<u>Original Research Article</u>

Evaluation of Association of Placental Growth Factor with Uterine Artery Diastolic Notch in Predicting the Onset of Preeclampsia in Early Weeks of Pregnancy

Kancharla Venkata Srilakshmi Devi[1*], Konide Sai Anudeep[2]

[1]Associate Professor, Department of Obstetrics & Gynaecology, Katuri Medical College & Hospital, Chinnakondrupadu, Guntur, Andhra Pradesh, India.
[2]Internee of Katuri Medical College, Chinnakondrupadu, Guntur, Andhra Pradesh, India

Abstract:

Aim: Current study aimed to predict effectiveness of uterine artery and placental growth factor (PlGF) in predicting the preeclampsia (PE) and outcome.

Materials and Methods: 100 antenatal women of 12 - 16 weeks of singleton pregnancy were studied. Uterine artery Doppler were studied in all cases and again rescanned at 24-26 weeks of gestation by Trans abdominal USG.

Results: Uterine artery Doppler notching at <20 weeks is observed in 35% and uterine artery Doppler notching at 24 weeks is noted in 16% of women. Uterine artery Doppler notching at <20 weeks is observed in 34.3% of preeclamptic women. Uterine artery Doppler notching at 24 weeks is observed in 75% of preeclamptic women. In PE cases, the median PLGF level in PE was 15 pg/ml. The sensitivity of bilateral uterine artery notching is 52.3%, specificity is 84.6% positive predictive value is 54.5%, and negative predictive value is 70.5% in prediction of preeclampsia. PlGF in pre-eclamptic women found to have the optimal cut off using ROC curve was 1.2 with sensitivity being 90% and specificity being 23.4%, positive predictive value of 15.5% and negative predictive value of 93.8%. In preeclampsia women, 4 babies were associated with IUGR, IUFD in one preeclamptic woman. Study observed 85.6% sensitivity rate and 84.62% specificity with 98.2% of Negative predictive value regarding Notch + RI with >0.65 Optimal cut off to predict the PE.

Conclusion: The combined measurement of maternal placental growth factor concentration along with mean pulsatility index (PI) of uterine arteries at <20 weeks of gestation has very predictive for pre-eclampsia. Uterine artery Doppler studies between <20 weeks help to categorize pregnant into low risk and high risk so that proper vigilance may be done in high risk women.

Keywords: preeclampsia, uterine artery, high risk pregnancy, placental growth factor.

Introduction

Preeclampsia affects 2-8% of pregnancies, and an estimated 8.3 million pregnant women experience preeclampsia every year globally. [1] In developing countries, there were 13 cases of preeclampsia in every 1,000 births, whereas in developed countries, only 2-3 cases of preeclampsia were found in every 10,000 deliveries. [2,3]

In preeclampsia will be found an increase in sFlt-1 and sEng levels and a decrease in PlGF levels. This situation will cause vascularity and angiogenesis disorders in the fetomaternal circulation, which will eventually lead to preeclampsia syndromes such as proteinuria, hypertension and endothelial dysfunction. [4] An imbalance of angiogenic and antiangiogenic factors has been observed when the diagnosis of preeclampsia is established, it can sometimes even be observed before clinical symptoms appear. Then angiogenic factors such as PlGF and antiangiogenic factors such as sFlt-1 and sEng can be a screening or assessment of risk factors for preeclampsia. [5]

There is growing evidence that an imbalance in these factors released from the placenta and maternal endothelium, including placental growth factor (PlGF), sEng (soluble Endoglin), and soluble Fms-like tyrosine kinase 1(sFlt-1) were associated with disorder. [6] PlGF was thought to induce the non-branching angiogenesis leading to a low-resistance placental vascular network. In a healthy pregnancy, PlGF increases with gestation in maternal circulation. [7] In preeclampsia, limited angiogenesis early in pregnancy with shallow vascular invasion of maternal spiral arteries leads to subsequent placental hypoperfusion. [8] PlGF

was abnormally low in preeclampsia when compared to healthy gestational age-matched controls. [9]

In a normal pregnancy, the pulsating index (PI) and resistance index (RI) values will decrease after 24 w of pregnancy, so that a permanent picture is formed, which is a picture of high and almost horizontal diastolic velocity. The picture of uterine artery waves in the first trimester of pregnancy has a winding diastolic peak (diastolic notch) that disappears after 24 w of pregnancy. If this indentation is permanent and the PI and RI values remain high after 20-24 w' pregnancy, it means that there is high pressure on the uterine arteries, which usually results in preeclampsia or stunted fetal growth. [10]

Uterine artery velocimetry Doppler examination to predict the incidence of preeclampsia is better done in the second trimester compared to the first trimester. The pulsality index with the diastolic notches examined in the second trimester obtained a pulsality index with a positive like hood ratio of 4.5 and the positive likelihood value of the resistance index is 3.5.6 It was shown that prevention of preeclampsia by examination of sFlt-1, sEng and PlGF levels in maternal blood is best done in the second trimester because the invasion of the spiralsal trophoblast has been completed. [11] Study aimed to investigate the efficacy of placental growth factor, and uterine artery diastolic notch to predict the early onset of preeclampsia.

Materials & Methods

Study design: Hospital based prospective clinical study.

Setting: Department of Obstetrics & Gynecology, Katuri Medical College & Hospital, Chinnakondrupadu, Guntur.

Study design: A hospital based prospective observative study conducted on normotensive, non-proteinuric women attending the OPD and admitted in antenatal ward of Department of Obstetrics & Gynaecology, Katuri Medical College & Hospital, Chinnakondrupadu, Guntur. The study protocol was approved by the Institutional Ethics Committee.

Preeclampsia patients defined as:

1. Blood pressure of > 140/90 mmHg after twenty weeks of pregnancy in women with previously normal BP.
2. Newly detected proteinuria (>300 mg of protein in twenty-four hours or a random/spot urine protein/creatinine ratio of >0.30).

Inclusion criteria: Primigravidae and second gravidae less than 20 weeks of gestation.

Exclusion criteria: Small for gestational age; IUGR cases; any vaginal infection; premature rupture of membranes; diagnosed preeclampsia, and patient not willing to participate.

A total of 100 pregnant were fulfilled the inclusion criteria among 300 pregnant with <20 wk gestation.

Methodology:

Data on research subjects were obtained, asked about the first Day of Last Menstruation, menstrual cycles and complaints during pregnancy. Furthermore, weight checks using digital scales, height using microtoise, vital signs (blood pressure, pulse, breathing frequency and body temperature), urinalysis, routine ultrasound and examination of uterine artery doppler.

The blood flow spectrum on Doppler is analysed by video, using an electronic gauge to measure the systolic peak, the diastolic end and the average blood flow velocity. The pulsatile index is obtained from the mean of 3 consecutive waves. Abnormal uterine artery velocimetry Doppler means that of 3 consecutive consistent waves found notches in either the unilateral or bilateral uterine arteries and/or the mean pulsatile index>1.45. Both groups had blood drawn and put into a vacuum tube with EDTA and sent to the laboratory and the PLGF level was estimated by ELISA based kit.

Scanning:

After completing the consent process, all women subjected to transvaginal ultrasound for dating and screening scan. Women were placed in the dorsal position with knee flexed, a trans-vaginal ultrasound scan was done and doppler assessment of uterine circulation for uterine artery indices using Philips USG machine with 7.5 Mhz transvaginal curvilinear transducer. Uterine artery is located on one side by placement of probe in that fornix and colour flow mapping was done. The utero placental circulation was measured by various uterine artery Doppler indices, Resistance Index (RI) and Pulsatility Index (PI). The total procedure was completed within 10 min. These women were again rescanned at 24 weeks of gestation by transabdominal USG HP image point color Doppler machine with convex probe 3.5 MHz. The external iliac artery is visualized at pelvic side wall with color Doppler. The transducer is then angled medially towards the uterine artery, where they cross the external iliac artery. The flow velocity waveforms on the right and left uterine arteries were taken when 3 or 4 waves of equal height were observed, and the image was recorded. Doppler indices were obtained directly from the machine and further followed up clinically.

The utero placental circulation were measured by various uterine artery Doppler indices i.e. resistance index (RI) and pulsatility index (PI).

Increased resistance to flow in the uterine artery is associated with the appearance of diastolic notch and increase in all these indices. Perinatal outcomes are considered are IUFD, Apgar at 5 minutes, birth weight and NICU admission.

Statistical analysis:

Data was analyzed using Statistical Program for Social Science (SPSS. ver. 22.0). Chi-square test of significance was used to compare proportions. Receiver operating characteristic analysis was used to find out the sensitivity and specificity at cut-off value. P value < 0.05 was considered significant.

54% of women were primigravida and 22% are associated with hypertensive disorders of pregnancy. Uterine artery Doppler notching at 24 weeks is noted in 16% of women. Uterine artery Doppler notching at <20 weeks is observed in 35% of women. 4.5% pregnant were diagnosed as pre-eclampsia among 300 pregnant with <20 wk gestation. Uterine artery Doppler notching at <20 weeks is observed in 34.3% of preeclamptic women which is statistically significant. Uterine artery Doppler notching at 24 weeks is observed in 75% of preeclamptic women which is statistically significant.

Result

Table 1: Association of Resistance index Uterine artery Doppler indices in preeclamptic and in normal pregnant women

Resistance Index:				
Resistance indices (RI)	**In preeclampsia women**		**In normal women**	
Gestation age	**Mean**	**SD**	**Mean**	**SD**
At <20 week	0.61	0.049	0.52	0.02
Resistance indices (RI)	In preeclampsia women		In normal women	
Gestation age	Mean	SD	Mean	SD
At 24 week	0.53	0.09	0.45	0.035

Table 2: Association of Uterine artery Doppler pulsatility index in preeclamptic and normal pregnant women

Pulsatility Index				
Pulsatility indices	**In preeclampsia women**		**In normal women**	
Gestation age	**Mean**	**SD**	**Mean**	**SD**
At <20 week	0.957	0.0905	0.878	0.03
Pulsatility indices	In preeclampsia women		In normal women	
Gestation age	Mean	SD	Mean	SD
At 24 week	0.796	0.20	0.605	0.07

The serum PLGF levels in preeclampsia were less than normal group with statistically significant. Uterine artery notching at <20 weeks gestation has 84.6% specificity, 70.5% negative predictive value. When notch and RI >0.6 taken together increases sensitivity by 85.7% and negative predictive value by 98.2%.

Uterine arteries PI in pre-eclamptic women found to have the optimal cut off using ROC curve was >0.95 with specificity of 84.6%, positive predictive value of 54.5% and negative predictive value of 70.5%.

PlGF in pre-eclamptic women found to have the optimal cut off using ROC curve was 1.2 with sensitivity being 90% and specificity being 23.4%, positive predictive value of 15.5% and negative predictive value of 93.8%.

Table 3: Diagnostic accuracy of mean PlGF and Uterine arteries PI in prediction of pre-eclampsia at <20 weeks

Variable	Optimal Cut off	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value
Notch + RI	>0.6	85.7%	84.7%	37.5%	98.2%
PlGF between 11-22.5	1.2	90%	23.4%	15.5%	93.8%
Uterine arteries PI at <20 wks	>0.95	52.3%	84.6%	54.5%	70.5%

In preeclampsia, 63.6% women delivered between 36-38 weeks of gestation age, 18.2% delivered between 34-36 weeks and 9.1% delivered between 32-34 week.

Table 4: Analysis of maternal and fetal measurements

Pre-eclampsia		Mean	SD	p – value
Gestational age at delivery	Pre-eclampsia	36.85 wk	2.55wk	0.002
	Normal	38.7 wk	2.82wk	
Birth weight	Pre-eclampsia	2.15 kg	550 gr	0.04
	Normal	2.74 kg	480 gr	

Incidence of pre-eclampsia showed 54.5% were primigravida and 45.45% were second gravidae. Out of all the pre-eclamptic women, 30% delivered by LSCS. Eight babies delivered preterm with minimum birth weight of 1.3 kg. The mean APGAR at 5 min is 8.7.

Table 5: Descriptive statistics for birth weight, APGAR score, NICU stay

Pre-eclampsia		Mean	SD	p – value
Birth weight	Pre-eclampsia	2.15 kg	550 gr	0.04
	Normal	2.7 kg	480 gr	
Ap1	Pre-eclampsia	7.7	0.95	
	Normal	7.6	1.12	0.09
Ap5	Pre-eclampsia	8.7	0.96	
	Normal	8.6	1.08	0.09
NICU Stay (days)	Pre-eclampsia	3.8	2.58	0.65
	Normal	2.9	2.55	

Discussion

Out of 100 women studied 22% women developed preeclampsia, which is similar to Gupta Shashi et al (20%) and high prevalence compared to that quoted by Bewley et al (4.6%) and Irion et al (4%). [12,13]

In preeclampsia women, the mean RI at <20 week is 0.6 and at 24 week is 0.5 which is statistically significant as compared to non-preeclampsia group (p<0.0001) and this will help in prediction of preeclampsia when combined with uterine artery notching which was similar to Gupta et al where mean RI in 37.5% was 0.6. Mean PI in current study is 0.8 at <20 weeks and 0.6 at 24 weeks. In preeclampsia mean PI at <20 weeks is 0.9 and at 24 weeks is 0.7, which is statistically significant (p<0.0001) as compared to non-preeclampsia women. Hence this will help in prediction preeclampsia when combined with uterine artery notching similar to Gomez et al. [14]

Out of 100 women, 42 patients had bilateral notching at <20 weeks and 22 women developed preeclampsia. The sensitivity of bilateral uterine artery notching is 52.3%, specificity is 84.6% positive predictive value is 54.5%, and negative predictive value is 70.5% in prediction of preeclampsia, which was similar to Gupta et al. Mean gestation age at delivery is 38 ± 1 week, 75% had full term vaginal delivery and 9% had preterm vaginal delivery and 16% had CS delivery, and eight babies delivered preterm with minimum birth weight of 1.3 kg and mean birth weight is 3.6 kg, mean Apgar at 1 min is 7 and at 5 min is 8.

In current study, we observed 85.7% sensitivity rate and 84.7% specificity with 98.2% of Negative predictive value regarding Notch + RI with >0.6 Optimal Cutoff. The current study results are accordance with the study by Bhattacharyya et al showed that Doppler velocimetry of uterine artery in 2nd trimester pregnancy was used as screening test for prediction of PE, these women were categorized into high risk and low risk groups according to the risk factors, 29.1% and 70.9% were in high risk and low risk groups, in low risk group which was similar to current study group, 10 women developed PE, uterine artery velocimetry showed increased RI (> 0.6) in 10.2% and among them, 7 developed PE, notching was not observed in any of them, hence, the sensitivity, specificity, PPV and NPV of abnormal uterine artery velocimetry were observed as 70.0%, 94.87%, 53.84% and 97.37%. [15] Current study results were consistent with other study, reported that uterine artery was abnormal in 30 patients, 20 patients had PE, 10 patients had pregnancy-induced hypertension, RI > 0.69 had sensitivity of 40% and specificity was 94.77%, PPV 28.56%, NPV 96.77%. [16] The finding of median PLGF levels being significantly lower in pre-eclampsia cases (15 pg/ml) compared to normal (20pg/ml) was replicated in current study. Study by Schneuer et al [17] also found median PLGF level in all PE cases and late PE cases significantly lower as compared to unaffected controls with median values as 21.3, 20.7 and 24.1 pg/ml. The findings of current study demonstrate that the maternal serum PlGF concentration at <20 weeks of gestation in normal pregnancies increased, whereas in preeclamptic women there was slight decrease with the cutoff value of < 1.2 with sensitivity of 90% and specificity of 23.4%. The PLGF levels in cases when plotted on (ROC) curve had more area for PE (0.8) as compared to normal pregnants (0.7) thereby, suggesting that PLGF assessment had better detection rate for PE with 90% of sensitivity,

and 93.8% of negative predictive value. This study demonstrated the feasibility of Doppler assessment of uterine arteries into the routine scan.

Conclusion

The combined measurement of maternal serum placental growth factor concentrations and mean PI of uterine arteries at <20 weeks of gestation has very predictive value for pre-eclampsia in pregnancy. Uterine artery Doppler exam between <20 weeks used to categorize pregnant into low risk and high risk.

References

1. English FA, Kenny LC, McCarthy FP. Risk factors and effective management of preeclampsia. Integrated blood pressure control. 2015 Mar 3:7-12.
2. Di Mario S, Say L, Lincetto O. Risk factors for stillbirth in developing countries: a systematic review of the literature. Sexually transmitted diseases. 2007 Jul 1:S11-21.
3. Jido TA, Yakasai IA. Preeclampsia: a review of the evidence. Annals African Med. 2013; 12:3.
4. Demers S, Bujold E, Arenas E, Castro A, Nicolaides KH. Prediction of recurrent preeclampsia using first-trimester uterine artery Doppler. American journal of perinatology. 2013 Mar 18:099-104.
5. Chaiworapongsa. Plasma soluble endoglin concentration in preeclampsia is associated with an increased impedance to flow in the maternal and fetal circulations. Ultrasound Obstet Gynecol. 2010; 35:155-62.
6. Allen RE, Rogozinska E, Cleverly K, Aquilina J, Thangaratinam S. Abnormal blood biomarkers in early pregnancy is associated with preeclampsia: a meta-analysis. Eur J Obstet Gyne col Reprod Biol. 2014; 182:194–201.
7. Cerdeira AS, Agrawal S, Staff AC, Redman CW, Vatish M. Angiogenic factors: potential to change clinical practice in pre-eclampsia? BJOG. 2018; 125:1389–1395.
8. Chappell LC, Duckworth S, Seed PT, Griffin M, Myers J, Mackillop L, Simpson N, Waugh J, Anumba D, Kenny LC, Redman CW, Shennan AH. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. Circulation. 2013; 128:2121–2131.
9. Agrawal S, Cerdeira AS, Redman C, Vatish M. Meta-analysis and systematic review to assess the role of soluble FMS-like tyrosine kinase-1 and placenta growth factor ratio in prediction of preeclampsia: The SaPPPhirE Study. Hypertension. 2018; 71:306–316
10. Alves. Reference range of uterine artery Doppler parameters between the 11th and 14th pregnancy weeks in a population sample from North East Brazil. Rev Bras Ginecol Obstet. 2013; 32:128-32.
11. Tardif C, Dumontet E, Caillon H, Misbert E, Dochez V, Masson D, et al. Angiogenic factors sFlt-1 and PLGF in preeclampsia: prediction of risk and prognosis in a high-risk obstetric population. J Gynecol Obstet Hum Reprod. 2018; 47:17-21
12. Gupta S, Gupta D and Amin P: 2nd Trimester uterine artery Doppler velocimetry in prediction of preeclampsia. Int. J. Res. Med., 2014;3(4): 120-123.
13. Bewley S, Cooper D, Campbell S. Doppler investigation of uteroplacental blood flow resistance in the second trimester; a screening test for pre-eclampsia and IUGR. Br J Obstet Gynecol. 1991; 98:871–879.
14. Gómez O, Figueras F, Martínez JM, et al. Sequential changes in uterine artery blood flow pattern between the first and second trimesters of gestation in relation to pregnancy outcome. Ultrasound Obstet Gynecol. 2006; 28(6):802–808
15. Bhattacharyya SK, Kundu S and Kabiraj S: Prediction of preeclampsia by mid-trimester uterine artery Doppler velocimetry in high risk and Low risk women. J Obstet Gynaecol India, 2012; 62(3): 297-300
16. Nagar T, Sharma D, Choudhary M, Khoiwal S, Nagar RP and Pandita A: The role of Uterine and Umbilical Arterial Doppler in High-risk Pregnancy: A Prospective Observational Study from India. Clinical Medicine Insights: Reproductive Health Clin Med Insights Reprod Health, 2015; 9:1-5.
17. Schneuer FJ, Nassar N, Guilbert C, Tasevski V, Ashton AW, Morris JM, et al. First trimester screening of serum soluble fms-like tyrosine kinase-1 and placental growth factor predicting hypertensive disorders of pregnancy. Pregnancy Hypertens. 2013; 3:215-21.