

## Role of Uterine Artery Doppler and Maternal Serum Pregnancy Associated Plasma Protein-A (PAPP-A) in Predicting Preeclampsia

Dr. Shinjini Narang<sup>1</sup>, Dr. Ankit Sahu<sup>2\*</sup>

<sup>1</sup>Senior Resident, Department of Obstetrics and Gynaecology, PGI, Chandigarh, India

<sup>2</sup>Assistant Professor, Department of General Surgery, Sharda University, Greater Noida, Uttar Pradesh, India

### Original Research Article

\*Corresponding author

Dr. Ankit Sahu

### Article History

Received: 03.09.2018

Accepted: 14.09.2018

Published: 30.09.2018

### DOI:

10.21276/sjams.2018.6.9.49



**Abstract:** Preeclampsia is a preventable cause of maternal mortality and should be detected and appropriately managed before the onset of convulsions (eclampsia) and other life-threatening complications. To assess the role of Uterine artery Doppler and Maternal serum pregnancy associated plasma protein-A (PAPP-A) at 11-14 weeks of gestation in prediction of preeclampsia. Seventy eight pregnant women with 11- 14 weeks of gestation were studied at the Department of Obstetrics and Gynaecology, King George Medical University, Lucknow from September 2014 to August 2015. The women who developed preeclampsia and related complications at the end of pregnancy were grouped under GROUP 1 (n=29) and the women who did not develop any of these complications were kept under GROUP 2 (n=49). After routine antenatal examination uterine artery doppler and PAPP-A were measured in each patients. The mean pulsatility index (PI) multiple of the median (MoM) of the women who developed preeclampsia and related complications was  $1.18 \pm 0.317$  and that of women who did not develop complications was  $0.90 \pm 0.316$  ( $p = 0.003$ ). The relative risk of development of complications in women with presence of 'notching' was 2.48 (95% CI = 1.479 – 4.159,  $p = 0.004$ ). The relative risk of development of preeclampsia in the presence of notch was 2.48 (95% CI = 0.742 to 0.832,  $p = 0.28$ ) but this was not statistically significant. The relative risk of development of IUGR in women with notch in uterine artery Doppler at 11-14 weeks of pregnancy is 2.22 (95% CI = 1.187-4.146,  $p = 0.037$ ). The mean PAPP-A MoM of women who developed preeclampsia, early onset preeclampsia, late onset preeclampsia, IUGR was  $4.97 \pm 3.89$  ( $p = 0.179$ ),  $5.77 \pm 4.61$  ( $p = 0.061$ ),  $3.39 \pm 1.12$  ( $p = 0.76$ ) and  $4.30 \pm 3.70$  ( $p = 0.43$ ) respectively. Uterine artery Doppler pulsatility index (PI) alone is the best screening method at 11-14 weeks of gestation for women at high risk of preeclampsia and related complications.

**Keywords:** Pregnancy-associated plasma protein-A, preeclampsia, IUGR, uterine artery Doppler.

### INTRODUCTION

Pre-eclampsia (PE) is a pregnancy-specific syndrome that can affect virtually every organ system. It affects 5-10% of pregnancies worldwide and 4.6% of pregnancies in India [1,2].

Attempts at prevention of preeclampsia by prophylactic interventions from late second trimester have largely been unsuccessful. It is uncertain whether interventions starting from the early second trimester rather than late second trimester would prove to be more effective in the prevention of preeclampsia, <sup>3</sup> but before this can be investigated, it is essential to develop a method of effective and early identification of the high-risk group.

As ours is a developing nation, it is not practical to use an expensive screening tool universally.

Thus, we have restricted ourselves to using only three parameters (uterine artery Doppler and PAPP-A).

In present study we tried assess the role of Uterine artery Doppler and maternal serum pregnancy associated plasma protein-A (PAPP-A) at 11-14 weeks of gestation in prediction of preeclampsia.

### MATERIALS AND METHODS

Present prospective study included 78 pregnant women at the Department of Obstetrics and Gynaecology, King George Medical University, Lucknow over a period of one year from September 2014 to August 2015. Pregnant women were enrolled in the antenatal OPD at 11- 14 weeks of gestation and followed till delivery.

All pregnant women with singleton pregnancy who attended the antenatal OPD at 11-14 weeks of

gestation and were willing for follow up were enrolled after taking informed consent. Women who did not give consent, with multifetal pregnancy and women with essential hypertension were excluded from the present study.

The women who developed preeclampsia and related complications (gestational hypertension, small for gestational age (SGA) babies, abruption placentae or intrauterine fetal demise) at the end of pregnancy were grouped under GROUP 1 and the women who did not develop any of these complications were kept under GROUP 2. Out of the 78 women, 29 women (37.18%) developed the above mentioned complications and constituted Group 1 and the other 49 (62.82 %) were Group 2.

After routine antenatal examination uterine artery doppler and PAPP-A was measured in each patients. Uterine artery Doppler was done according to the ISUOG Practice Guidelines for use of Doppler Ultrasonography in obstetrics[4].

The values of serum PAPP-A were matched for age of women, gestational age, height, weight, racial origin, type of conception, obstetric history, past history, family history of preeclampsia and history of

smoking and converted to multiples of median (MoMs) using the Fetal Medicine Foundation algorithm for prediction of preeclampsia[5].

The women enrolled in the study were then kept under follow up for the subsequent development of preeclampsia, gestational hypertension, small for gestational age (SGA) babies, placental abruption and other maternal or fetal complications. The gestational age of development of these complications was recorded along with their severity.

At delivery gestational age at delivery, type of delivery, indication of Caesarean section and baby details (weight, sex, APGAR score, NNU admission) were recorded.

The data was analyzed using SPSS (Statistical Package for Social Sciences) Version 20.0 statistical analysis software. For the categorical data in the study, relative risk was calculated and chi square test was applied. For the MAP and Mean PI, mean ± SD was calculated and these were analysed by student t test. 95 % confidence interval was calculated for all the parameters.

**RESULTS**

**Table-1: Comparison of mean PI MoM of various outcomes compared to control group**

Variable	Group 1					Group 2
	All (n=29)	PE (n=9)	IUGR (n=25)	EO-PE (n=6)	LO-PE (n=3)	N=49
Mean MAP	1.18 ± 0.31	1.17 ± 0.36	1.16± 0.32	1.19 ± 0.42	1.13 ± 0.27	0.90 ± 0.31
P value	0.003	0.023	0.001	0.046	0.216	
CI (95%)	0.13-0.42	0.03 – 1.50	0.10 – 0.42	0.005-0.57	-0.13 – 0.61	

PE; preeclampsia, IUGR, Intrauterine growth restriction, EO-PE; early onset preeclampsia, LO-PE, late onset preeclampsia, MAP; mean arterial pressure, CI; confidence interval, N; no of patients, MoM; multiple of the median

Nineteen (24.36 %) of the women enrolled had presence of an early diastolic notch on Uterine Artery Doppler at 11-14 weeks of pregnancy. 13 of these women developed complications and 6 did not develop complications. The relative risk of development of complications in women with presence of ‘notching’ was 2.48 (95% CI = 1.479 – 4.159, p = 0.004). This value was statistically significant.

Of the women who had uterine artery ‘notching’ at 11-14 weeks of pregnancy, 4 developed

preeclampsia. The relative risk of development of preeclampsia in the presence of notch was 2.48 (95% CI = 0.742 to 0.832, p = 0.28) but this was not statistically significant.

Ten (of 19) women, who had notching at 11-14 weeks of pregnancy, had a small for gestational age (SGA) baby. The relative risk of development of IUGR in women with notch in uterine artery Doppler at 11-14 weeks of pregnancy is 2.22 (95% CI = 1.187-4.146, p= 0.037) and this was statistically significant.

**Table-2: Comparison of development of IUGR with presence of notch in uterine artery Doppler**

Notch status	IUGR developed(n = 25)	IUGR did not develop(n = 53)
Notch present(n = 19)	10	9
Notch absent (n=59)	15	44

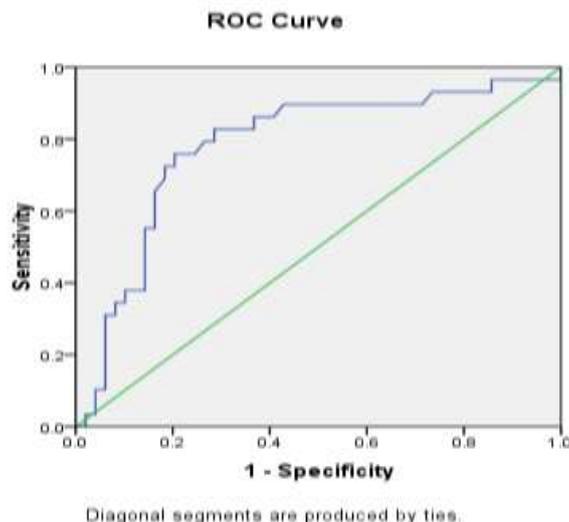
Relative risk = 2.22 (95% CI = 1.187 – 4.146) (of development of IUGR in women with notch in uterine artery Doppler at 11-14 weeks of pregnancy),p = 0.037 ;  $\chi^2 = 4.36$ . IUGR; intrauterine growth restriction

The mean PAPP-A MoM of women who developed preeclampsia was 4.97 ± 3.89 (p = 0.17, 95% CI = 0.57 – 2.99). The mean PAPP-A MoM of the

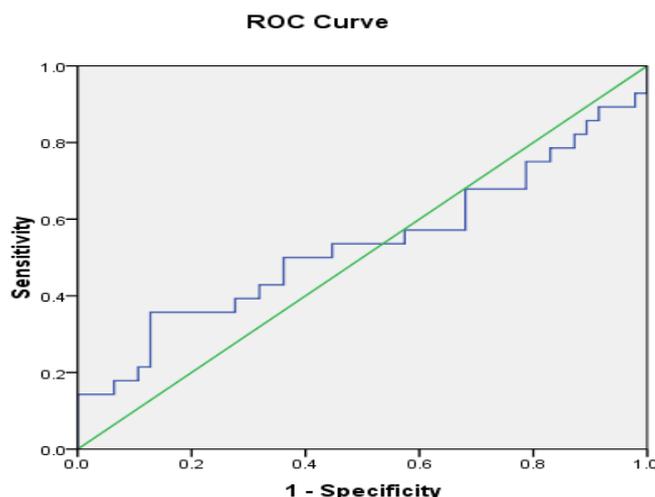
women who developed early onset preeclampsia was 5.77 ± 4.6163 (p = 0.061, 95% CI = -0.13- 4.13) and that of women who developed late onset preeclampsia

was  $3.39 \pm 1.12$  ( $p = 0.76$ , 95% CI = 0.19-6.59). The mean PAPP-A MoM of the women who developed IUGR was  $4.30 \pm 3.70$  ( $p = 0.43$ , 95% CI = -0.84 -

1.92). When compared to women who did not develop complications, none of these values were statistically significant.



**Fig-1: Receiver Operating Characteristic (ROC) curve for mean PI MoM**  
Area under curve (AUC) = 0.782, (95% CI = 0.670 – 0.894), Cut off for mean PI MoM= 1.005



**Fig-2: Receiver Operating Characteristic (ROC) curve for PAPP-A MoM**  
Area under curve (AUC) = 0.531, (95% CI = 0.385 – 0.678), Cut off for PAPP-A MoM= 2.15

## DISCUSSION

In the case of preeclampsia, effective early identification of the high risk group could potentially improve the outcome by directing close surveillance of these women and would be the basis for future studies investigating the potential role of pharmacological interventions, such as aspirin[3] starting from the early second trimester to reduce the prevalence of the disease or at least prevent adverse complications.

The values of PI and serum PAPP-A were converted to their respective multiples of median (MoMs) which was matched for age of women, gestational age, height, weight, racial origin, type of conception, obstetric history, past history, family

history of preeclampsia and history of smoking using the Fetal Medicine Foundation algorithm for prediction of preeclampsia. These patients were followed till delivery and the development of preeclampsia and related complications were recorded.

Uterine artery Doppler is known to be one of the best first-trimester PE markers. The underlying mechanism for PE is thought to be impaired trophoblastic invasion of the maternal spiral arteries and their conversion from narrow muscular vessels to wide nonmuscular channels.<sup>6</sup> An early diastolic “notch” appears to be a common feature of the uterine artery Doppler waveform in pregnancy, as it is present in 46–64% of normal gestations in the first trimester. The

poor reproducibility of uterine artery notching has led to inclusion of more objective measures of vascular impedance, favoring PI[7].

As the formula for the calculation of the PI includes the area below the waveform, the PI indirectly includes the presence or absence of an early diastolic notch. But a study by Gomez *et al.* [8] found the inter-observer repeatability of uterine artery Doppler velocimetry, showing high reproducibility, confirm that both bilateral notching and mean PI may be useful parameters in a clinical setting (the  $\kappa$ -coefficient for inter-rate reliability on bilateral notching was 0.76 and that of uterine artery PI was 0.91. But the study found that bilateral notch was present in 41% of the women and it is therefore unlikely to be useful in screening for these complications.

Results obtained in present study are consistent with the theory that early onset PE and IUGR arise due to impaired trophoblastic invasion whereas late onset preeclampsia develops due to maternal factors.

The area under the curve (AUC) of the receiver operating curve (ROC) of mean PI Mo M was 0.618. The sensitivity of mean Mo M at [11-14] weeks of pregnancy for predicting complications is 75.9 % and specificity is 79.6 %. Mean PI was found to be the best single investigation to predict preeclampsia and related complications of the three parameters under study as it has the highest AUC.

A recent meta-analysis by Velautharet *al.* [9] done in 2014, reviewed the accuracy of uterine artery Doppler analysis in the first trimester in the prediction of FGR and preeclampsia. Eighteen studies involving 55 974 women were evaluated, with fifteen of these studies enrolling women with low risk pregnancies. Uterine artery RI or PI  $\geq$  90th centile and the presence of notching (unilateral/bilateral) were used to define abnormal flow velocity waveforms. An abnormal uterine artery PI in the first trimester was predictive of preeclampsia and early-onset preeclampsia with sensitivities of 26.4% and 47.8%, respectively. Fetal growth restriction was predicted at 15.4%. The sensitivity achieved for placental abruption was 44.4%. First-trimester Doppler indices showed a low predictive accuracy for stillbirth, with a sensitivity of 14.5%. But in the present study there was only one case of abruptio placentae, so its relation with uterine artery mean PI could not be assessed.

There are only few studies evaluating the role of uterine artery notching at [11-14] weeks of gestation as it was found to have a high prevalence (46 -64 %) in the low risk populations even though it was found to be associated with higher incidence of complications compared to normal outcomes[10, 11].

PAPP-A is a protease for insulin like growth factor binding protein-4 (IGFBP- 4).A low PAPP-A level is associated with higher IGFBP-4 and lower free Insulin like growth factor(IGF). Maternal serum PAPP-A has been shown to be relatively low in the first trimester of pregnancies complicated by SGA and/or pre-eclampsia [11].

Multiple biochemical markers have been studied individually and in combination as potential markers for adverse pregnancy outcomes.<sup>12</sup> As first-trimester combined screening for fetal aneuploidy has been widely adopted, the biochemical markers used in this testing—PAPP-A and free  $\beta$ hCG- have been evaluated extensively.<sup>13</sup> Previous studies have reported that maternal serum PAPP-A below the 5<sup>th</sup> percentile in early pregnancy could detect 10 to 18% of pregnancies delivering SGA neonates 14-16.

Although a low PAPP-A in itself is not a strong indicator of preeclampsia; studies have previously shown a significant improvement in detection by combining first trimester PAPP-A measurement with uterine artery Doppler velocimetry [17,18]. In present study, PAPP-A was not found to be statistically significant ( $p = 0.575$ ) when comparing groups of women who developed complications to those who did not.

The area under the curve (AUC) of the receiver operating curve (ROC) of PAPP-A MoM was 0.531. The sensitivity of PAPP-A MoM at 11-14 weeks of pregnancy for predicting complications is 34.5 % and specificity is 83.7 %. PAPP-A at 11- 14 weeks of pregnancy was found to have a high specificity to rule out preeclampsia and related complications. This study has been conducted in a limited number of pregnant women and results cannot be extrapolated to a larger population. Nevertheless, the trends of uterine artery Doppler PI have been similar to international studies. A larger study is needed in an Indian scenario to validate the findings of this study.

## CONCLUSION

Uterine artery Doppler pulsatility index (PI) alone is the best screening method at 11-14 weeks of gestation for women at high risk of preeclampsia and related complications. Effective early identification of the high risk group could potentially improve the outcome by directing close surveillance of these women and would be the basis for future studies investigating the potential role of pharmacological interventions, such as aspirin, starting from the first trimester to reduce the prevalence of the disease or at least prevent adverse complications.

## REFERENCES

1. Cunningham FG, Lenovo KJ, Bloom SL, Spong KY, Dashe JS, Hoffman BL, Casey BM, Sheffield JS. Williams Obstetrics. Twenty-Fourth Edition.

- United States of America: McGraw-Hill Education. 2014. pp 728-779
2. Bilano VL, Ota E, Ganchimeg T, Mori R, Souza JP, Risk Factors of Pre-Eclampsia/Eclampsia and Its Adverse Outcomes in Low- and Middle-Income Countries: A WHO Secondary Analysis. *PLoS ONE* 9(3): e91198.
  3. Roberge, Giguère, Early Administration of Low-Dose Aspirin for the Prevention of Severe and Mild Preeclampsia: A Systematic Review and Meta-Analysis. *Obstetrics: medical complications of pregnancy* 2012; 67(12): 1-6.
  4. ISUOG Practice Guidelines: use of Doppler ultrasonography in obstetrics. *Ultrasound ObstetGynecol* 2013; 41: 233-9.
  5. Preeclampsia Risk Assessment Calculator [Internet]. The Fetal Medicine Foundation 2015 (cited 2018). Available form <https://fetalmedicine.org/calculator/preeclampsia>
  6. Figueras F and Gratacós E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. *Fetal Diagnosis & Therapy* 2014; 36:86–98.
  7. Khong SL, Kane SC, Brennecke SP, da Silva Costa F. First-Trimester Uterine Artery Doppler Analysis in the Prediction of Later Pregnancy Complications. *Disease Markers*. Volume 2015, Article ID 679730
  8. Gomez O, Martinez JM, Figueras F. Uterine artery Doppler at 11-14 weeks of gestation to screen for hypertensive disorders and associated complications in an unselected population. *Ultrasound in Obstetrics and Gynecology* 2005; 26(5): 490-4.
  9. Velauthar L, Plana ML, Kalidindi M. First-trimester uterine artery Doppler and adverse pregnancy outcome: a metaanalysis involving 55 974 women. *Ultrasound in Obstetrics & Gynecology* 2014; 43(5):500-7.
  10. van den Elzen HJ, Cohen-Overbeek TE, Grobbee DE, Quartero RWP, Wladimiroff JW. Early uterine artery Doppler velocimetry and the outcome of pregnancy in women aged 35 years and older. *Ultrasound ObstetGynecol* 1995; 5: 328–33.
  11. Dugoff L, Lynch AM, Cioffi-Ragan D, Hobbins J, Schultz LK, Malone FD, D’Alton ME, for the FASTER Trial Research Consortium. First trimester uterine artery Doppler abnormalities predict subsequent intrauterine growth restriction. *Am J ObstetGynecol* 2005; 193: 1208-12.
  12. Kwik M, Morris J. Association between first trimester maternal serum pregnancy associated plasma protein-A and adverse pregnancy outcome. *Aust N Z J ObstetGynaecol* 2003; 43:438–442.
  13. Dugoff L, Hobbins JC, Malone FD, Porter TF, Luthy D, Comstock CH et al. For the FASTER Trial Research Consortium. First-trimester maternal serum PAPP-A and free-beta subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: A population-based screening study (The FASTER Trial). *Am J ObstetGynecol* 2004; 191: 1446–1451.
  14. Ong CYT, Liao AW, Spencer K, MunimS, Nicolaides KH. First trimester maternal serum free  $\beta$  human chorionic gonadotropin and pregnancy associated plasma protein A as predictors of pregnancy complications. *BJOG* 2000; 107: 1265-70.
  15. Yaron Y, Heifetz S, Ochshorn Y, Lehavi O, Orr-Urtreger A. Decreased first trimester PAPP-A is a predictor of adverse pregnancy outcome. *PrenatDiagn* 2002; 22: 778–82.
  16. Tul N, Pusenjak S, Osredkar J, Spencer K, Novak-Antolic Z. Predicting complications of pregnancy with first-trimester maternal serum free- $\beta$ hCG, PAPP-A and inhibin-A. *PrenatDiagn* 2003; 23: 990-6.
  17. Pilalis A, Souka AP, Antsaklis P, Daskalakis G, Papantoniou N, Mesogitis S, Antsaklis A. Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler and PAPP-A at 11–14 weeks’ gestation. *UltrasoundObstetGynecol*. 2007; 29: 135-40.
  18. Spencer K, Cowan NJ, Nicolaides KH. Low levels of maternal serum PAPP-A in the first trimester and the risk of pre-eclampsia. *PrenatDiagn*. 2008; 28: 7–10.