INTRODUCTION

The double marker screening test consists of two tests, PAPP-A and free β-human chorionic gonadotrophin (hCG) level. Along with the nuchal translucency USG scan, 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 follows. Pregnancy-associated plasma protein A, a protease, helps to release free insulin like growth factor (IGF) for its action. Studies show that IGF helps in the activation of cell division, differentiation and decidual invasion by trophoblasts. It affects fetal growth by regulating the use of amino acids and glucose in the trophoblast. 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, IUGR, PIH, stillbirth and neonatal death. The circulating PAPP-A is formed in Syncytiotrophoblast during pregnancy. 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 is to see the correlation between low levels of PAPP-A with pregnancy outcomes and complications. The secondary

TO STUDY THE CORRELATION OF PREGNANCY ASSOCIATED PLASMA PROTEIN-A LEVELS WITH PREGNANCY RELATED COMPLICATIONS AND OUTCOME

Dr Indu Lata* and Dr Prabhakar Mishra

Additional Professor, Department of Maternal and Reproductive Health, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, UP

ABSTRACT

Background: 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 to see the correlation of levels of PAPP-A with pregnancy outcomes and complications.

Methods: This retrospective study was done on the patient visiting the antenatal OPD for first-trimester screening (11-13 weeks), undergone USG nuchal translucency scan, and blood sample test for double marker were included. Based on of the PAPP-A, Multiple of Median (MOM) value, 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 level) was considered as the study group and data was collected and analyzed. Pregnant women were followed until delivery for pregnancy outcome and to know any complications.

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 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 (46.6% 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 dolichohydramnios (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.

Conclusions: 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.
Objective to compare the normal to low PAPP-A levels to pregnancy outcome and complications.

**METHODS**

This retrospective study was done from January 2017 to December 2018 on pregnant patient visiting for ANC checkup at the department of Maternal and Reproductive Health, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, UP, India. We advise all patients to visit the antenatal OPD for first-trimester screening at 11-13 weeks of gestation, for USG nuchal translucency scan and blood sample for double marker test. The double marker test includes 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 and having screening data USG 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 analyze.

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 are taken as the cut of value.22The 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 are 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 females were followed till delivery and the outcome of the baby was examined in the neonatal period by a neonatologist. All the newborn were without any congenital malformation and infections.

Pregnancy outcome 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, PROM, fetal distress, IUGR, IHCP were compared between two study groups. The definition of the above outcome and complications of pregnancies studied and listed in table 2, were taken as per standard guidelines of the American College of Obstetrics and Gynecology (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 of gestation or having multiple gestations.

The continuous variable’s presented as mean ± 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 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 patients’ 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. Mean (SD) and the median age of the patients was 30.41(4.73) and 30 years. 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) 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)Figure 1.

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, 4 (26.6%) had IUGR (mostly asymmetrical) due to an increase in uteroplacental resistance. There was a significantly high incidence of IHCP, preterm labor, 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), 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).
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 labor) 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-A levels. 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.

In the study group, patients had a higher incidence of ICHP, 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. Thenormal 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 PAPP-A is associated with increased risk of ICHP 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 ICHP. 25 However, there is no specific cause is known for ICHP, it may be multifactorial and not yet fully explained. In previous studies also PAPP-A has been suggested as an early marker of ICHP development. 20

To make a strong recommendation to use PAPP-A, MOMs value to predict the pregnancy outcome, a large number of patients should be included, which is the limitation of this study. The more precise cut off values of PAPP-A levels. 26 These results were also comparable to findings of low PAPP-A is associated with increased risk of ICHP as compared to average PAPP-A levels. 27 Physiological and hormonal changes during pregnancy, abnormal biliary transport and excretion, genetic, environmental and other multiple factors may be responsible for the pathogenesis of ICHP. 28 However, there is no specific cause is known for ICHP, it may be multifactorial and not yet fully explained. In previous studies also PAPP-A has been suggested as an early marker of ICHP development. 29

DISCUSSION

In the antenatal period, if an ultrasound scan is normal, even then the possibility of adverse pregnancy outcomes cannot be ruled out. 14 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. 15-17 In this retrospective study found that low PAPP-A level was associated with a high chance of preterm delivery, IUGR, ICHP, and adverse fetal outcome. PAPP-A is synthesized by extravillous cytotrophoblasts 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, Intrauterine growth restriction, pregnancy-induced hypertension, intrauterine fetal death, preterm labor. 14 The rate of the cesarean section may be high due to fetal or maternal complications.

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

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Control group (N=126)</th>
<th>Study group (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>%</td>
<td>Frequency</td>
</tr>
<tr>
<td>&lt;28 Weeks</td>
<td>2</td>
<td>1.59</td>
</tr>
<tr>
<td>28-36 weeks 6 days</td>
<td>23</td>
<td>18.25</td>
</tr>
<tr>
<td>≥37 weeks</td>
<td>101</td>
<td>80.16</td>
</tr>
</tbody>
</table>

**Table 2** Pregnancy outcomes between two study groups (significant *)

<table>
<thead>
<tr>
<th>Pregnancy Outcome</th>
<th>Control group (N=126)</th>
<th>Study group (N=15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>%</td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>No complications</td>
<td>34</td>
<td>26.9</td>
<td>3</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>21</td>
<td>16.6</td>
<td>3</td>
</tr>
<tr>
<td>ICHP</td>
<td>18</td>
<td>14.28</td>
<td>7</td>
</tr>
<tr>
<td>IUGR</td>
<td>11</td>
<td>8.73</td>
<td>4</td>
</tr>
<tr>
<td>PIH</td>
<td>10</td>
<td>7.93</td>
<td>2</td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td>10</td>
<td>7.93</td>
<td>2</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>25</td>
<td>19.84</td>
<td>7</td>
</tr>
<tr>
<td>PROM</td>
<td>1</td>
<td>0.79</td>
<td>1</td>
</tr>
<tr>
<td>IUD</td>
<td>1</td>
<td>0.79</td>
<td>2</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fetal distress</td>
<td>2</td>
<td>1.58</td>
<td>2</td>
</tr>
<tr>
<td>Abortion</td>
<td>1</td>
<td>0.79</td>
<td>0</td>
</tr>
</tbody>
</table>

**Figure 1** Distribution of age between the study groups (low PAPP-A and normal PAPP-A)
to establish a strong association between PAPP-A level and pregnancy outcome.

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**References**


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