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Pregnancy-associated Plasma Protein A Levels with Pregnancy Outcomes: A preliminary study

Indu Lata, M.D.*,
Prabhaker Mishra, PhD.#

** Department of Maternal and Reproductive Health, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India*
 # Biostatics and Health Informatics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

ABSTRACT

Objectives: In the first trimester serum screening pregnancy-associated plasma protein-A (PAPP-A) levels are estimated in pregnant women. Its low values are leading to more risk of preterm delivery, isolated intrauterine growth restriction (IUGR), intrauterine death (IUD) or neonatal death, pregnancy-induced hypertension (PIH), and intrahepatic cholestasis of pregnancy (IHCP). The objective of this study was to find the correlation of PAPP-A levels with pregnancy outcomes and complications.

Materials and Methods: This retrospective study was done on the patients visiting the antenatal outpatient department for first trimester screening (11-13 weeks). Ultrasonographic nuchal translucency scan and blood sample test for double marker were performed. Based on the multiple of median (MOM) value of PAPP-A, two groups were made. MOM value ≥ 0.5 (normal PAPP-A levels) was considered as the control group and MOM value < 0.5 (low PAPP-A levels) was considered as the study group. Data were collected and analyzed. Pregnant women were followed-up until delivery. Pregnancy outcomes and complications were recorded.

Results: A total of 141 patients qualified and included in the study, 126 patients had normal (control group) and 15 had low PAPP-A values (study group). The study group had significant higher complications when compared to control group as IHCP (46.6% vs 14.3%, p = 0.002), IUGR (26.6% vs 8.7%, p = 0.034), preterm delivery (46.67% vs 19.84%, p = 0.017), IUD (13.3% vs 0.79%, p = 0.001) and fetal distress (13.3% vs 1.58%, p = 0.009). The patients of study group having more gestational diabetes (20% vs 16.6%, p = 0.744), both PIH and oligohydramnios (13.3% vs 7.93%, p = 0.482) and premature rupture of membranes (6.66% vs 0.79%, p = 0.069) that were insignificantly higher as compared to control groups.

Conclusion: The PAPP-A levels measurement is a valuable marker during the first -trimester screening for predicting adverse outcomes and complications, as low PAPP-A level was associated with a high chance of preterm delivery, IUGR, IHCP, and adverse fetal outcome.

Keywords: PAPP-A level, pregnancy, outcome, complications.

Correspondence to: *Indu Lata, M.D., Department of Maternal and Reproductive Health, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, UP-226014, India, Email: drindusandeep @gmail.com*

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Introduction

The double marker screening test consists of two biochemical markers, pregnancy-associated plasma protein -A (PAPP- A) and free β-human chorionic gonadotrophin (hCG) level. Along with the nuchal translucency ultrasound examination, it is used to assess the risk for trisomy 21 and other fetal aneuploidies in the first trimester. How PAPP-A can be associated with bad pregnancy outcomes, the answer can be as following. PAPP- A, a protease, helps to release free insulin like growth factor (IGF) for its action[1]. Studies show that IGF helps in the activation of cell division, differentiation and decidual invasion by trophoblasts[2]. It affects fetal growth by regulating the use of amino acids and glucose in the trophoblast[3]. The low levels of maternal serum PAPP-A will lead to low levels of active IGF and finally affect fetal growth. This effect on fetal growth may also cause other adverse pregnancy complications, such as preterm delivery, intrauterine growth restriction (IUGR), pregnancy-induced hypertension (PIH), stillbirth and neonatal death[4-6]. The circulating PAPP-A is formed in syncytiotrophoblast during pregnancy[7]. One has to give more attention to patients who have low PAPP-A levels during the first trimester of pregnancy.

Hence, we hypothesize the use of low PAPP-A, as an important marker of pregnancy and useful to predict outcome and complications in pregnant women. The primary objective of this study was to find the correlation between low levels of PAPP-A with pregnancy outcomes and complications. The secondary objective was to compare the normal to low PAPP-A levels to pregnancy outcome and complications.

Materials and Methods

This retrospective study was performed from January 2017 to December 2018 on pregnant patients visiting for antenatal clinic (ANC) checkup at the department of Maternal and Reproductive Health, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, UP, India. We advised all patients to visit the antenatal out patient department (OPD) for first trimester screening at 11-13 weeks 6 days of gestation, for nuchal translucency ultrasound and blood sample for double marker test. The double marker test included the free β-HCG and PAPP-A levels.

The selection of patients was done based on inclusion criteria from pregnant patients with singleton pregnancy presented between 11-13 weeks 6 days and having nuchal translucency ultrasound and double marker with complete follow up to delivery and complications. We screened 605 patients, who attended the OPD for ANC checkup at first trimester during the study period, but only 141 patients had a complete dataset in terms of follow-up, outcome and complications that were found eligible as per inclusion criteria to include in this study and analyzed.

Blood samples were collected in a vacutainer tube without anticoagulant and sent for analysis to the molecular medicine laboratory of our institute. The samples were analyzed on the device-Siemens-IMMULITE 1000 automated immunoassay system, using automated chemiluminescent immunoassays. The risk calculation was done with Siemens software PRISCA, which uses biochemical markers, ultrasound measurements, and demographics data to make calculations. Data of the double marker test of all the patients were collected and analyzed. PAPP-A, multiple of median (MOM) value was taken to analyze the results. Based on previous studies results from the patients with PAPP-A MOM value 0.5 were taken as the cut of value[22]. The patients were divided into two groups as per the results, the patients having MOM value ≥ 0.5 was considered to control group (normal PAPP-A levels) and MOM value < 0.5 was considered as a study group (low PAPP-A level). The results were presented in absolute values and percentages. The data of the patients were collected on proforma that includes demographic, obstetric, and other details. All the pregnant women were followed-up till delivery and the outcome of the baby was examined in the neonatal period by a neonatologist. All the new born were without any congenital malformation and infections.

Pregnancy outcomes as of preterm and term deliveries were determined and adverse findings in fetus and mother including fetal congenital anomalies, PIH, and oligohydramnios, gestational diabetes noted. Pregnancy complications spontaneous abortion, stillbirth, premature rupture of membranes (PROM), fetal distress, IUGR, and intrahepatic cholestasis of pregnancy (IHCP) were compared between two study groups. The definition of the above outcome and complications of pregnancies studied were taken as per standard guidelines of the American College of Obstetricians and Gynecologists (ACOG)[18].

Exclusion criteria were patient with comorbidities as a history of diabetes, chronic hypertension, renal and liver diseases, autoimmune and metabolic disease and other medical diseases. The other criteria were the presence of congenital infection, anomalies and chromosomal abnormalities, and patient coming before, and after 11-13 weeks 6 days of gestation or having multiple gestations

The continuous variables presented as mean ± standard deviation (SD), whereas categorical variables were represented as frequency (%). Independent samples t-test was used to compare the mean age between patients. Chi-square test or Fisher exact test were used to compare the proportions between two groups. Adjacent bar diagram was used to compare the age (≤ 30 years, > 30 years) distribution of the patients between two patient groups. The p value < 0.05 was considered as statistically significant. Statistical package for social sciences, version 23 (SPSS-23, IBM, Chicago, USA) was used for statistical analysis.

Results

In this study, a total of 141 patients were included and analyzed. The control group had 126 patients (normal PAPP-A level) and the study group had 15 patients (low PAPP-A level) all were observed till delivery for outcome and complications. PAPP-A level with ≥ 0.5 MOM was considered normal (n=126, 89.3%), while levels < 0.5 MOM was marked as low (n=15, 10.7%). Mean (SD) age of the patients with study and control group were 30.11 (4.72) and 30.21 (4.73) years, respectively (p = 0.462). Similarly, proportions of patients with age ≤ 30 years were almost equal between control and study group (55.56% vs 53.30%, p=0.870) (Fig. 1).

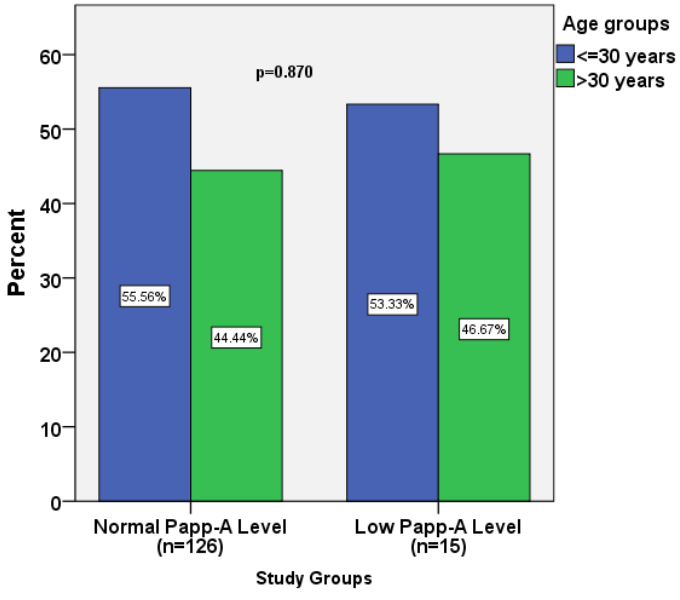

Fig. 1. Distribution of age between the study groups (low multiple of median (MOM) and control MOM).

Pregnancy outcome in the control group 80.16% patients and study group 53.33% had a delivery at ≥ 37 weeks of pregnancy (term delivery) (Table 1). The patients delivered at 28 - 36 weeks 6 days of pregnancy were 40% in the study group and were 18.25% in control group (Table 1). In the control group overall 19.84% of patients and in the study group 46.6% of patients delivered at < 37 weeks of pregnancy (preterm labor), which was significant (Table 2).

Pregnancy complications in the control group: 21 patients (16.6%) had gestational diabetes, 11 (8.73%) had IUGR and 10 (7.93%) had PIH (Table 2). In study group: 3 patients (20%) had gestational diabetes, 7 (46.6%) had IHCP, and 4 (26.6%) had IUGR (mostly asymmetrical) due to an increase in uteroplacental resistance. There was a significantly high incidence of IHCP, preterm delivery, and fetal growth restriction in the study group as compared to the control group (Table 2).

The study group patients had significant higher complications as compared to control group as IHCP (46.6% vs 14.3%, p = 0.002), IUGR (26.6% vs 8.7%, p = 0.034), preterm delivery (46.67% vs 19.84%, p = 0.017), intrauterine death (IUD) (13.3% vs 0.79%, p = 0.001) and fetal distress (13.3% vs 1.58%, p = 0.009). The patients of study group having more gestational diabetes (20% vs 16.6%, p = 0.744), both PIH and oligohydramnios (13.3% vs 7.93%, p = 0.482) and PROM (6.66% vs 0.79%, p = 0.069) that were insignificantly higher as compared to control groups (Table 2).

Table 1. Distribution of gestational age between the two groups.

Gestational age	Control group (n = 126)		Study group (n = 15)	
	Frequency	%	Frequency	%
< 28 Weeks	2	1.59	1	6.67
28-36 weeks 6 days	23	18.25	6	40.00
≥ 37 weeks	101	80.16	8	53.33

Table 2. Pregnancy outcomes between two study groups.

Pregnancy outcomes	Control group (n = 126)		Study group (n = 15)		p value
	Number	%	Number	%	
No complications	34	26.9	3	20	0.759
Gestational diabetes	21	16.6	3	20	0.741
Intrahepatic cholestasis of pregnancy	18	14.28	7	46.6	0.002
Intrauterine growth restriction	11	8.73	4	26.6	0.034
Pregnancy-induced hypertension	10	7.93	2	13.3	0.482
Oligohydramnios	10	7.93	2	13.3	0.482
Preterm delivery	25	19.84	7	46.67	0.017
Premature rupture of membranes	1	0.79	1	6.66	0.069
	1	0.79	2	13.3	0.001
Placental abruption	0	0	0	0	-
Fetal distress	2	1.58	2	13.3	0.009
Abortion	1	0.79	0	0	0.731

Discussion

In the antenatal period, if an ultrasound scan is normal, even then the possibility of adverse pregnancy outcomes cannot be ruled out[11]. A low PAPP-A level is not very sensitive test, but it is associated with more adverse pregnancy outcomes, that can be predicted with accuracy[8-13]. In this retrospective study found that low PAPP-A level was associated with a high chance of preterm delivery, IUGR, IHCP, and adverse fetal outcome. PAPP-A is synthesized by syncytiotrophoblasts in the placenta[14]. The PAPP-A, activate the IGF by releasing its binding protein from its cell receptor. The early development and vascularization of the placenta with trophoblast invasion occurs with the help of IGF[15]. When PAPP-A level is low, IGF level will be low and due to its low availability, it can lead to abortions, IUGR, PIH, IUD, preterm labor[16]. The rate of the cesarean section may be high due to fetal or maternal complications.

In this study, a total of 141 patients were included and analyzed. The control group had 126 patients (normal PAPP-A level) and the study group had 15 patients (low PAPP-A level, which is only 10.64 % of total patients). In the study group (low PAPP-A levels): more patients delivered at < 37 weeks of pregnancy (preterm delivery) as compared to the control group (normal PAPP- A level). Similar results were found by Cowan and Spencer analyzed PAPP-A in the first trimester of pregnancy without chromosomal abnormality and found a threefold increase risk of pregnancy loss with low PAPP-Alevels[17]. In another study, they find a linear relationship between low values and morphological small babies. In the first and second trimester evaluation of risk trial found that low PAPP-A were associated with more chances of pregnancy loss and other associated complications. So overall low PAPP-A levels appeared to be a strong independent marker of aneuploidy and a risk factor for spontaneous abortion but not a risk factor for structural anomalies[19] .

In the study group, patients had a higher incidence of IHCP, IUGR, fetal distress, PROM, and IUD. The gestational diabetes, PIH and oligohydramnios were also more in the study group, but statistically not significant. Low PAPP-A and the associated adverse outcomes are supposed due to poor placental function, leading to morphologic and histopathological anomalies and changes. Low PAPP-A was predictive of adverse pregnancy outcomes. The normal PAPP-A levels were almost having normal fetal growth, term delivery and favorable pregnancy outcomes, similar as per the results of this study[20, 21].

In a recent study explaining the high association of a low PAPP-A level and pregnancy outcome with complications (as pregnancy loss, IUGR, preterm delivery, PIH), as seen by this study[22, 23]. These results were also comparable to findings of low level of PAPP-A was associated with increased risk of IHCP as compared to average PAPP-A levels[24]. Physiological and hormonal changes during pregnancy, abnormal biliary transport and excretion, genetic, environmental and other multiple factors may be responsible for the pathogenesis of IHCP[25]. However, there is no specific cause is known for IHCP, it may be multifactorial and not yet fully explained. In previous studies, PAPP-A has been suggested as an early marker of IHCP development[26].

To make a strong recommendation to use PAPP-A MOM value to predict the pregnancy outcome, a large number of patients should be included, which was the limitation of this study. The more precise cut-off values of PAPP-A should be taken, that has a significant impact on pregnancy outcome. For example, Australian national policy recommends for follow-up and management of patients with low PAPP-A values[27]. With an extensive follow-up of patients with low PAPP -A levels, as a warning sign, so we can prevent an adverse pregnancy outcome and further decreasing maternal and fetal morbidity and mortality.

The PAPP-A levels measurement is a valuable marker during the first trimester screening for predicting adverse outcomes and complications. Lower the PAPP-A MOM value, higher is the chance and incidence of adverse outcomes. In present study, we found an increased chance of preterm delivery, IHCP, and IUGR in low PAPP-A group. We recommend the

larger study to establish a strong association between PAPP-A level and pregnancy outcomes.

Conflict of interest

The authors declare that there is no conflict of interest

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