nature and purpose of the study were explained to the enrolled women in detail and informed consent was obtained. Baseline demographic characteristics of the study population were recorded which included maternal age, gravida, parity, and body mass index. The study participants were selected from a population of dependents of army personnel, all of whom belonged to the middle and upper middle socio-economic classes as determined by the revised Kuppuswamy scale. History was taken in detail and clinical evaluation was done. Serum PAPP-A levels were assessed at 11 to 13+6 weeks of gestation for each patient and PAPP-A values were converted in multiples of the median (MoM). Based on PAPP-A values in MoM, the study population was divided into two groups, Group A with low PAPP-A levels (< 0.5 MoM) and Group B with normal levels (> 0.5 MoM). These women were followed up till the end of pregnancy and outcomes were recorded. Maternal outcomes studied were the development of

gestational diabetes mellitus, gestational hypertension, preeclampsia, eclampsia, placental abruption, abortion, and IUFD. Fetal outcomes studied were FGR, APGAR at 1 minute and requirement of neonatal intensive care unit (NICU) facilities, and perinatal death. Collected data were analyzed statistically to find an association of the above-mentioned outcomes with levels first trimester of PAPP-A.

Statistical analysis

Data was coded and recorded in MS Excel Software. Descriptive statistics were elaborated in the form of means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. Group comparisons were made using the t-test/ Mann-Whitney U test for normally/non-normally distributed continuous data respectively and the chi-square test for categorical variables. SPSS v23 was used for analysis. p-value < 0.05 was considered statistically significant.

Results

During the specified period total of 680 pregnant women were evaluated and followed up. 68 patients were lost to follow-up and were not available till the culmination of pregnancy. Six hundred and twelve patients were followed up till the end of pregnancy and outcomes were recorded. As described, they were categorized into two groups. 53 (8.66%) women had PAPP-A levels < 0.5 MoM (Group A) and 559 (91.33%) women had PAPP-A levels > 0.5 MoM (Group B).

The socio-demographic characteristics of the study population are tabulated in table I. The baseline characteristics of the study population showed no significant difference between groups A and B, which included maternal age (p=0.15), BMI (p=0.73), and gravidity (p=0.82). The mean age of the study participants was 25.48 years + SD 3.75. The minimum age was 18 years while the maximum age of study participants in our study was 38 years. Almost half of the patients belonged to the age group of 21-25 years followed by 26-30 years.

Table I: *Characteristics of the study population in subgroups*

Demographic characteristics	Group A MoM <0.5 (n=53)	Group B MoM ≥ 0.5 (n=559)	p
Maternal age (years ± SD)	25.48±4.75	24.5±4.82	0.15
Body mass index BMI (kg/m^2 ± SD)	26.08±3.42	25.89±4.013	0.73
Gravidity			
Primigravida	19	192	0.82
Multigravida	34	367	

Table II suggests that there was no significant association between low PAPP-A (MoM < 0.5) and preterm delivery (p=0.09), gestational diabetes (p=0.16), and placental abruption (p=0.22). However, a statistically significant association was observed for gestational hypertension and preeclampsia (p<0.001) with RR of -2.92 and odds of 3.54 for gestational hypertension and RR of -6.33, odds of 7.42 for pre-eclampsia. Also, there was a significant association between abortion and intrauterine fetal demise (p=0.01 and p=0.04, respectively)

Table II: *Obstetric outcomes among women with low or normal PAPP-A levels*

Characteristics	**Group A MoM < 0.5**		**Group B MoM ≥ 0.5**		*p*
	(n=53)	**%**	**(n=559)**	**%**	
Gestational Diabetes	12	22.64	84	15.02	0.163
Gestational Hypertension	13	24.52	47	8.40	<0.001
Pre-eclampsia	9	16.98	15	2.68	<0.001
Preterm delivery	9	16.98	52	9.30	0.09
Abruptio placentae	3	5.66	16	2.86	0.22
Abortion	4	7.54	9	1.61	0.01
Intrauterine fetal demise (IUFD)	3	5.66	7	1.43	0.04
Comparison by mode of delivery					
	(n=49)		**(n=550)**	**%**	
Vaginal delivery	26	53.06	321	58.36	0.54
Cesarean section	23	46.93	229	41.63	
Neonatal outcomes					
	(n=49)	%	(n=550)	%	
APGAR at 1 min < 5	7	14.28	31	5.6	0.02
APGAR at 1 min > 5	42	85.71	519	94.36	RR -2.53
					Odds ratio 2.79
Birth weight < 5th centile	10	20.40	39	7.09	0.001
Birth weight > 5th centile	39	79.60	511	92.90	RR -2.88
					Odds ratio 3.36
Neonatal intensive care unit (NICU) admission	8	16.32	36	6.54	0.02
Neonatal demise within 7 days	2	4.08	2	0.36	0.03

with RR of -4.69 and odds of 4.99 for abortions, and RR of -4.52 and odds of 4.73 for intrauterine fetal demise. No significant difference was observed for the mode of delivery i.e. vaginal or cesarean delivery in the two groups (p=0.54).

Adverse neonatal outcomes showed a significant association with low PAPP-A levels. APGAR < 5 at 1 min and low birth weight of < 5th centile showed significant association with low PAPP-A (p=0.02 and p=0.001, respectively) with RR of 2.53 and odds of 2.79 for low APGAR at birth and RR of 2.88 and odds of 3.36 for low birth weight in the group A. The requirement of NICU admission and neonatal demise within seven days was significantly high in group A i.e. (p=0.02) with RR of 2.49 and odds of 2.79 for NICU admission and RR of 11.22 and odds of 11.66 for early neonatal death within seven days.

Discussion

The first trimester of pregnancy is the most important period when the growth and development of the fetus take place. Any deviation from the normal physiological processes may cause considerable risk to both mother and fetus. The antenatal care visits are planned to ensure a healthy mother along with a healthy newborn and to identify women at high risk of developing complications later in pregnancy. Early preventive intervention and effective management can be offered if the women at high risk are identified. First-trimester PAPP-A levels can be used as a predictor of adverse outcomes in the later stages of the pregnancy (17). Low PAPP-A levels cause decreased free IGF levels which results in abnormal placentation and thus results in adverse pregnancy outcomes such as gestational hypertension, preeclampsia, preterm deliveries, placental abruption, FGR, and low birth weight (15). PAPP-A is a promising maternal serum marker for pregnancy outcome prediction, but more studies are needed to fully understand and exploit its potential as a prognostic biomarker. However, before making an accurate conclusion, it should be kept in mind that low levels of PAPP-A are poorly sensitive except when their levels are extremely low, which increases its predictivity for adverse maternal and neonatal outcomes. Likewise, most patients whose pregnancies were complicated with high-risk pregnancy conditions and adverse neonatal outcomes did not have low levels of PAPP-A (18,19).

Taking into consideration the conflicting data available, our study was formulated to find the effect of low PAPP-A levels in the first trimester on adverse maternal and fetal outcomes.

Low PAPP-A is considered between 0.3-0.5 MoM in different studies (20). In our study < 0.5 MoM was considered low and the incidence of low PAPP-A was 8.66% whereas in the study by Yaron et al, the reported incidence was 15.4% (21). In our study, a statistically significant association was observed for the incidence of gestational hypertension and preeclampsia (p<0.001) with an RR of -2.92, and odds of 3.54 for gestational hypertension and RR -of 6.33, odds of 7.42 for pre-eclampsia in women with low PAPP-A levels. A similar positive but strong correlation was found in various other studies (21,22). Also, there was a significant association between abortion and intrauterine fetal demise (p=0.01 and p=0.04, respectively) with RR of -4.69 and odds of 4.99 for abortions, and RR of -4.52 and odds of 4.73 for IUFD in women with low PAPP-A levels. The study by Barrett et al (20), observed a strong correlation for increased pregnancy loss, and Kaijomaa et al (22), also reported an OR of 7.7 for spontaneous abortions in the low PAPP-A group, suggesting a strong risk factor. These can be explained by defective placentation, inflammatory cascade activation, and rejection of the fetus resulting in various complications. However, the incidence of gestational diabetes, preterm delivery, and placental abruption did not show a significant correlation with low PAPP-A levels in our study. We noticed no statistically significant increase in the rate of cesarean section in women with low PAPP-A levels which was in contrast with the study by Singh et al (15).

Singh et al (15) also observed that fetal outcomes like IUFD, low birth weight, SGA babies, prematurity, and NICU admissions were significantly associated with low (<0.5 MoM) serum PAPP-A levels. Our study too corroborated the association of adverse neonatal outcomes with low PAPP-A levels. APGAR <5 at 1 min and low birth weight of < 5th centile showed a significant association with low PAPP-A (p=0.004 and p=0.001, respectively) with RR of 1.74 and odds of 1.95 for low APGAR at birth and RR of 2.88 and odds of 3.36 for low birth weight in the group A. The requirement of NICU admission and neonatal demise within seven days was significantly high in group A (p<0.05) with an RR of 2.61 and odds of 3.19 for NICU admission and RR of 11.22 and odds of 11.66 for early neonatal death within seven days.

Limitations

The limitations of the study are acknowledged. Firstly, the study was conducted at a single center and the sample was representative of a relatively privileged segment of the population, which may limit the generalizability of the findings to other populations. Secondly, the sample size was relatively small, which may have affected the statistical power of the study and its ability to detect significant associations. Also, although the study controlled for several potential confounding factors, there may be other unmeasured confounders that could affect the observed associations.

Conclusion

A single biomarker, serum PAPP-A levels in the first trimester of pregnancy has the potential of being used as a validated marker for adverse pregnancy outcomes. Distinguishing these high-risk pregnancies with low levels of

PAPP-A can help in optimizing maternal and fetal outcomes by closer surveillance, timely intervention, and referral to tertiary care centers if needed. Further research on the subject would help the fraternity in developing a prediction model and formation of a preventive strategy for various obstetric adverse events.

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Compliance with Ethical Requirements: All participants signed informed written consent before being enrolled and the study was conducted in accordance with the Declaration of Helsinki. The study was approved by the institutional ethical committee of Base Hospital & Army College of Medical Sciences, Delhi Cantt, New Delhi India 24 Aug 2020 vide IEC No IEC/08/2020/02.
Availability of data and materials: The dataset used and/or analyzed during the current study are available from the corresponding author on reasonable request.
Authors' Contributions: Each author contributed to the conception and design, data collection and analysis, experiments, writing of the manuscript, and supervision. Each author contributed to the writing of the paper and has read and approved the final manuscript.
Conflicts of Interest: Dey Madhusudan, Chaudhury Priyanshi, Chawla Sunil, Dhume Pranjali, Goel Suyash, Shah Ankur, Gowda KN Mounica declare that they have no conflict of interest.

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