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Original Research Article

Effect of first trimester maternal serum pregnancy associated plasma protein: a level on fetomaternal outcome

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ABSTRACT

Background: Serum pregnancy-associated plasma protein-A (PAPP-A) levels fluctuate in continuation with the pregnancy and thus become an important standalone marker in monitoring the adverse outcomes that may occur in pregnancy.
Methods: A prospective observational study was conducted in the department of obstetrics and gynaecology. A total of 240 pregnant women in their first trimester were included in the study. Serum PAPP-A levels were measured at 11-13+6week of gestation and were evaluated with respect to the feto-maternal outcome. The data was entered in MS excel spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.
Results: The mean age of the study population was 27 years. Among the maternal pregnancy parameters, PIH, pre-term labor and Emergency LSCS were significantly associated with low (<0.5 MoM) Serum PAPP-A levels, P<0.05. All the fetal outcome measures: IUGR, IUD, low birth weight, SGA babies, prematurity and NICU admissions, were significantly associated with low (<0.5 MoM) Serum PAPP-A levels, p <0.05.
Conclusions: Serum PAPP-A in the early pregnancy showed significant correlation with feto-maternal outcome. Thus, it has the potential to be used as a prognostic factor and in the management of adverse outcomes by increasing surveillance for pregnant women with high-risk factors.

Keywords: Early pregnancy, Feto-maternal outcome, Pregnancy-associated plasma protein-A, Prognostic marker

INTRODUCTION

Pregnancy-associated plasma protein-A (PAPP-A), a large glycoprotein, is proteolytic in nature. In the very start of pregnancy, it causes activation of insulin-like growth factor (IGF-1) which causes local proliferative processes such as trophoblastic invasion leading to vascularization and early development of placenta.[1]

It has many other functions such as -Prevention of recognition of the fetus by the maternal immune system, matrix mineralization, wound healing, bone remodeling, and angiogenesis.[2] Thus, its role is very crucial in the early development of fetus, placenta and outcome of pregnancy. Decreased level of PAPP-A during 1st trimester can lead to adverse feto-maternal outcomes such as late abortions, IUGR, preterm delivery, preeclampsia, and stillbirth.[3]

Although its role in conjunction with free serum beta HCG and fetal nuchal translucency has been well established in the 1st trimester screening of chromosomal abnormality but its significance as an individual predictor for adverse outcomes associated with pregnancy like

early abortion stillbirth, intrauterine uterine growth retardation (IUGR), gestational diabetes mellitus (GDM), intrauterine death (IUD), preterm delivery, Pregnancy-induced hypertension (PIH) is still being studies. Morris RK et al, reviewed 32 studies and concluded that first trimester low maternal serum PAPP-A is associated with adverse pregnancy outcomes, but predictive values are poor and further work should be done to address PAPP-A as an adverse prognostic marker.[4]

In India and worldwide, high literacy and assisted reproductive technology (ART) especially among urban women is contributing a lot in starting late family life. Therefore, if PAPPA, as an individual marker, can be established as a predictor for such adverse outcomes, preventive steps could be taken to either rectify or modify the course of the disease well in time for the better fetomaternal outcome.

Thus, this study was conducted to correlate the levels of PAPP-A in early pregnancy with the maternal and fetal outcome so that it can act as an indicator to start preventive measures at the earliest.

METHODS

The prospective observational study was conducted in the department of obstetrics and gynecology, at a tertiary hospital, New Delhi, from November 2017 - March 2019. The study was approved by the institutional ethics and review board.

A total of 300 consenting pregnant women, fulfilling inclusion and exclusion criteria were registered for this study, 18 women were lost to follow up, 20 women did not report for sampling and 22 samples were hemolysed. Finally, 240 subjects were followed up throughout pregnancy and labor for the fetomaternal outcome with PAPP-A levels.

Inclusion criteria

- Pregnant woman in the first trimester
- Age 20-35 years
- Singleton pregnancy
- Dating confirmed.

Exclusion criteria

- Congenital anomaly
- Family history of chromosomal anomalies
- Known case of chronic diseases (coronary artery disease, chronic kidney disease, type II DM, hypertension, connective tissue disorder and hypothyroidism)
- IVF conception.

A detailed clinical, menstrual, obstetric, past, and family history were taken.

Clinical examination

General physical and systemic examination was done. All routine antenatal investigations were advised and reviewed.

Estimation of Serum PAPP-A

- 4 ml of blood was collected through venepuncture and sent to the department of biochemistry, for measuring serum PAPP- A levels
- Samples were centrifuged at 4000 rpm for 5 min. 22 samples were hemolysed during centrifugation
- The serum was separated and stored at -20ºC. PAPP-A levels were analyzed in batches of 80 samples using the Chemiluminescence method on Beckman coulter UniCel DxI 600 Analyser by using Access PAPP-A reagent kit
- Auto analyser instantly provided the result of PAPP-A levels in ng/mL within one hour
- For comparison and statistical analysis individual results were converted into mIU/mL and multiple of median (MoM) by using formulae [5]
  a. 1ng/mL= 411×1 mIU/mL
  b. MOM = individual result (mIU/mL)/median of study population× 2400
- Results in MoM were recorded in a preformed Performa along with the clinical data of the patient
- 240 Study subjects were followed up throughout pregnancy and during labour
- Correlation of first-trimester maternal serum PAPP-A level in MoM and the fetomaternal outcome was observed by suitable methods.

Maternal outcome measures

- Abortions
- Preterm labor or delivery
- Fetal growth restriction
- Gestational diabetes mellitus (GDM)
- Pregnancy-induced hypertension (PIH)
- Mode of delivery (VD/LSCS)

New-born outcome measures

- Prematurity Apgar score AGA, SGA, LGA
- IUD
- NICU admission
- Indication and duration of stay.

Statistical analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean±SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used.

Statistical tests were applied as follows

- Quantitative variables were compared using the Independent t test/Mann-Whitney test (when the data sets were not normally distributed) between the two groups and ANOVA/Kruskal Wallis test between three groups
- Qualitative variables were correlated using Chi-Square test/Fisher's exact test. A p-value of <0.05 was considered statistically significant.

The data was entered in MS excel spreadsheet and analysis was done using statistical package for social sciences (SPSS) version 21.0.

RESULTS

Pregnant women included in the study underwent complete clinical evaluation during their OPD visit. serum PAPP-A were measured at 11-13+6 weeks of gestation. Results of laboratory investigations were recorded and converted in multiple of median (MoM) for study in a preformed proforma.

To study the fetomaternal outcome according to various levels of PAPP-A. It was divided into two groups. At low PAPP-A levels (<10 centile, <0.5 MoM) and normal level (>10 centile, 0.5 MoM).

Table 1: Age distribution.

Age distribution in years	Serum PAPP-A levels(MOM)		Total	p-value
	<0.5	>=0.5		
20-25 years	5 (20.83%)	78 (36.11%)	83 (34.58%)	0.227
26-30 years	16 (66.67%)	105 (48.61%)	121 (50.42%)	
31-35 years	3 (12.50%)	33 (15.28%)	36 (15.00%)	
Total	**24 (100.00%)**	**216 (100.00%)**	**240 (100.00%)**	

Table 2: Association of maternal outcome with serum PAPP-A levels.

Maternal outcome		Serum PAPP-A levels(MOM)		Total (n)	p-value
		<0.5	>=0.5		
PIH	No	16 (66.67%)	199 (92.13%)	215	0.0001
	Yes	8 (33.33%)	17 (7.87%)	25	
Preterm labor	No	20 (83.33%)	206 (95.37%)	226	0.039
	Yes	4 (16.67%)	10 (4.63%)	14	
GDM	No	23 (95.83%)	196 (90.74%)	219	0.704
	Yes	1 (4.17%)	20 (9.26%)	21	
Mode of delivery	Em LSCS	7 (29.17%)	26 (12.04%)	33	0.017
	Instrumental	1 (4.17%)	1 (0.46%)	2	
	LSCS	5 (20.83%)	37 (17.13%)	42	
	NVD	11 (45.83%)	152 (70.37%)	163	

Table 3: Association of fetal outcome with Serum PAPP-A levels.

Fetal outcome		Serum PAPP-A levels (MOM)		Total	p-value
		<0.5	>=0.5		
IUGR	No	21 (87.50%)	186 (86.11%)	207	1.000
	Yes	3 (12.50%)	30 (13.89%)	33	
IUD	No	21 (87.50%)	215 (99.54%)	236	0.003
	Yes	3 (12.50%)	1 (0.46%)	4	
Birth weight (kg)	<2.5 kg	12 (50.00%)	54 (25.00%)	66	0.009
	>=2.5 kg	12 (50.00%)	162 (75.00%)	174	
SGA/AGA/LGA	AGA	12 (50.00%)	182 (84.26%)	194	<.0001
	IUD/still birth	3 (12.50%)	2 (0.93%)	5	
	LGA	1 (4.17%)	2 (0.93%)	3	
	SGA	8 (33.33%)	30 (13.89%)	38	
Prematurity	No	15 (71.43%)	190 (88.79%)	205	0.023
	Yes	6 (28.57%)	24 (11.21%)	30	
NICU admission/indication/duration of stay	No	12 (57.14%)	171 (79.91%)	183	0.016
	Yes	9 (42.86%)	43 (20.09%)	52	

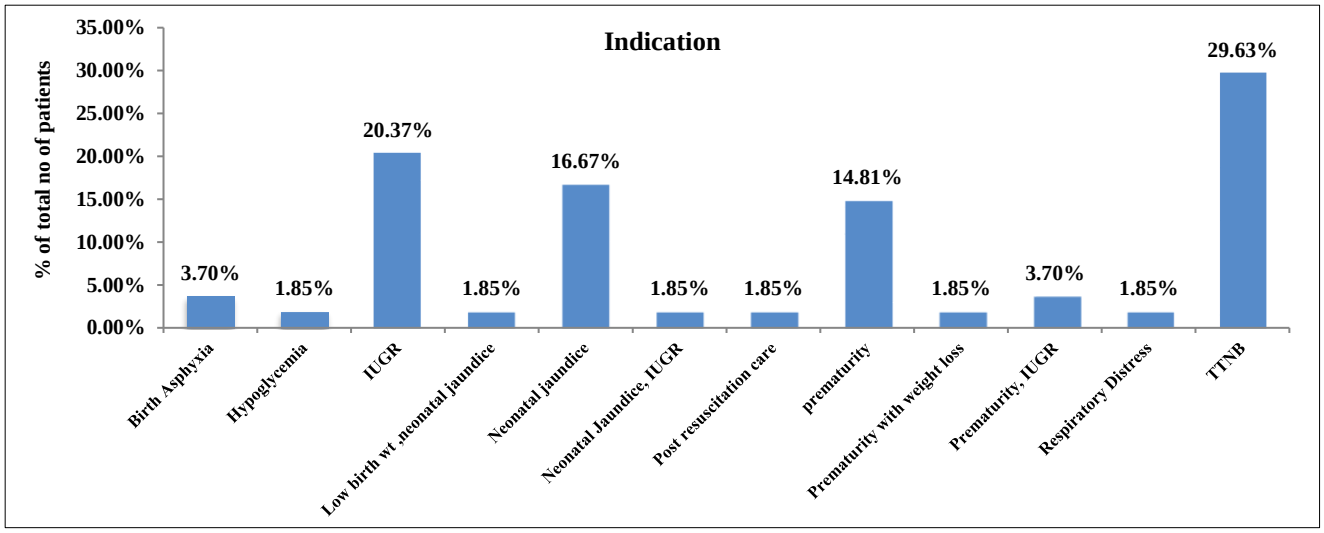
The mean age of the study population was 27 years. It ranges from 20 to 35 years with a maximum study subject in the age group of 26 to 30 years. The youngest study subject was 20 years old and the oldest was 35 years of age (Table 1).

In the study population, median BMI was 23.56 kg/m^2 with minimum BMI-18.2 and maximum 35.15 kg/m^2. The median PAPP-A level of the study population was 1.01 MoM with a minimum of 0.02 MoM to Max of 3.24 MoM.

There were 50.83% pregnant women who were primigravida and 49.17% were multigravida.

PIH, pre-term labor and emergency LSCS were significantly associated with low (<0.5 MoM) Serum PAPP-A levels, p <0.05 (Table 2).

Fetal outcome measures: IUD, low birth weight, SGA babies, prematurity and NICU admissions, were significantly associated with low (<0.5 MoM) serum PAPP-A levels, p <0.05 (Table 3).



TTNB: Transitory tachypnea of newborn, IUGR: Intra-uterine growth retardation

Figure 1: Indications of NICU admission.

In this study, transitory tachypnea of new-born was the most common indication of NICU admission followed by growth retardation and neonatal jaundice (Figure 1).

DISCUSSION

Antenatal care universally aims for a healthy mother with a healthy newborn. But pregnancy carries considerable risk to both mother and fetus in due course of these 280 days long journey. So, the primary objective of prenatal care is to detect women at high risk of developing complications later in pregnancy, preferably in the first trimester for early preventive intervention.

PAPP-A can serve as a predictor for detecting women with adverse pregnancy outcomes. Several studies have reported the ethnicity of the study population influencing the level of PAPP-A biochemical marker. Krantz et al, suggested that all ethnic groups should have their reference range for PAPP-A levels in pregnancy, Leuwan S established a cut off range of PAPP-A and adverse outcomes associated with them in Thai population.[6,7] There were limited studies for assessing the effect of serum PAPP-A levels on the fetomaternal outcome for the Indian population. In the current study, efforts were made to assess various outcomes at different thresholds of PAPP-A among the Indian population. The objective was to assess fetomaternal outcomes at various levels of serum PAPP-A, that is, less than 10% centile (<0.5 MoM), and more than or equal to 10% centile (>0.5 MoM).

Most of the studies have taken a single parameter for evaluating the role of PAPP-A in fetomaternal outcome. In the present study, multiple parameters were evaluated concerning different PAPP-A levels.

Among the study population (n = 240) it was observed that significant adverse fetomaternal outcome was seen in 164 (68.33%) pregnant woman. 3 out of 4 intrauterine deaths occurred in <0.5 MoM group. On further analysis, <0.5 MoM PAPP-A level was a strong predictor for LBW (50%), PIH (33%), and preterm birth (16.67%).

A low level of PAPP-A causes abnormal placentation which is a proven etiopathogenesis of PIH, IUGR and in extreme cases IUD. PAPP-A is secreted from trophoblastic septal X cells, which causes the proteolysis of IGFBP-4 in placental bed at the fetomaternal interface to release IGF-1.[8] IGF causes trophoblastic invasion into

maternal decidua for the establishment and early development of the placenta and its vasculature. Distribution of adverse outcomes with various levels of PAPP-A, clearly indicates the inverse relation of serum PAPP-A at 1st trimester. The current study supports that the lower value of PAPP-A that is <0.5 MoM (<10% centile) is associated with increased risk of IUD, PIH, preterm labor, emergency LSCS, SGA, prematurity, and NICU admission.

In the present study, the incidence of PIH was more in women with PAPP-A level less than 0.5 MoM as compared to other groups. Similar results were concluded by Gorden C et al; that low PAPP-A levels were associated with increased risk of PIH (7.6% versus 3.5%).[9] The study conducted by Yarou et al, showed that low PAPP-A (<0.25 MoM) levels are predictive for pre-eclampsia with a relative risk of 6.09.[10] In another study conducted by Kaijomaa M et al, there was an increased incidence of PIH in the study group (<0.3 MOM) compared to the control group (0.9 - 1.1 MOM) (4.7% versus 2.5%).[11] Weaver A et al, reported that low PAPP-A (≤0.3 MOM) is associated with a higher incidence of PIH.[12] The difference in statistical analysis between the current study and other studies can be due to different cut off ranges in various studies. Contrary to above findings Saruhan Z et al, calculated 5th and 10th centile of PAPP-A levels with no significant relation was between low PAPP-A values and fetomaternal outcome such as PIH, IUGR, SGA, preterm delivery, increase rate of emergency LSCS.[13] They could not furnish any explanation for the same and attributed it to retrospective small size study along with the genetic background of population.[7]

The burden of IUGR is concentrated mainly in developing countries especially in Asia which accounts for nearly 75% of all affected infants. In India, the prevalence of LBW has been reported as 26% and IUGR 14.56%. This was in consensus with the present study where the Incidence of IUGR was 13.75% (33/240). Low PAPP-A group (< 0.5 MoM) had only 3/33 patients who developed IUGR. On summing the < 0.5 MoM and 0.5-1 MoM groups, 25/33 patients developed IUGR. 75.75% of women could have been predicted with 1 MoM as PAPP-A cut-off. With timely intervention, this problem could have been reduced. According to Saruhan Z et al, PAPP-A is not the only factor that controls IUGR as higher levels of PAPP-A could be expected in cases of macrosomia.[13] On the other hand, many studies have reported that a low level of serum PAPP-A was responsible for abnormal placentation and vascularization which causes reduced growth of the fetus. Vandenberghe G et al concluded that PAPP-A MoM was significantly lower than control (p = 0.003) in a growth-restricted fetus.[14] Montanari L et al, reported that low serum PAPP-A levels (< 10% centile) were associated with increased risk of IUGR due to placental dysfunction with OR of 3.9 (11% versus 8%).[15] According to Lau H et al, PAPP-A can be a useful tool to screen for impaired placentation associated with IUGR, as PAPP-A levels (<0.45 MOM) <1st percentile had a PPV value for IUGR (15% versus 2.8%).[16] The discrepancy in the current study and other studies can be explained based on ethnicity, geographical distribution, the genetic potential of the population, small sample size of the study and other confounding factors not included in this study.

New-born babies born to women with low PAPP-A (<0.5 MOM), more incidence (33.33%) of SGA was noted. Montanari L et al, also reported that the prevalence of SGA was significantly higher (17% versus 8%) among women with serum PAPP-A level below 10% centile compared to those with levels >10th centile.[16] According to Spencer K et al, detection rates of SGA were 12%, 14% and 16% with PAPP-A level below 10th, 5th and 3rd centile of normal respectively.[17] Kirkiguard I et al, predicted the strong association between PAPP-A <0.3 MoM and SGA (Odds Ratio 3.0).[18] Serum PAPP-A promotes the proteolysis of IGFBP and releases IGF, regulates steroidogenesis and causes transport of glucose and amino acids in villus at materno-fetal interface hence low levels of PAPP-A decreases the growth of the fetus. Contrary to the majority in agreement to the present study, Saruhan Z et al, did not observe any association between PAPP-A levels and SGA.[13] They reasoned it with the fact that the study had a retrospective design and had a small sample size.

In the present study, 16/24 (66.67%) subjects with PAPP-A <0.5 MoM had babies with birth weight less than 2.5 kg. This can be explained by abnormal placentation as discussed above. Kaijomaa M et al, also found a significant difference in the birth weight of Low PAPP-A cohort and normal PAPP-A cohort (3121±720.5 g versus 3511±572.3 g; p= <0.001).[19]

Out of the total study population, 5.83% (14 out of 240) subjects developed preterm labor. Women with PAPP-A level <0.5 MoM had highest incidence of preterm labor i.e. 28.5% (4/14) (p = 0.006). Every 4th pregnant woman with low PAPP-A (<0.5 MoM) is most likely to have preterm delivery. Many studies postulated that lower the concentration of PAPP-A in 1st trimester, more the likelihood of preterm labor in women. This was evident in the present study also. Similar results were reported by Gordon C et al, (10%) deriving association between extreme premature delivery and lowest centile of PAPP-A.[9] Goetzinger et al, stated that the risk of preterm delivery (<35 weeks) increased with <10% centile of PAPP-A.[19] Dane B et al, established an association of low PAPP-A levels (<0.35 MoM, <5% centile) with early preterm labor.[20] According to Jelliffe-Pawlowski L et al, early preterm labor was associated with PAPP-A level <5% centile.[2] It has been shown that IGF-1 is the key factor for autocrine and paracrine control of trophoblastic invasion into the decidua and IGF is regulated by PAPP-A protein, this abnormal trophoblastic invasion leads to poor placentation and further development of preterm labor. Contrary to the above studies, Montanari L et al,

could not demonstrate a significant association between PAPP-A values and preterm delivery (6.3% of pregnant women).[15] This could be due to the small sample size of the study. Various levels of PAPP-A were studied for their correlation with preterm labor.

In current study, 12.5% subjects in <0.5 MoM group had stillbirth while only 0.8% subjects with >1.0 MoM. It indicates that the risk of IUD increased to more than 15 times as the value of PAPP-A levels lowers down from >1 MoM to <0.5 MoM. This can be attributed to preterm birth as 3 preterms (weight 462 g, 700 g, and 1.4 kg) IUD were recorded with PAPP-A level <0.5 MoM. One full term sudden IUD (2.4 kg) was noted with PAPP-A level >1 MoM, where the cause could not be established. Similarly, Gorden CS et al, reported that 0.9% pregnant women in the study group (<5% centile) had stillbirths compared to >5% centile.[9] Patil M et al, observed no stillbirth in subjects with normal PAPP-A levels while only one stillbirth reported out of 72 study subjects with PAPP-A levels <0.5 MoM.[22] In Kaijomaa M, who studied 961 pregnant women with low (<0.3 MoM) PAPP-A levels, 9 (0.9%) pregnancy resulting in stillbirth were observed in this group compared to normal population group (0.9-1.1 MoM).

The total number of GDM cases in the current study was 21 (8.75%) which was not comparable with a prevalence of GDM in Asia (5-8%) including India.[23] The highest percentage of GDM was seen in PAPP-A >1 MOM i.e 12.30% as compared to PAPP-A levels <0.5 MOM i.e 4.17% and 0.5 -1 MOM i.e. 5.32% which was not statistically significant (p = 0.14). Similarly, Cheuk QK et al did not observe any difference in 1st-trimester serum PAPP-A levels in women with or without GDM.[24] According to Savvidou MD et al, median PAPP-A was reduced only in type 2 diabetes and there were no significant differences in maternal PAPP-A between GDM and type 2DM.[25] According to Saruhaan Z et al, no significant association (p = 0.99) was determined between GDM and PAPP-A levels <10% centile (2.9%) and > 10% centile (4.9%).[13] In the Indian scenario, we cannot give importance to PAPP-A levels and predict GDM in later pregnancy. India being capital of diabetes, one step and two-step glucose challenge test as per ACOG and FOGSI guidelines is mandatory in high-risk population and diabetes mellitus were included in the exclusion criteria of the study. Depending on the presence or absence of risk factors in the first visit and 2nd trimester, the patient should be screened for diabetes. Large studies are required to develop a correlation between GDM and 1st-trimester serum PAPP-A levels.

No association of PAPP-A levels and second-trimester abortion could be established in this study. In contrast, other studies demonstrated a positive correlation between low PAPP-A levels and abortion. According to Gupta S et al, 148/1640 women had PAPP-A values <0.4 MoM.[26] Out of which 18 (12%) women had spontaneous/missed abortion. According to Lau H et al, PAPP- A <0.29 MoM can be a useful tool to screen for impaired placentation and a significantly higher ratio of spontaneous fetal loss ≤24 weeks.[16]

The main limitations of the study were small sample size and the lack of the genetic analysis of the patients and the family.

CONCLUSION

It was concluded that PAPP-A can assess adverse maternal and fetal outcomes. Thus, it has the potential to be used as a prognostic factor in the management of adverse outcomes by increasing surveillance for pregnant women with high-risk factors.

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