

## Usefulness of PAPP-A in predicting adverse pregnancy outcome

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### Abstract

**Objective:** The First trimester Pregnancy-associated plasma protein-A (PAPP-A) is one of the marker for the screening. The purpose of this study was to evaluate whether low levels of first trimester PAPP-A alone is predictive for adverse pregnancy outcomes such as intrauterine growth restriction, gestational hypertension, pre-eclampsia, low birth weight and preterm labour.

**Study design:** This study included patients with singleton pregnancies who underwent combined first trimester screening using nuchal translucency (NT) and maternal serum free beta-human chorionic gonadotrophin (free beta-hCG) and PAPP-A at 11-13+6weeks gestation. The incidence of various adverse pregnancy outcomes such as spontaneous preterm labor, fetal growth restriction (FGR), pre-eclampsia and gestational hypertension and low birth weight were correlated in relation to Abnormal PAPP-A values(<0.4MOM).

**Results:** In our study out of the 1100 patient were enrolled 167 women were lost to follow up and 9 were excluded.924 patients followed up for adverse pregnancy outcome. Abnormal PAPP-A was found in 12.5%. IUGR was found in 10.5% (n=12;OR-5.1) preeclampsia in 8.8%(n=10;OR-2.7), Gestational hypertension 3.5% (n=4;OR-0.552), Preterm labour 15.8% (n=18;OR-2.6) and Low birth weight in 33.3% (n=38; P value-0.001) women of which 25.4% delivered at term and only 7.9% delivered as preterm.

**Conclusion:** This study demonstrated that maternal serum PAPP-A is low in pregnancies resulting in Intrauterine growth restriction, Pre-eclampsia, Preterm labour and Low birth weight. However the sensitivity of Abnormal PAPP-A to predict adverse pregnancy outcomes is poor. Thus, PAPP-A is a good predictor for adverse pregnancy outcome mainly IUGR but hence cannot be used for screening test.

**Keywords:** Intrauterine growth restriction, Pregnancy associated plasma protein A, Fetal Growth restriction, Growth factor binding protein, Multiples of median, Adverse pregnancy outcome

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### Introduction

First-trimester impaired placental function may be one of the potential underlying processes that result in adverse pregnancy outcomes.<sup>(1,2)</sup> Recently, retrospective studies have shown that low levels of maternal serum PAPP-A is associated with development of pregnancy complications. PAPP-A is known to be a protease for IGF binding proteins (IGF BPS), so its level can affect the level of free IGF by reversing the inhibitory effects of the IGF BPs and therefore contribute to fetal growth. However, there have been little retrospective studies regarding this subject and the results of previous studies are controversial, and there is no general agreement about the relation between PAPP-A and adverse pregnancy outcomes such as IUGR, pre-eclampsia, gestational hypertension, preterm labour and low birth weight. The aim of this prospective study was to evaluate any association between serum levels of PAPP-A at 11 to 13 + 6 weeks of pregnancy with intrauterine growth restriction, preeclampsia, gestational hypertension, preterm labour and low birth weight in order for them to benefit from the increased surveillance of these conditions.

### Aim

The aim of the study is predict adverse pregnancy outcome in women with abnormal PAPP-A.

### Materials and Methods

This was a prospective observational study carried out at Sri Ramachandra University from August 2014 to September 2016. This study was approved by the ethics committee ethics number CSP-MED/14/NOV/20/213. Women attending antenatal OPD at SRU were subjected to First trimester screening which was done between 11-13weeks & 6days of gestation. These patients were carefully followed for development of adverse pregnancy outcomes. Sample size for this study was determined by using the following formula: Sample size- $DEFF * Np(1-p) / [(d2/Z2 1\alpha / 2 * (N-1) + p * (1p))$ .

**Inclusion criteria:** Patients attending antenatal OPD between 11 to 13+6 weeks of pregnancy and due to deliver in our hospital.

**Exclusion criteria:** Structural abnormalities in the fetus or Chromosomal abnormalities in the fetus detected at anytime, Chronic hypertension, Diabetes Mellitus and Any other Chronic systemic diseases. At the time of initial visit detailed history, clinical examination and routine antenatal investigations were done for each patient. Gestational age was determined based on the best estimate from a reliable menstrual history and confirmed by a fetal dating scan done early in the first trimester. Women booked for maternity care at SRU were offered screening for aneuploides. NT was measured by sonologists who had undertaken training

and certification in FTS as specified by the Fetal medicine Foundation. The machine used was Voluson E6 with transducer probe RIC 5-9D and 4C-D. NT was measured according to the FMF protocol which is explained in detail in the following page. Serum concentration of Beta HCG and PAPP-A were analyzed by specific fluoroimmuno assay as a part of the routine screening for fetal Down's syndrome and all the results were expressed as multiple of the median of the expected normal median for a pregnancy of the same gestational age. In our study PAPP-A <0.4MOM was taken as reference range (SOGC). The following outcome measures were examined. A detailed anomaly scan was carried out at 18-20weeks period of gestation to rule out any obvious congenital anomalies. Ultrasound for fetal biometry (BPD/FL/AC/HC/AFI) and fetal Doppler were carried out at an interval of 3 weeks in women having an abnormal SFH and in pregnancies at risk of developing IUGR. The results obtained were obtained and analyzed with respect to adverse pregnancy outcomes.

**Results**

A total of 1100 women were enrolled in this study of which 167 were lost to follow up. Further 2 women had anomalous fetuses hence were excluded and 6 had abortions 1 had intrauterine fetal demise at 36weeksof gestation. Hence a complete follow up was obtained in 924 women. Women between 26-30 years age group was the highest of 46% (n=425). There was no significant difference in parity distribution and had nearly equal number of nulliparous women of 56% (n=521) and multiparous women 44% (n=410).

Abnormal PAPP-A was found in 12.5%. IUGR was found in 10.5% (n=12 women) with low PAPP-A whereas only 2.2% (n=18 women) had IUGR with normal PAPP-A which showed that there was an

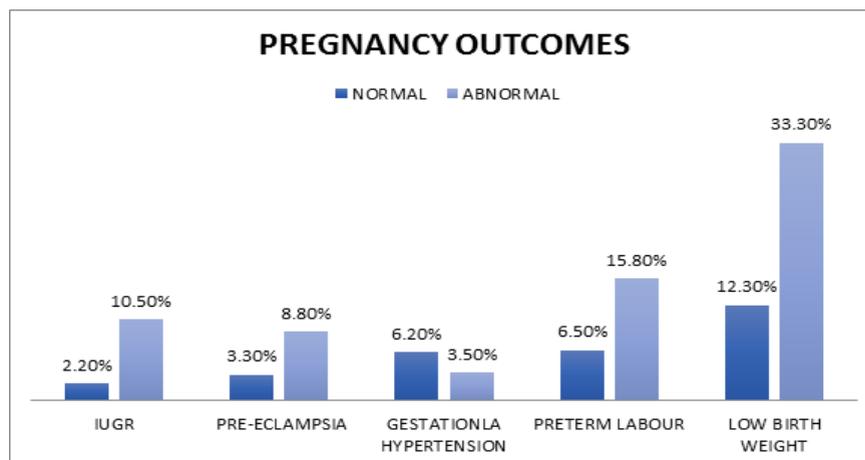
increased risk of IUGR in women with low PAPP-A with statically significant difference with p value of <0.0001 and the odds ratio was 5.1.

There was increased incidence of preeclampsia in women with low PAPP-A that is 8.8%(n=16) whereas only 3.3% (n=27) had normal PAPP-A which showed a p value of <0.01 with odds ratio of 2.7 which is significant.

Only 3.5% (n=4) women with low PAPP-A and 6.2% (n=50) normal PAPP-A developed gestational hypertension with a P Value-0.180 which is not significant.15.8% (n=18) women with low PAPP-A went into preterm labour whereas 6.5% (n=53) has around PAPP-A which shows that there is a significant increased risk in preterm labour with low PAPP-A with p value of 0.001 and odds ratio 2.6.33.3% (n=30) women with low PAPP-A and 12.3 (n= 100) women with normal PAPP-A delivered low birth weight neonates out of the 33.3% women; 25.4% delivered at term and only 7.9% delivered as preterm. In present study there was an association of low birth weight with low level of PAPP-A showed p value of 0.001.The above observation are tabulated in Table 1.

**Table 1: Adverse pregnancy outcome with PAPP-A**

Pregnancy Outcomes	Normal	Abnormal	P Value	OR
IUGR	18 2.2%	12 10.5%	<0.001	5.1
Pre-Eclampsia	27 3.3%	10 8.8%	<0.01	2.7
Gestational Hypertension	50 6.2%	4 3.5%	0.180	0.552
Preterm Labour	53 6.5%	18 15.8%	0.001	2.6
Low Birth Weight	100 12.3%	38 33.3%	0.001	



**Table 2: Sensitivity, Specificity, Positive predictive value and negative predictive value of PAPP-A**

Pregnancy Outcomes	Sensitivity	Specificity	Positive predictive value	Negative predictive value
IUGR	10.5%	97.7%	40%	88.6%
Pre-Eclampsia	27%	88.3%	8.7%	96.6%
Gestational Hypertension	7.4%	87.4%	3.5%	93.8%
Preterm Labour	25.6%	88.7%	15.8%	93.5%
Low Birth Weight	27.5%	90.3%	33.3%	87.6%

## Discussion

This study showed that there was a significant association between low PAPP-A and adverse pregnancy outcomes such as IUGR, pre-eclampsia, preterm birth and low birth weight. There was no association between low PAPP-A and gestational hypertension. The development of pregnancy induced hypertension and fetal growth restriction are thought to be the consequence of impaired placentation due to inadequate trophoblastic invasion of the maternal spiral arteriols.<sup>(3)</sup> 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 subsequent development of pregnancy induced hypertension and fetal growth restriction.

Gordon C.C. Smith et al<sup>(6)</sup> showed that women with PAPP-A within the lowest fifth percentile at 8-14weeks gestation had an increase risk of IUGR with odds ratio of 2.9 and p value of <0.0001 which is similar to present study. In this study the key maternal factors such as maternal age and smoking status was taken into account which was not done in our study. Two other studies Suzanne E. Peterson et al<sup>(8)</sup> and David Krantz et al<sup>(7)</sup> showed that PAPP-A < 5th percentile increased risk of IUGR with odd ratio of 2.7. The only other study which did not show statistical significance was Slavica Vujovic et al<sup>(9)</sup> when Analysis of crossing categories of PAPP-A MoM findings of pregnant women in relation to the distribution by IUGR showed that there was no statistically significant difference ( $p > 0.05$ ), as in all categories PAPP-A MoM percentage of the IUGR incidence was nearly equal. Our study differed in the odds ratio probably because of the sample size and study design.

In women with Low PAPP-A had a higher risk of developing preeclampsia in our study with significant p value <0.01 and odds ratio of 2.7. Gordon C.C. Smith et al<sup>(6)</sup> showed that PAPP-A less than 5<sup>th</sup> centile a significant association with pre-eclampsia with p value of <0.0001 and odds ratio 2.1. Poon et al<sup>(12)</sup> found that PAPP-A MoM was significantly lower in both the early Pre Eclampsia ( $P < 0.001$ ) and late Pre Eclampsia ( $P = 0.03$ ) group with odds ratio of 2. Similarly Ozkan Ozdamar et al<sup>(11)</sup> and Charas Y. Tong et al<sup>(4)</sup> showed that there was association of low PAPP-A with pre-eclampsia with both studies showing significant p value of <0.001. K. SPENCER et al<sup>(10)</sup> the 5th centile of normal for PAPP-A (0.415 MoM) the odds ratio for pre-

eclampsia was 3.7. This study had a larger sample size. Thus in all the studies including ours showed low PAPP-A was associated with preeclampsia.

The present study showed no association between Low PAPP-A and gestational hypertension. (P Value-0.180). In contrast to Charas Y. Tong et al<sup>(4)</sup> showed low PAPP-A in non-proteinuric pregnancy induced hypertension showed statically significant p value of 0.001. Our study did not concur with above study probably because of the difference in the sample size.

In the present study low levels of PAPP-A and preterm labour showed statically significant value of 0.001 and odds ratio 2.6. Women with low PAPP-A are at a higher risk to developed preterm labour. K.Spencer et al<sup>(13)</sup> showed that in women with PAPP-A less than the 5<sup>th</sup> centile the odds ratios for delivery before 37 weeks was 1.92 and before 34 weeks were 2.35. Goetzinger KR et al<sup>(15)</sup> showed that abnormally low PAPP-A was associated with an increased risk for PTB at < 35 weeks with an odds ratio of 2.0 and PTB at < 32 weeks had odds ratio of 2.7. In present study association of low birth weight with low level of PAPP-A showed p value 0.001. In a study by Canini et al<sup>(14)</sup> pregnancies with the lowest decile of PAPP-A the odds ratio for delivering an SGA newborn was 1.67.

Our study correlated with GORDON smith et al<sup>(6)</sup> and Sandie. L et al<sup>(15)</sup> which conclude that there is association between low PAPP-A, IUGR, pre-eclampsia, low birth weight and preterm labour. Sandie. L et al<sup>(15)</sup> results state that PAPP-A as a primary screening for adverse fetal outcomes is poor as sensitivity is 5% which was similar to our study which showed sentivity of 10.5%.

## Conclusion

This study demonstrated that maternal serum PAPP-A is low in pregnancies resulting in Intrauterine growth restriction, Pre-eclampsia, Preterm labour and Low birth weight. The sensitivity of Abnormal PAPP-A to predict adverse pregnancy outcomes is poor. Thus, PAPP-A is a good predictor for adverse pregnancy outcome mainly IUGR although PAPP-A but cannot be used as a screening test, it is useful parameter to follow up patients with low PAPP-A when encountered in routine First Trimester Screening.

### Limitations of our study

The number of women enrolled in our study was far less than the sample size in other studies. Certain maternal variables like smoking and BMI was not taken into account.

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