Background: Decreased levels of pregnancy-associated plasma protein-A (PAPP-A) in maternal serum can be a marker not only for some chromosomal disorders and anomalies in the fetus but also specific for adverse pregnancy outcomes too, such as preeclampsia, spontaneous preterm birth, gestational diabetes, and fetal growth restriction (FGR) and to the extent of stillbirth. Hence, measurement of early pregnancy PAPP-A levels may help identify the areas of intervention for reducing the adverse outcome in later gestations.

Materials and Methods: This was a prospective observational study. A total of 250 antenatal cases fulfilling the inclusion criteria were taken in the study. Early pregnancy serum levels of PAPP-A were measured for antenatal cases visiting outpatient department of tertiary level teaching hospital between 10 and 14 weeks period of gestation, and these cases were followed up for development of adverse pregnancy outcome.

Results: Two hundred and thirty-five patients had normal outcomes, among which 24 patients had PAPP-A values ≤0.4 multiples of the median (MoM) and 211 patients had PAPP-A level >0.4 MoM. Twenty-nine patients out of 250 in our study group had PAPP-A level <0.4 MoM, 1 patient developed preeclampsia ($P = 0.211$) but underwent normal vaginal delivery at term, and 1 had FGR ($P = 0.513$). Three patients had preterm delivery and the PAPP-A values in preterm group were lower as compared to term group, and this result was statistically significant ($P = 0.005$).

Conclusion: The study concludes that the patients with low early pregnancy PAPP-A levels may be deemed to develop preterm labor subsequently and effective measures may be taken to prevent the same. However, it would be prudent to replicate the study in a wider and more representative sample over multiple centers to see if the results hold true.

Keywords: Delivery, high-risk pregnancy, preeclampsia, pregnancy, preterm delivery

INTRODUCTION

Pregnancy-associated plasma protein-A (PAPP-A) is a large glycoprotein which is produced by the placenta and decidua and is thought to have various functions, including prevention of recognition of the fetus by the maternal immune system, matrix mineralization, and angiogenesis.[1,2] PAPP-A is produced by the placental extravillous cytotrophoblasts.[3] It has the ability to help release insulin-like growth factor (IGF) from the binding proteins so that it is free to interact with its cell receptor because it is a “protease” for IGF-binding proteins (IGFBP) 4 and 5.[3] The elevated levels of PAPP-A and IGFBP-4 proteolysis are normally detected in the maternal circulation in early gestation. Therefore,
low maternal PAPP-A serum levels in the first trimester are supposed to be an early sign of placentation defect during the implantation processes.\cite{4,5} It has been shown that low levels of PAPP-A, resulting in less release of IGF, could be a pathway by which placentation abnormalities occur that contribute in these poor or adverse pregnancy outcomes. A low PAPP-A is defined as a maternal serum PAPP-A value <0.4 multiples of the median (MoM), with increased frequency of adverse obstetrical outcomes noted below this level.\cite{1}

The study was planned so as to determine whether the first-trimester measurements of placenta-derived serum markers PAPP-A has association with adverse outcomes or obstetric complications or to identify women at increased risk of subsequent adverse perinatal outcomes.

**Materials and Methods**

A prospective observational study was planned and executed in the department of obstetrics and gynecology in a tertiary care center, from January 2017 to June 2018. The study population included all antenatal cases between 10 and 14 weeks period of gestation (POG) attending the antenatal outpatient department (OPD). The study excluded all women with:

- Previous history of induced abortion or preterm delivery
- Pregnancy following assisted reproductive techniques
- Multiple gestations
- Chronic hypertension
- Diabetes mellitus.

The prevalence of low PAPP-A levels in early pregnancy is about 17%, hence taking a power of 80% for various parameters, we needed to study 250 pregnant women to get 26 women with low PAPP-A levels.

A total of 250 pregnant women attending antenatal OPD of a tertiary level teaching hospital were included and recruited after a positive urine pregnancy test. The pregnancy, POG, and viability were confirmed with ultrasonography done in the outpatient department. In case of unsure dates, ultrasonography calculated expected date of delivery was taken to calculate the POG. Serum PAPP-A levels were measured by using enzyme-linked immunosorbent assay technique and the cases were followed till the termination of pregnancy.

The levels of PAPP-A were expressed as MoM for gestational age. All women with PAPP-A levels <0.4 MoM of the first-trimester biochemical screening were selected and followed up closely and compared with women with similar gestational age and with normal serum PAPP-A levels. Values of 0.4 MoM were taken, as this value had previously reported with adverse pregnancy outcome.

The variables and the outcomes studied were – age, body mass index (BMI), parity, and systolic and diastolic blood pressure at recruitment. The study was to measure the following outcomes:

**Primary outcome**
- Preeclampsia
- Fetal growth restriction
- Preterm labor.

**Secondary outcome**
- Abruptio placentae
- Spontaneous abortion
- Stillbirth.

**Statistical analysis**
Data collected was thereafter statistically analyzed by SPSS version 22.

**Ethical approval**
The study was approved by the Institutional Ethics Committee (IEC). IEC reference no. IEC Nov 10 dated 15 Nov 2016.

**Results**
Out of 250 patients in the study, 221 had PAPP-A level >0.4 MoM and a total of 29 patients out of 250 in our study group had PAPP-A level <0.4 MoM. Table 1 shows the characteristics of the patients.
The maximum bulk of patients, i.e., 109 patients (43.6%) were between 21 and 25 years. Ninety-two patients (36.8%) were between 26 and 30 years of age. Rest 17 patients (6.8%) were >30 years. The majority of the study population comprising 235 patients (94%) had BMI in the range 18.6–24.5 kg/sqm. In our study, a total of 250 newborns were delivered. 40 newborns (16%) in our study were low birth weight weighing <2.5 kg; 206 newborns (82.4%) were >2.5 kg at birth. Six low birth weight babies who delivered at preterm gestation required admission to neonatal intensive care unit (NICU).

Out of 250 patients in study group, 221 had PAPP-A level >0.4 MoM. Two hundred and eleven had normal outcomes, 3 patients underwent spontaneous abortion, 5 had fetal growth restriction (FGR), 1 patient developed preeclampsia but delivered at term without any complications, and 1 patient had preterm delivery at 32 weeks POG which required prolonged NICU admission.

Twenty-nine patients out of 250 in our study group had PAPP-A level <0.4 MoM. Twenty-four patients had normal outcome, 1 patient developed preeclampsia ($P = 0.211$) but underwent normal vaginal delivery at term, and 1 had FGR ($P = 0.513$). Three patients had preterm delivery and the PAPP-A values in preterm group were lower as compared to term group, and this result was statistically significant ($P = 0.005$) [Table 2].

Among 250 patients in our study, 235 patients had normal outcomes, among which 24 patients had PAPP-A values ≤0.4 MoM and 211 patients had PAPP-A level >0.4 MoM [Table 3].

Comparing the outcomes, a total of 15 patients had adverse outcome in the form of FGR, preterm delivery, abortion, and preeclampsia. Among the adverse outcomes, a total of 5 patients had PAPP-A level <0.4 MoM and 10 had PAPP-A >0.4 MoM. Hence, using Chi-square test, there is significant association between PAPP-A levels with adverse pregnancy outcome.

**DISCUSSION**

The formation of the placenta is important for the pregnancy outcome, and when abnormal, it has been associated with abortion, FGR, pregnancy-induced hypertensive disorders, stillbirth, premature or preterm delivery, and even leading to cesarean section for indications of fetal or maternal compromise.[4,5] An unexplained low levels of PAPP-A is strongly related to preterm delivery and various other adverse outcomes of pregnancy.[6,7]

Out of the 250 patients included in the study, 2 had preeclampsia, making an incidence of 0.8%, 6 (2.4%) had adverse outcome in the form of FGR, but $P$ value was not statistically significant. Four (1.6%) patients had preterm delivery and PAPP-A values in preterm delivery group were lower as compared to term group or normal outcome group, and this result was statistically significant (Fisher’s exact test used). PAPP-A: Pregnancy-associated plasma protein-A, FGA: Fetal growth restriction, MoM: Multiples of the median

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**Table 1: Demographics**

| Particulars          | n (%) |
|----------------------|-------|
| Age                  |       |
| <20                  | 32 (12.8) |
| 21-25                | 109 (43.6) |
| 26-30                | 92 (36.8) |
| >30                  | 17 (6.8) |
| Parity               |       |
| 0                    | 107 (42.8) |
| 1                    | 91 (36.4) |
| 2                    | 37 (14.8) |
| 3                    | 13 (5.2) |
| 4                    | 2 (0.8) |
| Previous abortions   |       |
| 0                    | 240 (96) |
| 1                    | 7 (2.8) |
| 2                    | 2 (0.8) |
| 3                    | 1 (0.4) |
| BMI                  |       |
| <18.6                | 15 (6) |
| 18.6-24.5            | 235 (94) |
| POG                  |       |
| 10-11                | 74 (29.6) |
| 11-12                | 75 (30) |
| 12-13                | 77 (30.8) |
| 13-14                | 24 (9.6) |
| Mode of delivery     |       |
| Vaginal              | 228 (91.2) |
| Cesarean             | 19 (7.6) |
| NA                   | 3 (1.2) |
| Birth weight         |       |
| <2.5                 | 41 (16.3) |
| >2.5                 | 206 (82.4) |

BMI: Body mass index, POG: Period of gestation, NA: Not available

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**Table 2: Delivery outcome and pregnancy-associated plasma protein-A values comparison**

| Outcome          | PAPP-A MoM level | Total | $P$  |
|------------------|------------------|-------|------|
|                  | ≤0.4             | >0.4  |      |
| Normal           | 24               | 211   | 235  |
| Abortion         | 0                | 3     | 3    |
| FGR              | 1                | 5     | 6    |
| Preeclampsia     | 1                | 1     | 2    |
| Preterm          | 3                | 1     | 4    |
| Total            | 29               | 221   | 250  |

*Significant (Fisher’s exact test used). PAPP-A: Pregnancy-associated plasma protein-A, FGA: Fetal growth restriction, MoM: Multiples of the median.
Table 3: Pregnancy-associated plasma protein-A values versus outcome

| PAPP-A | Outcome | Total | P     |
|--------|---------|-------|-------|
| ≤0.4   | 5       | 24    | 29    | 0.001 |
| >0.4   | 10      | 211   | 221   |       |
| Total  | 15      | 235   | 250   |       |

PAPP-A: Pregnancy-associated plasma protein-A

significant \( (P = 0.005) \). These results were nearly comparable with the studies conducted by Goetzinger et al. 2010 for PAPP-A.[10] The level of the first-trimester serum PAPP-A expressed in MoM, was compared between the normal outcome group and that of patients who had adverse outcomes.

In our study, the mean PAPP-A value in the adverse outcome group was 3.94 MoM, whereas in the normal outcome group, the mean value was 9.16 MoM and \( P = 0.003 \) showing a statistically significant difference. A prospective observational study by Smith et al., involving 8839 pregnancies at 8–14 weeks POG, showed that the control of the IGF system in the first and early second trimester may have a role in determining subsequent pregnancy outcome, demonstrating importance of the first-trimester measurement of maternal serum PAPP-A level.[9]

Spencer et al. confirmed an association between low PAPP-A and low for gestational age birth weight babies and found a linear relationship between the decrease in PAPP-A levels and severity of growth restriction.[10] A study by Patel et al., involving 524 pregnant patients with their PAPP-A tested between 11 and 13 weeks showed that, 18 patients with PAPP-A level <0.5 MoM developed preterm labor and preeclampsia.[11] Radoi and Bohiltea studied 484 cases between 10 and 13 + 6 weeks POG and found that the maternal circulating concentrations of PAPP-A at 10–13 + 6-week gestation are highly predictive of adverse perinatal outcome in later pregnancy period.[11] Lin et al. showed that the level of PAPP-A was raised in preeclamptic pregnancies. Mostly, the change was marked in severe grades of preeclampsia and the increase of PAPP-A preceded the advent of hypertension and albuminuria.[12]

PAPP-A in trisomy 18 is significantly reduced (PAPP-A MoM – 0.108), and the low values continue across the first trimester and second trimester.[13] In the pregnancies resulting in preeclampsia and FGR, the median first-trimester PAPP-A was found to be lower compared to the normal patients.[14] In conclusion, proform of eosinophil major basic protein (proMBP) has been shown to be a first- and second-trimester marker of trisomy 21 and low levels of proMBP are associated with intrauterine growth restriction, preterm delivery, and preeclampsia.[15,16] Low maternal serum PAPP-A at 10–14 weeks of gestation may be a marker of inadequate placentation, and this may be the explanation for the association of low PAPP-A and subsequently development of pregnancy-induced hypertension and FGR.[16]

No studies have shown an adverse obstetrical outcomes with elevated PAPP-A levels in the first trimester of pregnancy, demonstrating that it is the low levels of PAPP-A in the first trimester which is associated with adverse outcome later. Hence, PAPP-A in the first trimester can be used as a predictor of adverse pregnancy outcome, especially preterm labor. The results were comparable to studies mentioned above. The mean levels of PAPP-A in the adverse outcome group were found to be lower than that in the normal outcome group. The difference between the two mean values did show statistically significant association with a \( P = 0.001 \) (<0.05).[17,18]

CONCLUSION

As per the study, patients who developed preterm labor had lower PAPP-A levels. However, the results for FGR and preeclampsia were not statistically significant. Hence, we conclude that low maternal serum level of PAPP-A in early pregnancy can predict the adverse pregnancy outcomes, specifically the onset of preterm labor at a later gestation. However, being a single-center study with a limited sample size, the possibility of the other confounding from unmeasured covariates cannot be excluded.

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Conflicts of interest

There are no conflicts of interest.

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