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Original Article

Association of Low Pregnancy-associated Plasma Protein-A Level in Late First Trimester with Various Pregnancy Complications

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Abstract

Aim and Objective: This study aims to see association of low pregnancy-associated plasma protein-A **(**PAPP-A) level in late first trimester (10–13 weeks) with various pregnancy complications.

Materials and Methods: Pregnant women (*n* = 491) at 11–13 weeks of gestation were recruited from antenatal clinic after confirmation of fetal viability. Two milliliters of blood sample were collected and serum PAPP-A level was measured.

Results: Out of 491, 461 followed till term. During course of follow-up, adverse pregnancy outcome noted in 117 (25.3%) subjects, as small for gestational age (SGA) in 10.8%, preterm labor in 4.7%, preeclampsia in 4.6%, premature rupture of membrane (PROM) in 2.4%, abruption in 1.5%, and intrauterine fetal death (IUFD) in 1.3%. The median (IQR) PAPP-AMOM for preterm labor 0.50 (0.42–0.63), PROM 0.45 (0.23–0.59), preeclampsia 0.27 (0.19–0.39), abruption 0.30 (0.08–2.05), intrauterine demise was 0.166 (0.078–0.389), and SGA 0.62 (0.26–0.74). The median (IQR) PAPP-AMOM for pregnancy without any complication was 2.12 (0.8–5.03). The median PAPP-AMOM value was significantly lower ($P < 0.05$) in cases of SGA, preterm labor, preeclampsia, PROM, abruption, and IUFD in comparison to normal pregnancy.

Conclusion: Low serum PAPP-A levels from in late 1st trimester are a good predictive marker of various pregnancy complications.

Key words: Defective implantation, Intrauterine fetal death, Preeclampsia, Pregnancy-associated plasma protein-A, Small for gestational age

INTRODUCTION

Pregnancy-associated plasma protein-A (PAPP-A) is a glycoprotein and produced by syncytiotrophoblast and decidual cells and detected in maternal serum, placental tissue, and amniotic fluid and coelomic fluid.[1] It is a Zn metalloproteinase with an elongated Zn-binding motif which has been identified as insulin-like growth factor-binding protein-4 proteinase that increase bioavailability of insulin-like growth factor 1 and 2. At maternal fetal interface, insulin-like growth factor 2 (IGF-2) bioavailability mediated by PAPP-A enables trophoblast invasion into maternal decidua, steroidogenesis, and glucose and amino acid transport into chorionic villous cytotrophoblast.[2] Literature suggest that inadequate trophoblast invasion is risk factor for various adverse pregnancy outcomes.

Maternal serum PAPP-A along with beta-hCG and nuchal translucency widely used as marker of aneuploidy in the 1st trimester. The low levels of PAPP-A are associated with adverse pregnancy outcomes. Similar test can be used for prediction for various pregnancy complications along with aneuploidy. Thus, the current study planned to see association of low 1st trimester PAPP-A levels with various pregnancy complications such as preeclampsia, fetal growth restriction, preterm, abruption, and intrauterine fetal death (IUFD) in Indian population.

PAPP-A starts appearing in maternal serum after the 5th week of pregnancy and its levels continue to increase with

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time. PAPP-A level increases exponentially with doubling time of 3–4 days during the 1st trimester of pregnancy. Peak levels of PAPP-A are observed at the end of pregnancy and levels are downregulated subsequently at delivery.[1]

Various factors affect maternal serum PAPP-A level like gestational age and maternal characteristics including weight, racial origin, cigarette smoking, diabetes mellitus, and method of conception. PAPP-A level is more in twin pregnancy.[3,4]

MATERIALS AND METHODS

This was an observational, cross-sectional study conducted in the Department of Obstetrics and Gynecology in collaboration with the Department of Biochemistry at University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, from November 2016 to April 2018. Pregnant women presenting to the outpatient department of obstetrics and gynecology were recruited on the basis of inclusion criteria such as spontaneously conceived, ultrasound confirmed intrauterine singleton pregnancy at 10–13 weeks of gestation with maternal age between 20 and 30 years, and normal body mass index (BMI). They were excluded from study if history of medical disorders such as diabetes mellitus, hypertension, asthma, antiphospholipid syndrome, thyroid dysfunction, liver and renal disease, and history of smoking present. Pregnancy with anomalous fetus detected during follow-up and women unwilling to participate were excluded from the study.

A total of 491 pregnant women were enrolled from antenatal OPD on the basis of inclusion criteria at 10–13 weeks of gestation. Ethical clearance was obtained from Institutional Ethical Clearance Committee for human research. An informed written consent was taken from all the subjects after enrollment. Confirmation of gestational age was done on the basis of definite last menstrual period (with 3 previous cycle regular) and first trimester ultrasonography (using CRL).

All cases enrolled were interviewed to collect information on age, address, occupation, religion, education, socioeconomic status, substance abuse, trauma, family history of genetic anomaly, etc., in a properly designed questionnaire.

Two milliliters of peripheral blood sample in plain vial were collected at the time of enrollment along with routine antenatal investigation, clotted sample was centrifuged at 3000 rpm for 15 min, and separated serum was stored at −20°C in the department of biochemistry for analysis of PAPP-A level in all subjects. All pregnant women were followed till term to observe various pregnancy outcomes.

Serum samples of all subjects were evaluated for PAPP-A levels by PAPP-A ELISA Kit (DRG International, Inc., USA) which was based on solid phase enzyme-linked immunosorbent assay (sandwich ELISA). Microsoft Excel (version 2013) and statistical software SPSS for Windows (version20.0) were used for data presentation and statistical analysis. PAPP-A levels were calculated in multiple of median (MOM). Independent t-test and Chi-square test were applied to compare continuous data that are normally distributed such as age, BMI, and sociodemographic profile. Mann-Whitney *U*-test to compare data that was not normally distributed like PAPP-A MOM.

RESULTS

We had followed 461 out of 491 pregnant women till term pregnancy to observe various other pregnancy outcomes. Thirty women lost to follow up. Out of 461 subjects, 27 had spontaneous abortion before 20 weeks and 117 women developed complication such as preterm delivery, small for gestational age (SGA), abruption, preeclampsia, and IUFD. Rest of 317 delivered without any complications. PAPP-AMOM of various adverse pregnancy outcomes was compared with PAPP-AMOM of normal pregnancy outcome.

Study population largely comprised females between 20 and 24 years of age (61.1%) followed by between 25 and 29 years of age (33%) and majority of study subjects were Hindu by religion (77.4%) and 22.6% were Muslim. Mean age of the study population was 24.08±2.92. Most of the subjects in the study population belonged to either lower middle (42.6%) or upper lower (40.1%) socioeconomic status. Most of the study subjects were educated (96.6%). Most of them were

Table 1: Sociodemographic characteristics of the study population

Characteristics	Study population (*n*=491) *n* (%)
Age (years) mean	24.08±2.92
20–24	300 (61.1)
25–29	162 (33)
30–34	29 (5.9)
Religion	
Hindu	380 (77.4)
Muslim	111 (22.6)
Socioeconomic status*	
Upper	3 (0.6)
Upper middle	80 (16.3)
Lower middle	209 (42.6)
Upper lower	197 (40.1)
Lower	2 (0.4)
Education	
Illiterate	17 (3.4)
Primary/middle	156 (31.8)
High	211 (43)
Intermediate	57 (11.6)
Graduate/professional	50 (10.2)

*Modified Kuppuswamy's socioeconomic status scale

housewife [Table 1]. The mean BMI of the study population was 21.58±1.69 kg/m^2 [Table 2]. Most of women in the study population were primigravida (45.6%) followed by 2nd gravida (37.7%) and 16.7% were 3rd and more gravida [Table 3].

During course of follow-up, adverse pregnancy outcome noted in 117 (25.3%) subjects, as SGA in 10.8%, preterm labor in 4.7%, preeclampsia in 4.6%, premature rupture of membrane (PROM) in 2.4%, abruption in 1.5%, and IUFD in 1.3% [Table 4].

The median (IQR) PAPP-AMOM for preterm labor 0.50 (0.42–0.63), PROM 0.45 (0.23–0.59), preeclampsia 0.27 (0.19–0.39), abruption 0.30 (0.08–2.05), intrauterine demise was 0.166 (0.078–0.389), and SGA 0.62 (0.26–0.74). The median (IQR) PAPP-AMOM for pregnancy without any complication was 2.12 (0.85–5.03). The median PAPP-AMOM value was significantly lower ($P < 0.05$) in cases of SGA, preterm labor, preeclampsia, PROM, abruption, and IUFD in comparison to normal pregnancy [Table 5]. Hence, low PAPP-AMOM value is a very good predictive marker for various adverse pregnancy outcomes.

Table 2: Maternal body mass index at time of enrolment in the study population

Body mass index (kg/m^2)	Study population (*n*=491)
(Mean)	21.58±1.69
18.5–22.5	358 (72.9%)
22.6–24.9	133 (27.1%)

Table 3: Distribution of parity in the study population

Parity	*n* (%)
Primigravida	224 (45.6%)
2nd gravida	185 (37.7%)
3rd gravida or more	82 (16.7%)

Table 4: Incidence of various pregnancy outcomes in the study population (*n*=461) as described above

Pregnancy outcome group	*n* (%)
Miscarriage	27 (5.9)
Preterm labor	22 (4.7)
Premature rupture of membrane (PROM)	11 (2.4)
Preeclampsia	21 (4.6)
Abruption	7 (1.5)
Intra uterine fetal death	6 (1.3)
Small for gestational age	50 (10.8)
Normal pregnancy	317 (68.8)

DISCUSSION

The mechanism involved in most of adverse pregnancy outcome is same as that of miscarriage. Decreased PAPP-A levels leading to decrease free IGF levels which possibly leads to diminished fetal growth, placental growth and abnormal placentation. This is the main pathophysiology of adverse pregnancy outcome such as SGA, preeclampsia, preterm, PROM, abruption, and IUFD.

In our study, subjects were comparable in respect to sociodemographic profile, parity, and BMI. We found that median PAPP-AMOM value was significantly lower ($P < 0.05$) in cases of SGA, preterm labor, preeclampsia, PROM, abruption, and IUFD in comparison to normal pregnancy. These findings were in consensus with the study of Barrett *et al.*, Dugoff *et al.*, Cohen *et al.*, and Krantz *et al.*[5-8]

Patil *et al.*[9] recruited 524 subjects at 11–13 weeks of gestation for the 1st trimester fetal surveillance who registered for delivery in their hospital. They defined low PAPP-A cutoff <0.5 MOM and observed that significant rise in incidence of preterm labor, fetal growth restriction, and preeclampsia with low PAPP-A levels in the 1st trimester. They did not calculate median PAPP-AMOM value in respective adverse outcome group. Gupta *et al.*[10] also noted incidence of adverse pregnancy outcome in subjects whose PAPP-AMOM levels ≤0.4 MOM and >0.4 MOM. They observed that incidence of FGR ($P = 0.001$), preterm delivery ($P = 0.046$), low birth weight ($P = 0.0001$), but statistically no difference in preeclampsia ($P = 0.075$), and with abruption (0.394).

Table 5: Comparison of median (IQR) of PAPP-AMOM value of adverse pregnancy outcome group with normal pregnancy outcome group

Pregnancy outcome	Median (IQR) of adverse pregnancy outcomes	Median (IQR) of normal pregnancy	*P value
Preterm labor (*n*=22)	0.50 (0.42–0.63)	2.12 (0.85–5.03)	0.001
Premature rupture of membranes (*n*=11)	0.45(0.23–0.59)	2.12 (0.85–5.03)	0.001
Premature rupture of membrane (PROM)			
Preeclampsia (*n*=21)	0.27 (0.19–0.39)	2.12 (0.85–5.03)	0.001
Abruption (*n*=7)	0.30 (0.08–2.05)	2.12 (0.85–5.03)	0.036
Intrauterine fetal death (*n*=6)	0.166 (0.078–0.389)	2.12 (0.85–5.03)	0.001
Small for gestational age (*n*=50)	0.62 (0.26–0.74)	2.12 (0.85–5.03)	0.001

*P<0.05 was considered significant, Mann–Whitney U-test

Low PAPP-A levels may be indictor of impaired placental function and implantation and this may be explanation for the association of low PAPP-A levels and subsequent development of adverse pregnancy outcome including preeclampsia, SGA, preterm, abruption, and IUFD.

First trimester low PAPP-A levels can be used to classify patients as high risk or low risk for some adverse pregnancy outcome apart from Down syndrome screening. It helps clinician in the management of high-risk pregnancy, early initiation of treatment, and prognostication of patient.

The study was limited by small number of study population. Analysis of PAPP-A level in large population was not possible because of time and financial constraints.

CONCLUSION

Low PAPP-A level at late first trimester is associated with various pregnancy complications. It may be useful tool for assessing risk of adverse fetal outcome in high-risk pregnancy or in combination of other test.

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