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Original Research Article

Adverse pregnancy outcome in low PAPP-A levels: First trimester screening hospital based study

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ABSTRACT

Objectives: To assess the adverse pregnancy outcome in Low Pregnancy Associated Plasma Protein -A (PAPP-A) levels in serum.
Materials and Methods: This is a prospective cohort study, which included 2150 pregnant women who attended the antenatal clinic of Obstetrics and Gynecology in the Lok Nayak Hospital, New Delhi, India. Blood samples were collected by the venipuncture method for First trimester screening to assess free β-hCG and PAPP-A concentrations were measured by Auto DELFIA^R (Perkin Elmer, Turku, Finland).
Results: In this study a total of 210 women who have the low PAPP-A value less than 0.4 MoM were under the closer surveillance for serious pregnancy outcome. 33(15.6%) women had pre-eclempsia, 27 (12.9%) cases showed intra-utrine growth retardation (IUGR), 6 (3.0%) cases have intra-utrine death. 48 (22.8%) women have pregnancy induced hypertension, and 96(45.6%) cases have other pregnancy related complication.
Conclusion: Low PAPP-A levels gives an indication of adverse pregnancy outcome in the early gestation age during the first trimester.

1. Introduction

The most effective method of first trimester screening for chromosomal abnormalities is by a combination of maternal serum free β human chorionic gonadotropin (β-hCG) and pregnancy associated plasma protein-A (PAPP-A) with nuchal translucency at 11 to 13 weeks 6 days of gestation. Final results in First trimester combined screening βhCG and PAPP-A not only screens chromosomal aneuploidy in the fetus but also the Multiples of median (MoM) of both the analytes is predictive of an adverse pregnancy outcome.[1]

PAPP-A is a glycoprotein which is secreted from the trophoblastic tissues of the placenta. PAPP-A enhances the bioavailability of insulin like growth factor (IGF) locally by cleaving the inhibitors IGFBP-4 and -5 (insulin like growth factor- binding protein-4 and-5).[2–5] IGF is mitogenic and anti-apoptotic and is vital for the growth of human cells in most tissues.[6,7] It has a pivotal role in the development of the placenta and spiral artery remodelling as it stimulates cytotrophoblast proliferation and extravillous trophoblast migration in the first trimester.[8]

A low PAPP-A is defined as maternal serum PAPP-A value < 0.4 MoM, and it has been observed that low PAPP-A is associated with increased frequency of adverse obstetrical outcomes.[9] One more study which check the association between low PAPP-A value ≤0.41have adverse pregnancy outcome in first trimester.[10] Decreased levels of PAPP-A in maternal serum can be a sign of impaired placental function and implantation. Identification of women at increased risk of adverse pregnancy outcome in the first trimester

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of gestation would be quite advantageous as it facilitates increased surveillance of high risk pregnancy and offer timely intervention. Low PAPP-A could be an important marker for the same.

The aim of present study was to check the correlation of low PAPP-A with adverse pregnancy outcome in the first trimester. Adverse pregnancy outcome can be defined as pregnancy ending in several complication like – miscarriage, pre-eclampsia (PE), fetal growth restriction (FGR), pregnancy induced hypertension (PIH), still birth and preterm delivery and other pregnancy related complication (oligohydroamnios, low birth weight, bleeding).

2. Materials and Methods

This was a prospective study performed at the Maulana Azad Medical College (MAMC) and associated Lok Nayak Hospital New Delhi, India. This study was done over a period of three years from September 2016 to August 2019. A total of 2311 women who attended the antenatal clinic were enrolled in the first trimester between 11 to 13 weeks of gestation age. As per exclusion criteria of the study like multiple gestation and fetal demise a total of 161 women were excluded from the study. A total of 2150 eligible women were screened. The study was approved by the institutional ethical committee (IEC) of MAMC with reference number F.I/IEC/MAMC/(44)/3/2013/No:155.

After taking informed consent, maternal blood sample was collected by venipuncture. Serum was separated and stored at -20°C. Test were performed in the time frame for β-hCG and PAPP-A using the Time resolved fluroimmunoassay (Perkin Elmer, Turku, Finland) in Genetic Lab at both the centers. Final concentration of β-hCG and PAPP-A were measured and converted to MoM by dividing the absolute concentration of the analytes with median concentration at specific gestational age and corrected for maternal age to identify the pregnancy complications.

Pregnancy induced hypertension was defined as hypertension at or after 20 weeks' gestation (at least 2 readings of Blood Pressure >140 mmHg systolic or >90 mmHg diastolic). Patients with hypertension were further divided into proteinuric and non-protenuric. Proteinuric patients are those having protein (>300 mg/day or >30 mg/mmol/ spot urine protein.

Fetal growth restriction was defined as baby birth weight below the 5^{th} percentile for gestation age. Spontaneous preterm delivery was defined as before completed 37 weeks of gestation age. Intra-Uterine death defined as fetal death before 23 weeks of gestation. Oligohydramnios was defined as an amniotic fluid index <5 cm.

3. Results

A total of 2150 women were screened, demographic details of the enrolled patients are provided in Table 1. The mean maternal weight was 57.28kgs ± 11.12 and mean maternal age (years) was 26.96 ± 4.35. All women belonged to the Asian ethnicity and the mean gestational age at the time of delivery was 38 weeks ranging from (21-40 weeks)& mean baby weight was 2720 grams ± 0.57.

Out of 2150 enrolled pregnant women, 210 (%age) women had low PAPP-A value (<0.4) MoM. The study cohort of 210 women 33(15.6%) had pre-eclampsia, 27 (12.9%) showed intra-uterine growth restriction (IUGR), 6 (3.0%) had intra-uterine death, 48 (22.8%) had pregnancy induced hypertension (PIH), and 96(45.6%) had other pregnancy related complications.

Table 1: Demographic details of the patients with age, weight and gestational age

Demographics of study population(n=2150)	Value
Mean maternal age (years)	26.96 ± 4.35
Mean maternal weight (Kg)	57.28 ± 11.12
Mean gestation age at delivery (weeks)	38 weeks (21-40)
Mean baby Weight (Kg)	2.72 ± 0.57

Maximum no. of women enrolled in this study were at 12 weeks of gestation age. (Table 2)

Table 2: Distribution of participants based on gestational age

Gestational Age	Frequency	Percentage
11 weeks	543	25.3%
12 weeks	1114	51.8%
13 weeks	493	22.9%
Total	2150	100.0%

Table 3: Adverse pregnancy events and outcome

Pregnancy outcome	Total no. of women	Percentage (%)	p value
Pre-eclampsia	33	15.6%	<0.001
Intra-uterine growth restriction	27	12.9%	0.098
Intra-uterine death	6	3.0 %	0.027
Pregnancy induced hypertension	48	22.8%	<0.001
Other pregnancy outcomes-(Oligohydramnios, low birth weight, bleeding)s	96	45.6%	<0.001

4. Discussion

First trimester aneuploidy screening is conventionally done by a combined test which consists of serum

based dual marker testing along with nuchal translucency measurement. Apart from screening for chromosomal aneuploidy low PAPP-A is a crucial parameter for predicting adverse pregnancy outcome. In our study, low PAPP-A levels have shown a correlation with adverse pregnancy outcome. In our result, (15.6%) women had pre-eclampsia, which was similar (15.38%) to the study by Gupta et.al. (2015).[11] However, this percentage was higher than Vesna Livrinova et al. study (10%).[12] The result of IUGR (12.9%) and pregnancy induced hypertension (22.8%) were comparable to studied by Patil Mithil et al.[13] Several other studies confirm the association of low PAPP-A with adverse pregnancy outcome. Recent study by Vesna Livrinova et al. found that the pre-eclampsia and preterm delivery are associated with low PAPP-A. J.D. Salvig reported that the PAPP-A value <0.3 significantly (p value 0.001) affect fetal growth rate (OR 1.84, 95% CI1.29-2.62).[14] Cowans and Spancer have also reported that low PAPP-A is associated with adverse pregnancy outcome. They found a linear relationship between the fetal growth restriction and low PAPP-A levels.[15] Some other studies also confirmed that first trimester PAPP-A <0.4 MoM was significantly associated with pregnancy complication.

In our study we concluded that low PAPP-A is a good marker for identifying women at high risk in early pregnancy. Pre-eclampsia is a leading cause of maternal mortality. Similarly, IUGR and low birth weight are major cause of neonatal morbidity and mortality and are a public health burden. A low PAPP-A detected in early gestation age is an indispensable tool for increased fetal and maternal surveillance in high-risk pregnancies. It would not only bring down the maternal mortality, neonatal morbidity and mortality but also reduce the health expenditure.

5. Conclusion

Low level of PAPP-A in the first trimester of pregnancy is associated with adverse pregnancy outcome. Early identification of patients with Low PAPP-A in pregnancy enables individualized prenatal care reducing the risk of complication in this group.

Low levels of PAPP-A have been reported more constantly with adverse pregnancy outcome, a clear cut-off value for the Indian region is not determined. So, further studies with large sample size will be required to determine the cutoff value for low PAPP-A for our country.

Justification for Cut off value of low PAPP-A has been discussed on page no. 2 and reference no. 12 and 13 has been given for this.

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7. Conflict of Interest

The Authors declares that there is no conflict of interest related to this manuscript.

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