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ORIGINAL ARTICLE

Pregnancy-Associated Plasma Protein A Levels in Late First Trimester Pregnancies with Small-for-Gestational Age Neonates: A Prospective Case–Control Study

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Abstract

Objective We aimed to investigate the association of pregnancy associated plasma protein A (PAPP-A) levels in late first trimester with small for gestational age (SGA) neonates and adverse pregnancy outcomes in a low-income setting.

Methods The inclusion criteria were late first trimester (11–13 + 6 weeks) women with singleton and non-anomalous pregnancy. Enrolled participants were sampled for PAPP-A and prospectively followed up for delivery outcome and antenatal complications. A multiple of median (MoM) was calculated and statistically compared between groups.

Results Out of total 284 subjects, 14.54% delivered SGA babies and formed cases (Group A), 66.5% delivered appropriate for gestational age (AGA) neonates with uneventful antenatal period (controls, Group B), and 19.3% were AGA group with adverse pregnancy complications (Group C). The late first trimester median PAPP-A MoM was significantly lower (0.61) in Group A compared to Group B (1.47). Using receiver operating characteristic (ROC) curve for PAPP-A MoM, optimal cutoff value was found at 0.45 MoM, with positive predictive value of 56.2%, specificity of 92.6% and sensitivity of 45%. The median interquartile range (IQR) of PAPP-A MoM value in Group C in comparison with Group B was significantly lower except for abruption. At PAPP-A MoM cutoff value <1, <0.8, <0.6 and <0.4, the odds ratio for adverse pregnancy outcome was 8.30, 7.29, 10.97 and 10.60, respectively, indicating an inverse relationship.

Conclusion With 0.45 MoM cutoff of PAPP-A, the detection rate, specificity and positive predictive value for SGA were 45, 92.6 and 56.2%, respectively. As PAPP-A MoM values decreased, the odds ratio of having adverse pregnancy outcomes increased.

Keywords Pregnancy-associated plasma protein A · Small-for-gestational age · Fetal growth retardation

Introduction

Small-for-gestational age (SGA) neonate refers to a neonate with a birth weight less than the 10th percentile. The condition is associated with increased risk of neonatal mortality and morbidity that can persist into adulthood. SGA is still a challenging disorder, and the detection rates achieved in routine care settings are generally low.

Fetal growth restriction (FGR)/SGA may occur when the fetus does not receive the necessary nutrients and oxygen through the placenta. Since several years, based on pathophysiology of placental dysfunction in SGA/FGR, many biophysical and biochemical markers have been investigated, e.g., β-HCG, inhibin A, pregnancy-associated plasma protein A (PAPP-A), placental protein 13, soluble endoglin and placental growth factor. Some of these markers like PAPP-A, β-HCG and inhibin A are already used for routine aneuploidy screening [1].

PAPP-A is secreted by syncytiotrophoblast and can be detected in maternal serum, placental tissue, amniotic fluid and coelomic fluid. PAPP-A is basically an enzyme that cleaves insulin-like growth factor binding protein (IGFBP), thereby increasing bioactivity of insulin-like growth factors, important for fetal growth [2]. Low serum PAPP-A indicates impaired placentation. This growth regulatory activity of PAPP-A explains the inverse relationship between its levels in maternal serum for FGR and adverse pregnancy outcomes. Whether this association of low levels of PAPP-A to abnormal placentation can be put to clinical screening to identify high-risk cases for SGA is still a debated. There have been many large Western studies [3, 4], but few from low-income countries where such burden has a major public health impact [5–7].

The aim of our study was to prospectively investigate the association of PAPP-A levels in late first trimester with SGA neonates in a low-income setting. In other words, we questioned whether PAPP-A has a role as a first trimester predictor of SGA.

Materials and Methods

The prospective case–control study was conducted in obstetrics department of a tertiary care center of a low-income country (2012–2014). Prior ethical committee clearance and patient consent were obtained for the study (enclosed). The inclusion criteria were late first trimester (11–13 + 6 weeks) pregnant women with singleton and non-anomalous pregnancy. Patients with unsure dates or irregular menses, known maternal diseases such as diabetes or gestational diabetes, Rh iso immunization disorders, thyroid dysfunction, chronic hypertension, smoking history, known collagen vascular disease, liver and renal disease were excluded. Patient selection is shown in Fig. 1.

Methodology

Enrolled participants were sampled for PAPP-A and followed up for antenatal complications and delivery outcome. During antenatal follow-up of study population, we noted the period of gestation of onset of FGR. Ultrasound fetal biometry was done at clinical onset of FGR antenatally. FGR was confirmed postnatally as cases who delivered neonates with birth weight <10th percentile (SGA) with or without any antenatal complications.

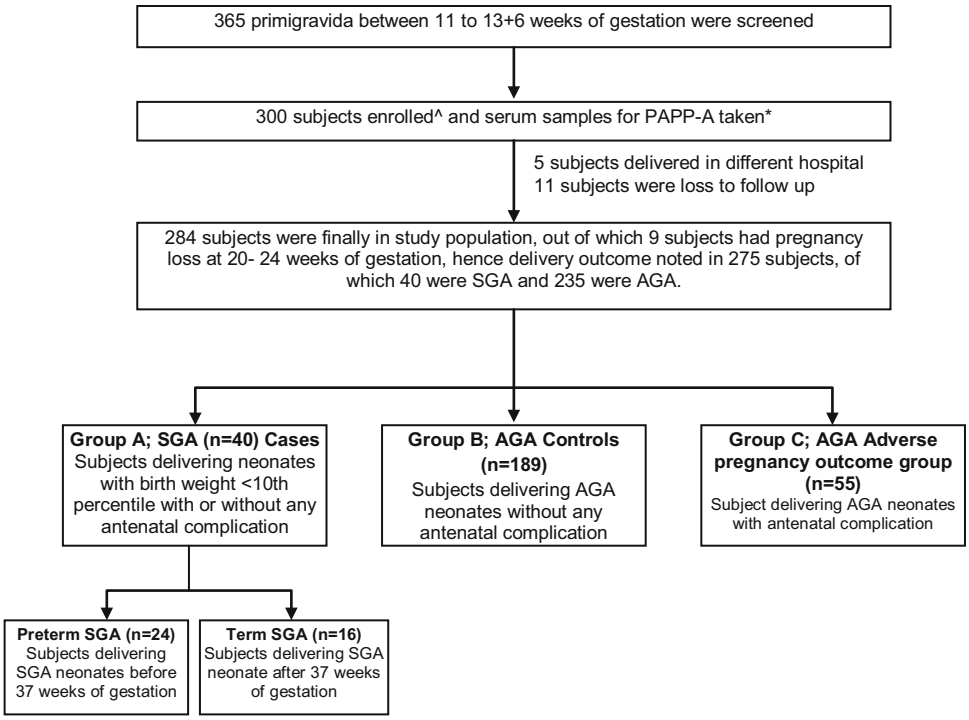

Fig. 1 Patient selection in the study. ^There was no subject with smoking hence no confounding factors to be adjusted for calculation of PAPP-A MoM value. *Estimated using PAPP-A ELISA Kit.

Out of total 284 subjects, 40 (14.54%) delivered SGA babies and formed cases (Group A). Of these 40 cases, 13 subjects (32.5%) who had onset <34 weeks were taken as early FGR and 27 subjects (67.5%) with onset ≥34 weeks were taken as late FGR. Remaining 189 (66.5%) participants delivered appropriate for gestation age (AGA) neonates with uneventful antenatal period (controls, Group B). Fifty-five subjects (19.3%) of AGA group with adverse pregnancy complications like pregnancy loss at 20–24 weeks, preeclampsia, intrauterine fetal demise, abruption, preterm labor and preterm prelabor rupture of membrane were taken as adverse pregnancy outcome group (Group C). All groups were statistically similar in terms of demographic profile and maternal physical characteristics.

Statistical Analysis

Statistical software SPSS (version 20.0) was used for statistical analysis. Chi-square test and independent *t* test were used to compare delivery outcomes. Parametric parameters were compared by one-way ANOVA and nonparametric parameters by Kruskal–Wallis test. PAPP-A multiple of median (MoM) was calculated and compared between groups.

Results

The mean gestation age at enrollment was 12.45 ± 0.87 weeks. The mean gestational age of delivery for Group A was 35.5 ± 5.1 weeks and Group B was 39.26 ± 1.05 weeks ($p = 0.000$). In Group A, 1 subject (2.5%) delivered before 34 weeks, 16 subjects (38.4%) delivered between 34 and 37 weeks and 23 subjects (58.9%) delivered at ≥37 weeks (Fig. 1). There were no adverse pregnancy outcomes such as preeclampsia, intrauterine fetal demise, abruption, spontaneous preterm labor and preterm prelabor rupture of membrane in Group A. Mean birth weight in Group A was 1.75 ± 0.44 kg, while in Group B it was 2.72 ± 0.32 kg ($p = 0.000$). The NICU admission rate (33.3 vs. 7.3%; $p = 0.000$) and mortality (10.2 vs. 0.5%; $p = 0.002$) were higher in Group A compared to Group B. The mean PAPP-A levels in Groups A and B were 17.5 ± 20.60 and 45.73 ± 87.44 µl/ml, respectively.

The Predictive Value of PAPP-A in SGA

The late first trimester median PAPP-A MoM value was significantly lower (0.61 MoM; range 0.30–2.68) in SGA Group A compared to control Group B (1.47 MoM; range 0.51–3.06) ($p = 0.001$). The odds ratio for predicting SGA using various cutoff values of PAPP-A MoM is depicted in Table 1. As PAPP-A MoM cutoff value lowered from 1 to 0.4, the odds ratio for SGA neonates increased significantly. At 10th percentile, PAPP-A MoM value of 0.33, the positive predictive value was 54.4% (specificity 95.8%, sensitivity 30%). At 5th percentile, PAPP-A MoM value decreased to 0.21 but the positive predictive value increased to 60% (specificity 97.1%, sensitivity 15%). Using ROC curve for PAPP-A MoM, the optimal cutoff value was found at 0.45 MoM, and area under the curve

Table 1 Odds ratio (95% confidence interval) for Group A neonates relative to different PAPP-A MoM values

PAPP-A MOM	Group A ($n = 40$)	Group B ($n = 189$)	OR (95% CI)	p value*
<1	23 (57.5)	72 (38.09)	2.336 (1.151–4.715)	0.018
<0.8	20 (42.5)	58 (30.68)	3.056 (1.519–6.147)	0.002
<0.6	17 (50)	26 (13.7)	6.269 (2.975–13.210)	0.000
<0.4	15 (42.5)	12 (6.3)	10.902 (4.626–25.692)	0.000

* p value <0.05 is significant, simple logistic regression

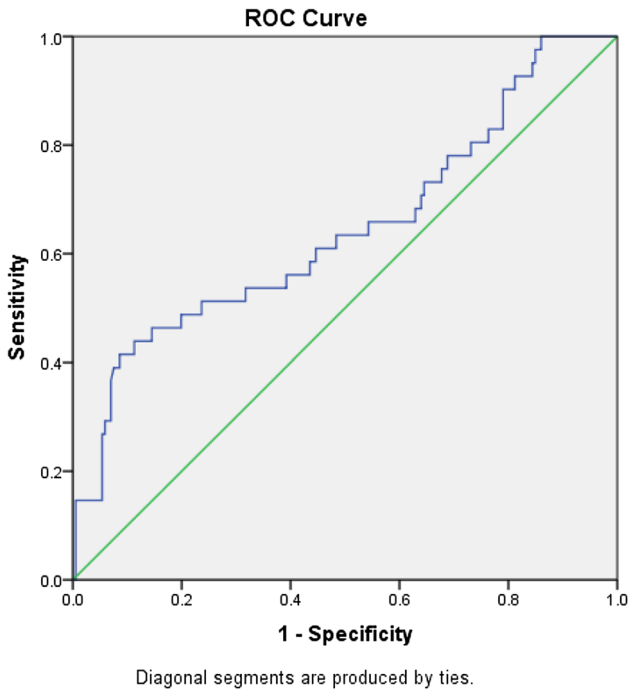

Fig. 2 ROC based on PAPP-A MoM values. Using ROC curve for PAPP-A MoM, the optimal cutoff value was found at 0.45 MoM

(AUC) was 0.667 (0.561–0.773) with positive predictive value of 56.2%, specificity of 92.6% and sensitivity of 45% (Fig. 2). Lower the percentile cutoff of serum PAPP-A value, higher was the specificity and positive predictive value for prediction of SGA. There was only one case of SGA delivering prior to 34 weeks and hence was not considered for statistical analysis. The median (IQR) for early and late FGR was 1.033 (0.27–3.14) and 0.54 (0.29–2.48), respectively ($p = 0.85$). PAPP-A MoM values when compared in early and late FGR groups were not statistically significant. Similarly, the PAPP-A MoM median (IQR) of preterm and term SGA was not statistically different ($p = 0.28$).

Adverse Pregnancy Outcomes in AGA and PAPP-A MoM Levels

Group C had following antenatal complications: 9 (3.1%) had pregnancy loss at 20–24 weeks, 13 (4.5%) had preeclampsia, 6 (2.1%) each suffered abruption and intrauterine fetal death ($n = 6$), 14 (4.9%) had preterm labor, and 7 (2.46%) patients were complicated with preterm prelabor rupture of membrane. The median (IQR) of PAPP-A MoM value in Group C in comparison with Group B (controls) was significantly lower except for abruption (Table 2). At PAPP-A MoM cutoff value <1, <0.8, <0.6 and <0.4, the odds ratio for adverse pregnancy outcome was 8.30, 7.29, 10.97 and 10.60, respectively. Thus, with decreasing PAPP-A MoM values, odds ratio (for adverse pregnancy outcomes) increased, a statistically significant finding compared to control group. Expressing it differently, the 10th percentile and 5th percentile of PAPP-A MoM for adverse pregnancy outcome were 0.242 and 0.142, respectively. In general for adverse pregnancy outcomes (except for abruption, intrauterine fetal demise), as PAPP-A MoM value was

Table 2 Comparison of median (IQR) of PAPP-A MoM value of Group C with Group B (controls)

Adverse pregnancy outcome	Median (IQR) Group C	Media (IQR) Group B	p value*
Pregnancy loss 20–24 weeks	0.09 (0.01–0.27)	1.47 (0.51–3.06)	0.024
Preeclampsia	0.38 (0.29–0.51)	1.47 (0.51–3.06)	0.031
Preterm labor	0.66 (0.56–1.05)	1.47 (0.51–3.06)	0.040
Preterm prelabor rupture of membranes	0.45 (0.21–0.86)	1.47 (0.51–3.06)	0.001
Abruption	1.20 (0.08–0.38)	1.47 (0.51–3.06)	**0.126**
Intrauterine fetal demise	0.31 (0.13–1.3)	1.47 (0.51–3.06)	0.023

* p value <0.05 is significant

Table 3 Performance characteristics of low PAPP-A MoM (≤10th and ≤5th percentile) levels for different adverse pregnancy outcomes

Adverse pregnancy outcomes	Specificity		Positive predictive value (PPV)		Negative predictive value (NPV)		Sensitivity/detection rate (DR)	
	10th (%)	5th (%)	10th (%)	5th (%)	10th (%)	5th (%)	10th (%)	5th (%)
Pregnancy loss 20–24 weeks	98.6	**97.4**	29.2	50	98.6	98.3	70	78
Preeclampsia	90.5	95.2	8.3	8.3	95	94.8	62	77
Abruption	91.6	95.4	16.7	**8.3**	98.6	97.4	57.1	**14.3**
Intrauterine fetal demise	92.7	**90**	29.2	41.7	98.2	97.4	63.6	**45.5**
Preterm labor	89.5	94.8	6.1	6.3	93.2	93.5	52	60
Preterm prelabor rupture of membranes	89.9	94.9	2.9	10.2	96.8	97	30	36

Table 4 PAPP-A median MoM values in the literature

References	Total subjects (*n*)	SGA subjects (*n*)	Median of MoM	*p* value
Ong et al. [10]	4692	395	0.96	0.002
Tul et al. [11]	1136	51	0.76	–
Ranta et al. [9]	2164	275	0.79	<0.001
Spencer et al. [12]	49,801	3539	0.82	<0.001
Baer et al. [4]	134,105	9922	0.49–2.09 (>10th–<90th MoM)	–
Gundu et al. [5]	1474	159	0.4	<0.001
Present study	284	40	0.61	0.001

lowered from 10th to 5th percentile, the detection rate (sensitivity) and the PPV increased (Table 3).

Discussion

Fetal growth restriction (FGR) represents pathological inhibition of fetal growth and failure of the fetus to attain its growth potential. The challenge is to identify this subset of SGA pregnancies in order to allow early intervention that would decrease morbidity and mortality. Recent studies have suggested that indicators for aberrant fetal growth may already exist in first trimester [8]. Of the several modalities investigated, pregnancy-associated plasma protein A (PAPP-A) is a potential maternal serum marker [3]. It is already commercially available for screening programs for trisomy 21 and other aneuploidies [1].

Our finding of lower PAPP-A median MoM in cases (Group A) replicates other studies (Table 4) [2, 4, 5, 8, 9]. The ideal levels of PAPP-A for use as marker and its predictive value remain a contested subject in the literature (Table 5), yet there is a gross agreement that as PAPP-A MoM value (percentile) cutoff decreases, the odds ratio for SGA increases [2, 5, 6, 7, 8, 9]. Contrary to other studies, the positive predictive value of PAPP-A MoM at ≤5th percentile was reasonably more (60%) in our study to postulate its use as a screening tool.

We found a lower median PAPP-A MoM for adverse pregnancy outcome (Group C) as compared to controls (Group B) analogous to other studies [2, 8]. Low PAPP-A seems to be consistent with the adverse pregnancy outcomes similar to SGA. Another finding was that the positive predictive value increased for adverse pregnancy outcomes (especially pregnancy loss at 20–24 weeks, preeclampsia, preterm labor and preterm prelabor rupture of membranes) as PAPP-A MoM value decreased from ≤10th percentile to ≤5th percentile.

There were several limitations of our study. The study population although relatively small compared to other Western series is one of the prospective case–control study from low-income countries having financial constraints (Table 4). Yet, despite the small sample, we were able to find low serum PAPP-A levels significantly associated with SGA compared to AGA group and adverse pregnancy outcomes. The analysis was, however, not possible for very low birth weight percentiles and early onset SGA because of few case numbers.

Impaired growth of the fetus is a serious complication in pregnancy and a major determinant of perinatal morbidity and mortality. Any screening tool permitting its timely detection could permit intervention in the form of close fetal monitoring and timing of delivery. Low PAPP-A had significant association with SGA and adverse pregnancy outcomes in our clinical setting. We believe that PAPP-A has potential of enhancing an obstetrician's armamentarium as

Table 5 Performance characteristic of low PAPP-A (≤5th percentile) for SGA in various studies

PAPP-A MoM at ≤5th percentiles in different studies	Detection rate/ sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)	False positive rate
Krantz et al. [2]	9.4	96.1	14.1	94.1	4.9
Dugoff et al. [13]	10.45	95.4	18.71	91.32	4.6
Leung et al. [14]	8.7	95.5	15.7	–	4.5
Gundu et al. [5]	35.85	–	20.88	–	–
Present study	15	97.1	44.2	60	2.6

an early marker of placental dysfunction. Further, PAPP-A tests are already routinely used for screening of Down syndrome in the first trimester [2]. Hence, the same test carried out in a single visit can be put to multiple uses. Our study contributed further information in this regard for establishing reference ranges, cutoff values, positive predictive value and specificity. However, the diagnostic accuracy and cutoff values of PAPP-A need further refinement. We therefore recommend further studies for validation of PAPP-A in larger sample of obstetric population in various clinical settings.

Conclusion

Lower the percentile cutoff of serum PAPP-A value, higher was the specificity and positive predictive value for prediction of SGA. With an optimal 0.45 MoM cutoff of PAPP-A, the detection rate, specificity and positive predictive value for SGA were 45, 92.6 and 56.2%, respectively. The PAPP-A MoM values also significantly correlated with adverse pregnancy outcome. As PAPP-A MoM values decreased, the odds ratio of having adverse pregnancy outcomes increased.

Compliance with Ethical Standards

Conflict of interest None of the authors have any conflict of interest or financial conflicts. The authors have nothing to disclose.

Informed Consent Informed consent was obtained from all individual participants, and ethical clearance was obtained for the study.

Human and Rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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