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Original Article

Obstetrics and Gynaecology Section

Early Prediction of Small for Gestational Age: The Predictive Role of Pregnancy Associated Plasma Protein-A

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ABSTRACT

Introduction: Small for Gestational Age (SGA) is a compelling obstetric adversity with multiple consequences. Early diagnosis, although a challenge, can help blunt the adverse effects. One of the markers is Pregnancy Associated Plasma Protein-A (PAPP-A) which can be an early predictor of SGA.

Aim: To find the association of low levels of pregnancy associated plasma protein-A with small for gestational age.

Materials and Methods: This prospective observational study was conducted in the Department of Obstetrics and Gynaecology at All India Institute of Medical Sciences, Raipur, Chhattisgarh, India, between June 2018 and September 2019. The demographic profile, PAPP-A Multiples of Median (MoM) levels, complications in pregnancy and birth outcome data of a total of 203 women were noted. For analysis of descriptive and categorical data, IBM Statistical Package for the Social Sciences (SPSS) statistical software version 23.0 was used. Shapiro-Wilk and Kolmogorov-Smirnov tests were performed to assess normality of distribution. Qualitative data were analysed by Chi-square test and categorical data, by Mann-Whitney's U test.

Results: The mean maternal age of the study sample was 27.4±2.23 years. The prevalence of SGA was 18.2%, out of which PAPP-A MoM levels were ≤0.49 in 59.4%. The association between PAPP-A levels and SGA was statistically significant (p-value=0.03) with unadjusted odds ratio of 8.27 (95% CI, 3.78-18.08). Simple logistic regression showed an inverse relationship of PAPP-A with SGA. At the cut-off of ≤0.49 considered in the study, sensitivity was 86.7%, specificity was 54.1%, positive predictive value was 29.5% and negative predictive value was 94.8%. Positive likelihood ratio was 1.88 and negative likelihood ratio was 0.24 and the diagnostic accuracy was found to be 59.9%.

Conclusion: An inverse relationship between levels of PAPP-A MoM (≤0.49) and SGA was found in the study. Low levels of PAPP-A MoM can be a useful early predictor of SGA.

Keywords: Early diagnosis, Foetal outcome indicator, Placental biomarkers

INTRODUCTION

Small for Gestational Age (SGA) is a neonate with birth weight less than 10th percentile of the expected birth weight [1]. It has a major influence on perinatal morbidity and mortality. Foetal Origins of Adult Diseases (FOAD), the Barker hypothesis, observes that the children born SGA suffer short and long-term cardiovascular, neurological and endocrinological adverse consequences [2]. Pregnancy Associated Plasma Protein-A (PAPP-A) is one of the several markers studied for early identification of adverse pregnancy outcomes. It is a well-established bio-marker for screening of Down syndrome in the first trimester (11 to 13+6 weeks) [1,3]. Studies indicate that a decreased level of PAPP-A may be a sign of impaired placental implantation and function [4,5].

The PAPP-A, a placental glycoprotein, cleaves Insulin-like Growth Factor Binding Protein-4 (IGFBP-4) and is a positive regulator of Insulin-like Growth Factor (IGF) [6]. The IGF is known to have a significant influence on foetal growth. Decreased levels of PAPP-A in the maternal serum, determined in the first trimester, are associated with poor placental function, a known etiology for SGA [7,8]. Therefore, PAPP-A can be used as a marker for early detection of the SGA [9]. Royal College of Obstetricians and Gynaecologists (RCOG) recommends that those pregnant women with a serum PAPP-A <0.4 Multiples of Median (MoM) in the first trimester must receive increased ultrasound surveillance for foetal growth disorders [1]. However, there exists no definition for low levels of PAPP-A and what cut-off of PAPP-A MoM is to be considered pathological, remains undefined. Thus, the aim of this research was to study the association of low levels of PAPP-A levels with SGA babies.

MATERIALS AND METHODS

This prospective observational study was conducted in the Department of Obstetrics and Gynaecology at All India Institute of Medical Sciences, Raipur, Chhattisgarh, India, between June 2018 and September 2019. Ethical clearance was obtained from the Institute Ethics Committee of All India Institute of Medical Sciences, Raipur (AIIMSRPR/IEC/2018/168).

Inclusion and Exclusion criteria: All women attending the antenatal clinic with singleton pregnancy, having reports of PAPP-A MoM levels and willing to participate in the study were included in the study. Those women with unsure dates, multiple pregnancy, congenital anomalies and known maternal chronic diseases like thyroid dysfunction, Diabetes Mellitus, collagen vascular diseases, chronic hypertension, liver and renal disorders were excluded from the study.

Sample size calculation: Sample size was calculated from prevalence of SGA using the formula:

$$\frac{Z^2p(1-p)}{d^2}$$

where,

Z=1.96, p=14.54% as per a study conducted by Agarwal R et al., et al., [9] and d=0.05. Considering a dropout rate of 10%, the sample size estimate was 210.

Study Procedure

Total 210 women with serum PAPP-A MoM levels, drawn between 11 weeks and 13 weeks and six days of gestation were recruited [9]. After initial evaluation, the women were followed-up in the antenatal clinic. At each visit, history taking and clinical examination were done and reports of routine investigations relevant to that particular gestational age (including the values of double marker) were noted. Ultrasonographic findings of dating scan, early anomaly scan (11-13+6 weeks), targeted imaging for foetal anomalies (18-22 weeks), growth scans and doppler studies were noted. After delivery, gestational age at birth of the baby, mode of delivery, the sex of the newborn and birth-weight were noted. The primary outcome was SGA. Birthweight <10th percentile for that gestational age was considered as SGA [1]. The birth weight was plotted on the INTERGROWTH-21st chart to determine the percentile. Low PAPP-A was defined as MoM ≤0.49, measured between 11 and 13+6 weeks of gestation [10,11].

Out of 210, four women were lost to follow-up and three women had abortion. The data of 203 women were analysed to find the association of low levels of PAPP-A MoM with SGA.

STATISTICAL ANALYSIS

Microsoft excel version 15.0 was used for compilation of data. For analysis of descriptive and categorical data, IBM Statistical Package for the Social Sciences (SPSS), statistical software version 23.0 was used. Shapiro-Wilk's and Kolmogorov-Smirnov's tests were performed to assess normality of distribution. Qualitative data were analysed by Chi-square test and Categorical data, by Mann-Whitney's U test. To obtain the strength of association, Odds ratio was used. Simple logistic regression estimate of PAPP-A in predicting SGA, using Wald T test, was obtained. Receiver Operator Characteristics (ROC) was used for analysis of the Area Under the Curve (AUC) for PAPP-A. The p-value of 0.05 was considered significant.

RESULTS

The mean maternal age was 27.4±2.23 years. Most women were urban residents (59.11%, n=120). Total 110 (54.18%) women were primigravida. The mean Body Mass Index (BMI) [12] was 23.92±1.33 kg/m^2.

The prevalence of SGA in the study was 18.2% (n=37). The incidence of SGA was found to be higher in urban residents (p-value=0.023) and in those women who had Assisted Reproductive Technology (ART) conceptions (p-value=0.007). No association of SGA with age, socio-economic status [13], gravidity or BMI was found [Table/Fig-1]. PAPP-A levels were not found to be significantly different in women belonging to different age groups, socio-economic status [13], residential status, gravidity and different BMI groups [Table/Fig-2].

Variables	SGA (n, %)	Non SGA (n, %)	Total (n, %)	p-value*
Age (years)				
18-20	7 (18.9)	54 (32.53)	61 (30.04)	0.104
21-25	17 (45.94)	82 (49.39)	99 (48.76)	
26-30	10 (27.02)	24 (14.45)	34 (16.74)	
31-35	3 (8.10)	6 (3.61)	9 (4.43)	
Socio-economic status class (Modified B G Prasad Scale) [13]				
I	26 (70.27)	143 (86.14)	169 (83.25)	0.119
II	6 (16.21)	13 (7.83)	19 (9.35)	
III	2 (5.40)	7 (4.21)	9 (4.33)	
IV	1 (2.70)	1 (0.60)	2 (0.98)	
V	2 (5.40)	2 (1.20)	4 (1.97)	
Residential status				
Rural	9 (24.32)	74 (44.57)	83 (40.88)	**0.023**
Urban	28 (75.67)	92 (55.42)	120 (59.11)	
Mode of conception				
Spontaneous	4 (10.81)	3 (1.80)	7 (3.44)	**0.007**
ART	33 (89.18)	163 (98.19)	196 (96.55)	
Gravidity				
Primigravida	14 (37.83)	96 (57.83)	110 (54.18)	0.076
Gravida 2	22 (59.45)	65 (39.15)	87 (42.85)	
Gravida 3	1 (2.70)	5 (3.01)	6 (2.95)	
Gravida 4 and above	Nil	Nil	Nil	
Body mass index (kg/m^2) [12]				
<18.5	1 (2.70)	6 (3.61)	7 (3.44)	0.281
18.6-22.9	8 (21.62)	58 (34.93)	66 (32.51)	
23.0-24.9	11 (29.72)	51 (30.72)	62 (30.54)	
>25.0	17 (45.94)	51 (30.72)	68 (33.49)	

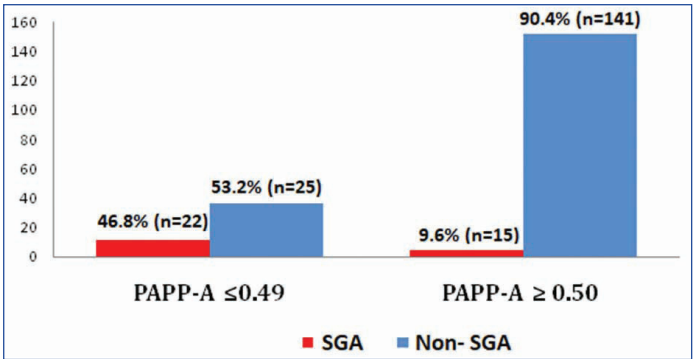
[Table/Fig-1]: Demographic profile of the study population and SGA.
*Chi-square test; ART: Assisted reproductive technology; p-value of 0.05 was considered significant

Variables	PAPP-A (n, %)	PAPP-A (n, %)	Total (n, %)	p-value*
Age (years)				
18-20	11 (23.4)	50 (32.05)	61 (30.04)	0.110
21-25	22 (46.80)	77 (49.35)	99 (48.76)	
26-30	13 (27.65)	21 (13.46)	34 (16.74)	
31-35	1 (2.12)	8 (5.12)	9 (4.43)	
Socio-economic status class (Modified BG Prasad Scale) [13]				
I	39 (82.97)	130 (83.33)	169 (83.25)	0.949
II	5 (10.63)	14 (8.97)	19 (9.35)	
III	2 (4.25)	7 (4.48)	9 (4.43)	
IV	0	2 (1.28)	2 (0.98)	
V	1 (2.12)	3 (1.92)	4 (1.97)	
Residential status				
Rural	23 (48.93)	60 (38.46)	83 (40.89)	0.336
Urban	24 (51.06)	96 (61.53)	120 (59.11)	
Mode of conception				
Spontaneous	42 (89.36)	154 (98.71)	196 (96.55)	**0.009**
ART	5 (10.63)	2 (1.28)	7 (3.44)	
Gravidity				
Primigravida	27 (57.44)	83 (53.20)	110 (54.18)	0.381
Gravida 2	20 (42.55)	67 (42.94)	87 (42.85)	
Gravida 3	0	6 (3.84)	6 (2.950)	
Gravida 4 and above	Nil	Nil	Nil	
Body mass index (kg/m^2) [12]				
<18.5	1 (2.12)	6 (3.84)	7 (3.44)	0.182
18.6-22.9	21 (44.68)	45 (28.84)	66 (32.51)	
23.0-24.9	10 (21.27)	52 (33.33)	62 (30.54)	
>25.0	15 (31.91)	53 (33.97)	68 (33.49)	

[Table/Fig-2]: Demographic profile of the study population and PAPP-A MoM.
*Chi-square test; ART: Assisted reproductive technology; p-value of 0.05 was considered significant

The lowest PAPP-A MoM level recorded was 0.21 and the highest was 5.54. The mean PAPP-A MoM level was 1.89±1.34. PAPP-A MoM levels were ≤0.49 in 47 (23.15%). Among women with PAPP-A MoM level ≤0.49, 22 (46.8%) had SGA whereas among women with PAPP-A MoM level ≥0.5, only 15 (9.6%) had SGA [Table/Fig-3]. The median PAPP-A MoM level among SGA neonates was significantly lower than neonates born non SGA (p-value=0.03) [Table/Fig-4].

The association between PAPP-A levels and SGA was statistically significant (p-value=0.03) with unadjusted odds ratio of 8.27 (95% CI) 3.78-18.08). Simple logistic regression showed inverse relationship of PAPP-A and SGA i.e. the lower the PAPP-A, the higher the SGA [Table/Fig-5].



[Table/Fig-3]: Distribution of SGA and PAPP-A.

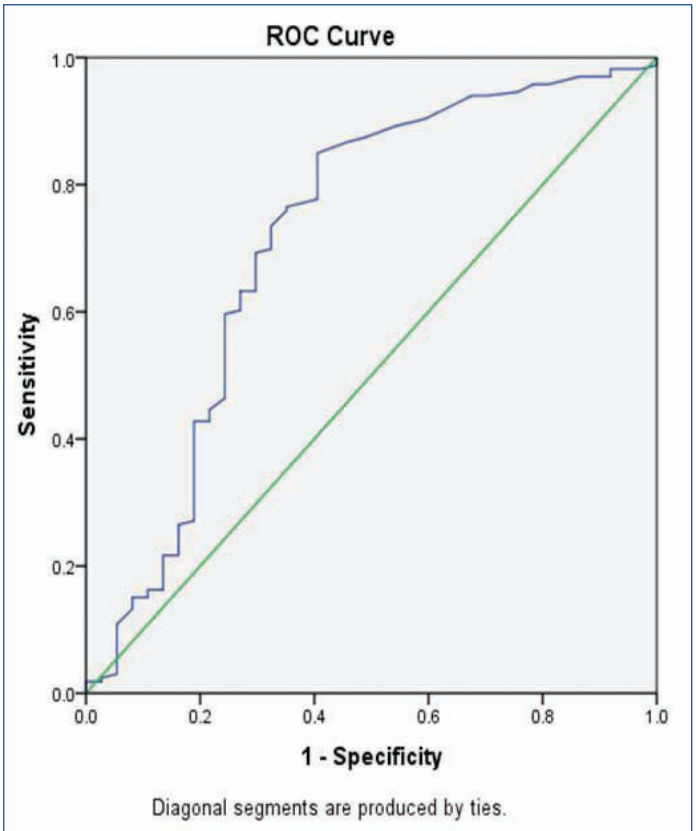
Variable	SGA Median (Q1,Q3)	Non SGA Median (Q1,Q3)	p-value*
PAPP-A	0.47 (0.42, 1.87)	2.05 (0.66, 3.14)	0.03

[Table/Fig-4]: Distribution of Median PAPP-A MoM amongst SGA and non SGA.
*Mann-Whitney U test; p-value of 0.05 was considered significant

Variable	Regression co-efficient	95% CI	p-value*
PAPP-A	-0.55	(-0.881, -0.211)	0.03

[Table/Fig-5]: Simple logistic regression estimate of PAPP-A in predicting SGA.
*Wald T test; p-value of 0.05 was considered significant

The strength of prediction was moderate. Area Under the Curve was 0.72 (95% CI, 0.611,0.823), p-value=0.03 reflecting an optimal cut-off of 0.665 for prediction of SGA of PAPP-A MoM with a sensitivity of 73.5% and specificity of 67.6% positive predictive value was 46.8% and negative predictive value was 90.3% with a positive likelihood ratio of 3.94 and negative likelihood ratio of 0.47 [Table/Fig-6].



[Table/Fig-6]: Receiver Operator Characteristics curve.

At the cut-off of ≤0.49 considered in the current study, sensitivity was 86.7%, specificity was 54.1%, positive predictive value was 29.5% and negative predictive value was 94.8%. Positive likelihood ratio was 1.88 and negative likelihood ratio was 0.24. At these values, the diagnostic accuracy was found to be 59.9%.

In this study, low levels of PAPP-A were found to be significantly associated with preeclampsia, preterm deliveries, and Caesarean deliveries and birth of male child [Table/Fig-7].

Parameters	≤0.49 (n, %)	≥0.50 (n, %)	Total (n, %)	p-value	Odds ratio (95% CI)
Preeclampsia					
Yes	17 (8.33)	6 (2.95)	23 (11.33)	**0.00001**	14.16 (5.16-38.89)
No	30 (14.77)	150 (73.89)	180 (88.66)		
Preterm deliveries					
Yes	8 (3.94)	4 (1.97)	12 (5.91)	**0.001**	7.79 (2.23-27.22)
No	39 (19.210	152 (74.87)	191 (94.08)		
Caesarean deliveries					
Yes	22 (10.83)	38 (18.71)	60 (29.55)	**0.003**	2.7 (1.38-5.39)
No	25 (12.31)	118 (58.12)	143 (70.44)		
Gender of the baby					
Female	18 (8.86)	88 (43.34)	106 (52.21)	**0.029**	2.08 (1.88-4.06)
Male	29 (14.28)	68 (33.49)	97 (47.78)		

[Table/Fig-7]: PAPP-A MoM levels and adverse pregnancy outcomes.

No significant association of low PAPP-A MoM was found with oligohydramnios (p-value=0.120) or increased need for NICU admissions (n=16, p-value=0.299).

DISCUSSION

Small for gestational age refers to the neonates with birth weight less than 10th percentile for the gestational age [1]. It is an adverse entity with recognised short- and long-term adverse consequences. The aim of this study was to find the association of low levels of PAPP-A MoM with Small for gestational age. Since, exists no standard cut-off for defining the low levels of PAPP-A MoM, ≤0.49 was considered, based on the findings of previous studies [9,10,11].

The mean maternal age was 27.4±2.23 years in the present study. The study by Hoseini MS et al., matches the present study where the mean age was 27.88±5.97 years (17-38 years) [14]. The mean maternal age in the study by Mula R et al., was 34.7±4.1years in the SGA group which is higher than that of the present study [15].

In the present study, 54.2% (n=110) women were primigravida. In their prospective longitudinal study, Mula R et al., found that those women with SGA neonates were more frequently nulliparous compared to those women who had normal birthweight neonates (78% vs 63.1%, p-value=0.04) [15]. Although this finding is comparable, the present study did not determine the causal association.

The mean BMI was 23.92±1.33 kg/m^2 in the present study but found no significant association with SGA. Robillard PY et al., found that 25% of SGA neonates were born to women with BMI between 10 and 14 kg/m^2 [16].

The present study found a significant association between ART conceptions and SGA (p-value=0.007). In the study by Gundu S et al., 5.8% (n=78) had ART conceptions but statistical association was not derived [10]. Mula R et al., found that 4% of ART conceptions had SGA neonates and noted no significant association (p-value=0.286) [15].

The mean PAPP-A MoM level in the present study was 1.89±1.34. In their study, Agarwal R et al., found that the median PAPP-A MoM value was significantly lower (0.61 MoM; range 0.30-2.68) in SGA group compared to control group (1.47 MoM; range 0.51-3.06) (p-value=0.001) [9]. Hoseini MS et al., found that the mean PAPP-A level at screening was 1.21±0.66 (range, 0.28-3.37) [14].

The prevalence of SGA was found to be 18.2% in our study which is comparable with the studies of Agrawal R et al., (14.54%) [9] and Hoseini MS et al., (14.5%) [14]. These numbers show that the prevalence is significant and demands attention. The role of PAPP-A in predicting SGA has been studied by other researchers. The findings of some previous studies are summarised in [Table/Fig-8] [9,14,17].

Author, Year	Place of study	Population	Incidence (%)	PAPP-A cut-off	PAPP-A percentile	Sensitivity (%)	Positive predictive value	Odds ratio
Morris RK et al., [17] (2017)	Systemic Review and meta-analysis Birmingham, United Kingdom	175240	-	0.5 0.3	10th 5th 3rd	16 13 3 19 6		1.88 2.08 3.04 1.6 1.55
Agarwal R et al., [9] (2017)	University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India	284	14.54	0.4	-	45	56.2	10.9
Hoseini MS et al., [14] (2020)	Imam Hossein Hospital, Tehran, Iran	715	14.5	0.75	5th	80.9	-	12.37
Present study (2022)	All India Institute of Medical Sciences, Raipur, India	203	18.2	0.49 0.665	5th	70.3 73.5	28.3 33.4	8.2

[Table/Fig-8]: Summary of studies of PAPP-A with SGA SGA [9,14,17].

Agarwal R et al., studied 284 women to investigate the association of PAPP-A levels in the late first trimester with SGA neonates in a prospective case control study [9]. They found that the prevalence of SGA was 14.54%. The found that lower PAPP-A median MoM levels were consistent with SGA. They noted a reasonably high positive predictive value of PAPP-A MoM at ≤5th percentile and opined that PAPP-A may be used as a screening toll for SGA. These findings are in line with the findings of the present study.

Morris RK et al., conducted a meta-analysis of 32 studies including 175,240 pregnancies. They studied various cut-offs of PAPP-A MoM [17]. From their results, they derived clinical interpretation that women with first trimester PAPP-A <5th percentile have one in 5.6 chances of SGA baby, and women with, 1st percentile have a one in 3.6 chance of SGA baby. They highlighted the need for future studies to develop robust and accurate predictive models. However, in contrast to the findings of the present study, they found that PAPP-A had poor predictive values.

Hoseini MS et al., conducted a cross-sectional study of 715 pregnant women in which the prevalence of SGA was 14.5% [14]. Their study found that the best cut-off of PAPP-A MoM was 0.75 at which the sensitivity was 80.9%, comparable to the present study, and that the specificity was 85%. They concluded that the measurement of serum PAPP-A levels at 11 to 13 weeks of gestation can effectively predict the increased risk of SGA neonates. In the present study, the ROC curve showed an optimum cut-off of 0.665 with a sensitivity of 73.5%, and specificity of 67.6%.

The present study showed, low levels of PAPP-A were found to be significantly associated with preeclampsia with OR 14.16 (95% CI: 5.16-38.89), p-value=0.00001. However, Mula R et al., found that the incidence of preeclampsia in SGA group was 8% (n=4), p-value=0.525 which is in contrast to the findings of the present study [15]. Agarwal R et al., found that the sensitivity was 77%, specificity was 95.2% for preeclampsia in <5th percentile of PAPP-A with median of 0.38 (IQR, 0.29-0.51) in the adverse pregnancy outcome group [9].

The present study found a significant association of preterm deliveries with low PAPP-A levels with OR 7.79 (95% CI: 2.23-27.22) p-value=0.001. Gundu S et al., found that PAPP-A <0.4 MoM had a sensitivity of 27.92% for preterm births [OR: 1.84 (95% CI: 1.26-2.68)] [10]. Agarwal R et al., found that the sensitivity was 60%, specificity was 94.8% for preterm births in <5th percentile of PAPP-A with median of 0.66 (IQR, 0.56-1.05) in the adverse pregnancy outcome group [9]. Both these studies indicate an increased incidence of preterm births in low PAPP-A.

The present study found a significant association of Caesarean deliveries with low PAPP-A levels with OR 2.7 (95% CI: 1.38-5.39) p-value=0.003. Mula R et al., found that the incidence of caesarean deliveries in the SGA group was 36% (n=18), p=0.5 which does not match the present study [15]. However, Gupta S et al., found that Caesarean delivery rates were higher in low PAPP-A group compared to controls (20% vs 9%), p-value=0.0017 [18]. This finding is comparable to the present study.

The present study also found a significant association of birth of male child with low PAPP-A levels with OR: 2.08 (95% CI: 1.88-4.06) p-value=0.029. Mula R et al., found that the neonatal feminine sex percentage was 32% (n=16), p-value=0.218 in the SGA group [15]. Their findings do not match with the present study.

Limitation(s)

This study was limited by a relatively small sample size and the results cannot be generalised to a population.

CONCLUSION(S)

The present study has demonstrated an inverse relationship between levels of PAPP-A MoM (≤0.49) and SGA. Therefore, PAPP-A MoM can be used as an early screening tool for the prediction of SGA. Research on large populations in varied study settings are needed in order to obtain conclusive evidence on cut-off percentiles and best predicting values.

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