Original Research Article

The role of pregnancy-associated plasma protein-a level in the first trimester of pregnancy and clinical outcome in an urban referral centre

Lavanya T.*, Premalatha R., Nandita A. Thakkar, Latha Jawahar, Priya Kannappa Rajendran, Geethanjali E., Swetha V. Rajan

Department of Obstetrics and Gynecology, Mehta Multispeciality Hospitals India Pvt. Ltd, Chetpet, Chennai, India

*Correspondence:
Dr. Lavanya T.,
E-mail: drlavanya16@gmail.com.

ABSTRACT

Background: Estimation of serum PAPP-A levels studied predictability for adverse perinatal outcome. This case control study tries to establish the association between low PAPP-A levels among the pregnant woman and adverse maternal foetal outcome.

Methods: This is an case-control study during 2017-2018 in the women delivered at Department of OBG at Mehta Hospitals. Women delivered in the labour room had a first trimester screening of PAPP-A level were explained, taken informed consent, questionnaire which include detailed antenatal history, mode of delivery and baby data. Depending upon outcome, the subjects are classified as case group or control group, out of the study sample of 264 subjects, 88 patients who had complications were taken as cases and 176 patients with no complications taken as control were undertaken.

Results: Low PAPP-A level (<0.5 MoM) showed high incidence of PIH and preeclampsia, followed by IUGR and Preterm. PAPP-A level >0.5 MoM, normal outcome is more than the adverse outcome. The difference in the PAPP-A levels is statistically significant. In women with low PAPP A level, low birth weight found statistically significant when compared with <0.5 PAPP A level. The sensitivity of PAPP A levels in identifying the complicated outcomes was 17.04%.The specificity was 98.85%. The positive predictive value of predicting the complications was 88.23% and negative predictive value of 70.44%.

Conclusions: The low PAPP-A levels confirmed during first trimester of pregnancy is associated with adverse maternal and foetal outcome such as PIH, preeclampsia, preterm, IUGR and LBW.

Keywords: Free beta HCG, IUGR, NT, PAPP-A, Preterm labour, Preeclampsia

INTRODUCTION

First trimester in pregnancy is considered as crucial period of pregnancy as both growth and differentiation of foetus takes place. Early identification of abnormalities helps in effective management of the pregnancy.[1-3] In the first trimester of pregnancy, biochemical markers derived from placenta, pregnancy-associated plasma protein A (PAPP-A) and beta-human chorionic gonadotropin (beta-hCG), are widely used together with ultrasound measurement of nuchal translucency (NT) thickness as part of screening programmes of chromosomal abnormalities.[4,5] Various studies have been done in the past to study the usefulness of PAPP-A in predicting the adverse outcomes of later stages of the pregnancy.[6-9]

Apart from the chromosomal abnormality, women undergoing biochemical screening and are found to have apparently lower PAPP-A levels in the first trimester are increasingly considered as being at increased risk for other

pregnancy related complications. Such adverse outcomes and related complications include miscarriage, preterm delivery, small-for-gestational-age (SGA) infant, neonatal intensive care unit (NICU) admission, and stillbirth.[10-16]

The association between PAPP-A or beta-hCG levels with various abnormal obstetric outcomes has been described by the fact that both hormones are produced in the placenta immediately after implantation, and reduced levels may possibly reflect abnormal placentation.[17-20] This in turn, account for adverse obstetric and neonatal outcomes.

A low PAPP-A is descriptive of poor early placentation and may result in adverse pregnancy outcomes such as[21,22]

- Mid trimester miscarriage
- Fetal growth restriction
- Intrauterine fetal death
- Preterm birth
- Preeclampsia
- Stillbirth.

Abnormal levels of maternal serum analyte and measurement of fetus during the first trimester screening can be a predictor for not only certain chromosomal disorders and fetal anomalies but also for certain specific complications of pregnancy.

Especially, decreased maternal serum pregnancy-associated plasma protein-A (PAPP-A), during 11-13 weeks of gestation, is associated with adverse outcomes of the pregnancy like stillbirth, preterm birth, intrauterine growth restriction (IUGR), and pre-eclampsia in chromosomally normal fetuses, while a increased nuchal translucency is associated with certain specific structural abnormalities and genetic syndromes.[23-31] A low or decreased level of PAPP-A is defined as a maternal serum PAPP-A value <0.4 MOM, with increased risk of adverse obstetrical outcomes noted below this level.[32,33]

Although data are few and often conflicting with each other, a review of literature on PAPP - A reveals some evidence of an association between low PAPP-A levels in the first trimester and adverse pregnancy outcomes including preterm delivery, hypertensive disorders of pregnancy, SGA, IUGR and stillbirth in low-risk populations.[34-36] Studies available in literature from 2008 conclude that a PAPP-A level below the fifth percentile (outside two S.D.) is significantly associated with an increased chance of spontaneous abortion before the age of viability (p<0.05).

Studies with bigger sample size studying the relationship between adverse pregnancy outcomes and decreased PAPP-A levels will require capture of placental pathology to test the hypothesis that abnormal placentation is the reason.[24] Clinically, low PAPP-A levels detected in the context of normal fetal aneuploidy screening is debatable, pregnant patients with such results should be counselled that at present no strong evidence exists to justify on-going ultrasound surveillance.

METHODS

This was an observational study/case control study done at Mehta Multispeciality Hospitals India Pvt. Ltd. from August 2017 to May 2018. Women delivered at the Department of OBG at Mehta Multispeciality Hospitals India Pvt. Ltd. were included in the study.

Inclusion criteria

- Delivered women who were screened for PAPP-A levels in the first trimester.

Exclusion criteria

- Multiple child birth.

Operational definitions

- Case: Adverse maternal and fetal outcome.
- Control: Normal maternal and fetal outcome.
- Adverse maternal and foetal outcomes.
- Preterm birth: Preterm birth is defined as birth before 37 weeks.
- Pregnancy induced hypertension; defined as development of hypertension to the extent of 140/90 mmHg or more with proteinuria after the 20weeks. of pregnancy in previously normotensive and non proteinuric patient.
- Fetal growth restriction: designed to identify fetuses with estimated weight below the 10th percentile for the gestation ages.
- Stillbirth: Defined as fetal death occurring after 20weeks of pregnancy or fetal weight more than 500g.

Confounding factors

- Urinary tract infection: Urinary tract infection in the pregnancy.
- Polyhydramnios: Excessive amniotic fluid.
- Incompetent cervix: Painless cervical dilatation in the second trimester.
- Chronic Hypertension: BP >140/90mmHg before pregnancy (or) diagnosed before 20weeks.
- Severe Anaemia: Haemoglobin concentration less than 7g/dL in the pregnant women.
- Cardiac disease: New York Heart Association based class3 and class4.
- Gestational Diabetes: Diabetes diagnosed during pregnancy.
- Overt diabetes: Diabetes diagnosed before pregnancy.
- PAPP-A Level:
  - Normal> 0.5 MoM
  - Low ≤0.5 MoM.

Sample size

With reference from Gordon. C.S. Smith,et al study, considering the proportion of adverse pregnancy outcome among women with normal PAPP-A level to be 29% and among women with normal PAPP-A level to be 12% with ratio of both groups as 1:2 at 95% confidence levels) and 80% power, the sample size is calculated as

$$N = \frac{(r + 1) * p * (1 - p) * (Z_\alpha + Z_\beta)^2}{r} \frac{}{(p1 - p2)^2}$$

Here Z_α=1.96, Z_β=0.84, p1=0.29, p2=0.12, p=(p1+p2) / 2 = 0.205, r=2

With the above formula, N = 88.[7] The sample size for cases is estimated to be 88 and control to be 176 and totally the study sample is 264 subjects. Case followed within one week control taken.

Study Method

Women delivered in the labour room who had a first trimester screening of PAPP-A level were explained about the study after getting informed consent (Annexure II and III), reviewed for antenatal card,questionnaire which include detailed antenatal history of mode of delivery and details of the baby data enter into the annexure II. Case review was done with same person. Depending upon outcome, the subjects are classified as case group or control group.

Statistical analysis

The collected data were entered in Microsoft Excel 2013 and exported to SPSS v21 for analysis. The frequency distributions of all variables were expressed in percentages and the association between pregnancy outcomes and low PAPP-A level by Chi square test. The strength of association is expressed as odds ratio with 95% Confidence Interval. The predictive efficiency of PAPP-A is calculated by positive predictive value. P < 0.05 is considered for the statistical significance.

RESULTS

The study had revealed that there is no statistically significant association of factors such as maternal age, parity, marital history, family history and previous obstetric complication between the case and control groups.

Mode of conception (ART, IUI, Ovulation induction) than spontaneous conception significantly represented more number in case group compared to control group which is proved statistically. In case group, 78% had deliveries <37 weeks and 18% had term deliveries and the difference was statistically significant with the control group. In the study there is high incidence of PIH and pre-eclampsia (17%), followed by preterm (9.1%) and IUGR (6.8%) with normal outcomes in 66.7%. In the study out of 264 deliveries,

LSCS rate is higher compared to the normal delivery. The percentage of normal delivery is 28%, while LSCS deliveries were 72%. In the study Low PAPP-A level (<0.5MoM) shows high incidence of PIH and Pre-Eclampsia, followed by IUGR and Preterm. PAPP-A level >0.5MoM, normal outcome is more than the adverse outcome. The difference in the PAPP-A levels is statistically significant.

Women with low PAPP-A level, low birth weight found statistically significant when compared with ≤0.5 PAPP A level. NICU admission and APGAR not found to be statistically significant. LBW babies prevalent high in low PAPP A level. In the present study, the sensitivity of PAPP A levels in identifying the complicated outcomes was 17.04% and the specificity was 98.85%. The positive predictive value of predicting the complications was 88.23% and negative predictive value of 70.44%.

DISCUSSION

This was a case -control study done in delivered women who were screened for PAPP-A levels in the first trimester, they were included.

When compared with the prospective cohort study done by Smith et al, to assess the risk of adverse perinatal outcome among 8839 women showed that, Women with a pregnancy-associated plasma protein A (PAPP-A) had an increased risk of intrauterine growth restriction with adjusted odds ratio of 2.9; (95% confidence interval (CI), 2.0-4.1), extremely premature delivery with adjusted odds ratio of 2.9(95% CI, 1.6-5.5), moderately premature delivery with adjusted odds ratio of 2.4(95% CI 1.7-3.5), preeclampsia with adjusted odds ratio of 2.3(95% CI, 1.6-3.3), and stillbirth with adjusted odds ratio of 3.6(95% CI, 1.2-11.0) (Table 1).[38]

Table1: Outcome compared with low PAPP-A level.

Outcome compared with low PAPP-A level	Odds ratio	
	Present study	**Smith et al**
IUGR	33.46 (5.9-189.4) 47	2.9 (2.0-4.1)
Preterm	7.9 (1.1-58.9) 29.4	2.4 (1.6-5.5)
Pre eclampsia /PIH	18.8 (3.8-92.2) 11.7	2.3 (1.6-3.3)

A population-based screening study (The FASTER Trial) by Dugoff et al was done, who studied first-trimester maternal serum PAPP-A and free-beta subunit human chorionic gonadotropin concentrations and nuchal translucency for its association with obstetric complications. They revealed that women with pregnancy-associated plasma protein A of ≤5th percentile were significantly more likely to develop spontaneous fetal loss at ≤24 gestational weeks, gestational hypertension, low birth weight, preeclampsia, preterm birth (p<0.001) and preterm premature rupture of membranes, stillbirth, and

placental abruption (p<0.02).[2] Almost all findings of this study were supported by the findings from the present study but we couldn't take account of fetal loss ≤24 gestational weeks since it was a case control study which considered those subjects came for delivery.[39]

In the Indian population study conducted by Jyoti Malik et al, to relate pregnancy outcome to PAPP-A level in the first trimester of pregnancy 524 antenatal patients were included in the study and found 452 patients were with normal PAPP-A level and 72 patients were in low PAPP-A level.

Out of 72 patients, 32(44%) patients developed preterm labour and 11(15%) patients developed foetal growth retardation and 16(22%) patients developed pregnancy induced hypertension. The obstetric outcome of patients with normal PAPP-A level was fairly uneventful as compared to others with a low PAPP-A level.[40]

The prevalence of all complications among low PAPP-A level subjects in the study was 88% which was close to Jyoti Malik et al study which showed 83%. There were mild differences in the individual complication prevalence in low PAPP-A level subjects which is dependent on the subjects. In the study, the sensitivity of PAPP A levels in identifying the pregnancy complications was 17.04% and the specificity was 98.85%. The positive predictive value of predicting the complications was 88.23% and negative predictive value of 70.44% of the population (Table 2).

Table 2: Validity of low PAPP-A levels.

Validity of low PAPP-A	Present study	Piyathida Pummara et al
Sensitivity	17.04%	20%
Specificity	98.85%	91.40%
Positive predictive value	88.23%	17.90%
Negative predictive value	70.44%	92.40%

CONCLUSION

The low PAPP-A levels confirmed during first trimester of pregnancy is associated with adverse maternal and foetal outcome such as PIH, preeclampsia, preterm, IUGR and LBW.

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