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Original Research Article

Serum placental growth factor levels and uterine artery pulsatility index at 11-13+6 weeks gestation as early predictors of pre-eclampsia: prospective observational study

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ABSTRACT

Background: To detect serum placental growth factor levels and uterine artery doppler pulsatility index for predicting pre-eclampsia and assess their association with the severity of pre-eclampsia.
Methods: A prospective observational study involving 160 antenatal women, from 11-13+6 weeks gestation attending antenatal clinic at tertiary care center during study period of 18 months. Serum placental growth factor levels and uterine artery doppler mean pulsatility index measured and patients were followed upto delivery and observed for the development of pre-eclampsia and its severity.
Results: Placental growth factor value cut-off was 40.33pg/ml with the sensitivity of 97.5 % and specificity was 98.3%. For the pulsatility index value of 1.85, the sensitivity was found to be 74.4% and specificity was found to be 92.5%. Mean serum placental growth factor levels for pre-eclampsia patients was 25.09pg/ml and for normotensive patients mean level was 65.05pg/ml. Mean uterine artery doppler pulsatlity index for pre-eclampsia patients was 2.02 and for normotensive patients was 1.39. Mean PI value increased with increasing severity of preeclampsia.
Conclusions: Early recognition of women will help initiation of prophylactic measures and enhanced surveillance. First trimester uterine artery doppler with serum placental growth factor together with maternal characteristics can be used as a reliable screening test for preeclampsia prediction and to reduce feto-maternal morbidity.

Keywords: Eclampsia, Placental growth factor levels, Pre-eclampsia, Uterine artery doppler pulsatility index

INTRODUCTION

Hypertensive disorders complicate nearly 5-10% of all pregnancies and together with hemorrhage and infections contribute majorly to maternal morbidity and mortality.[1] Among hypertensive disorders, pre-eclampsia syndrome is identified in 4-5% of pregnancies.[1] Apart from its most dreaded complication of progressing into eclampsia, preeclampsia itself can lead to substantial maternal and perinatal morbidity. The incidence of preterm birth due to preeclampsia is around 15%.[2]

Pre-eclampsia is a multi-system disorder specific to pregnancy and puerperium, which manifests by onset of hypertension, that is, systolic blood pressure >=140 mmHg and/or diastolic blood pressure >= 90mmHg 2 readings 4 hours apart and proteinuria after 20weeks of gestation and resolves by 12weeks postpartum.[6]

Pre-eclampsia is a multifactorial disease and the cause still remains unclear. A number of mechanisms proposed to explain the cause of preeclampsia include:

Abnormal trophoblastic invasion of uterine spiral arteries during with placental implantation.

Immunological intolerance between fetal, placental and maternal tissues. Maternal mal-adaptation to cardiovascular and circulatory changes in normal pregnancy. Genetic factors like inherited and epigenetic influences.

In pregnancy, during placentation, the trophoblast normally invades the decidual part of spiral arteries starting at 8th week and usually completed by 13th week. After this, the second stage of invasion occurs, wherein the myometrial portion of the spiral arteries are invaded by the trophoblast. This is usually completed by 18-19 weeks.[3] In majority of pre-eclamptics, this invasion fails to occur leading to increased resistance to flow into the intervillous space. The method of choice to indirectly monitor the status of the spiral artery bed is provided by uterine artery waveform.[2]

Placental growth factor (PlGF) is an angiogenic factor, part of vascular endothelial growth factor produced exclusively by trophoblast. In normal pregnancy, its levels increase throughout, peaking approximately at 26–30 weeks.[4]

Decreased levels of PlGF are consistent throughout gestation when associated with pre-eclampsia. PlGF level is reported to be reduced as early as the first trimester in women who are more prone to develop preeclampsia compared to normal pregnancy, suggesting its role as an early predictor of pre- eclampsia. Its predictive performance is based on detecting a decreased level from the expected normal distribution.[4]

Uterine artery is the vessel often used in the Doppler assessment studies for preeclampsia, as it describes maternal vascular status, through its pulsatility and resistive index and diastolic notching.[5]

Uterine artery doppler has been a non-invasive tool which can be used for prediction of PE at around 20 weeks, but 11-13 weeks 6 days scan may provide earlier information.[6] Pulsatility index (PI) is calculated as:

Pulsatility index = peak systolic velocity – end diastolic velocity/mean velocity (S-D/M)

Gradual increase in maternal uterine blood flow supports the fetus. As the vessels increase in capacity and volume, because of the trophoblastic invasion, the diastolic blood flow increases leading to decreased PI. Absence of this invasion during placentation results in increased vascular resistance. Uterine artery Doppler detect this finding in first trimester.[6]

Increasing peripheral resistance causes an increase in pulsatility and PI. The PI decreases from 2.0 to 1.3 from 8 to 14 weeks gestation.[7] This study helps to evaluate the usefulness of first trimester uterine artery Doppler with placental growth factor levels as early predictors of pre-eclampsia.

METHODS

This is a prospective observational study of 160 pregnant women of gestational age 11 to 13 weeks 6 days attending antenatal clinic at JSS Hospital, Mysuru constituted the study population.

After taking the informed written consent from the pregnant women willing to participate in this study, a preliminary data was collected to include:

Thorough history to know the patient demographics, obstetrics history, gestational age and any high risk factors associated with the pregnancy. General physical examination and obstetric examination was done.

Preeclampsia is defined as a blood pressure of more than or equal to 140/90 mmHg measured twice in a gap of 4 hours, with urinary protein of atleast 300 mg in 24 hours, or at least 1+ on dipstick test. NT scan done at 11 to 13 weeks 6 days along with uterine artery Doppler and its mean pulsatility index. Blood sample was collected for serum placental growth factor levels. Clinical examination was done at every follow up, every 4weeks upto 28 weeks, 2 weekly upto 36 weeks, once weekly thereafter. Routine investigations were done.

Inclusion criteria

All pregnant women between 11-13weeks 6 days of gestation attending antenatal clinic in JSSH OBG OPD, pregnant women with high risk factors like twin pregnancy, anemia, gestational diabetes mellitus, hypothyroidism, connective tissue disorders, and patients who gave written consent were included.

Exclusion criteria

Patients who did not give consent, history of pre-eclampsia in previous pregnancy and chronic hypertension in present pregnancy, and pregnant women with molar pregnancy, anomalous baby were excluded.

Methodology

At 11 to 13 weeks 6 days gestation, uterine artery waveform doppler was performed. Real time ultrasound using IU22 Philips machine with frequency of 2-5 MHz used. After emptying the bladder, woman is put in lithotomy position and sagittal view of cervix is obtained using transvaginal probe. The uterine artery is identified at the level of the internal cervical os by moving the probe laterally till paracervical vascular plexus is visualized. Using colour doppler, mean P.I value noted.

Total 3 ml of venous blood was drawn with aseptic precautions for the estimation of placental growth factor levels. Sample was stored at -40 degree. Serum PlGF levels were measured by ELISA method. These patients were followed up regularly till delivery.

RESULTS

This is a prospective study involving 160 pregnant women who visited outpatient department. Among 90 primigravidae, 25 patients (27.7%) developed pre-eclampsia and its complications. Among 70 multiparous, 15 patients (21.4%) developed pre- eclampsia and its complications. Early pregnancy tests along with history and examination for predicting the preeclampsia development have better specificity than sensitivity. Table 1 describes various demographic details and its relation with pre-eclampsia and its severity.

Table 1: Demographic details and their association to hypertensive disorder of pregnancy.

Demography details	Normotensive		Pre-eclampsia without severe features		Pre-eclampsia with severe features		Eclampsia	
	N	%	n	%	n	%	N	%
Age								
< 25yrs	70	73.7	11	11.6	11	11.6	3	3.2
26-30yrs	42	76.4	4	7.3	9	16.4	0	0
>30yrs	8	80	1	10	1	10	0	0
Parity								
Nullipara	65	72.2	13	14.4	10	11.1	2	2.2
Multipara	55	78.6	3	4.3	11	15.7	1	1.4
BMI								
Uunderweight	4	80	1	20	0	0	0	0
Normal	60	89.6	1	1.5	6	9	0	0
Overweight	34	82.9	6	14.6	1	2.4	0	0
Obese I	22	55	7	17.5	9	22.5	2	5
Obese II	0	0	1	14.3	5	71.4	1	14.3

Age

Among the subjects aged less than 25 years 11.6% of them had pre-eclampsia without severe features, 11.6% had severe pre-eclampsia and 3.2% presented with eclampsia. In patients above 30 years, 10% had pre-eclampsia without severe features and 10% had severe pre-eclampsia. Eclampsia was seen only in subjects who were aged less than 25 years.

Parity

Among 90 primigravidae women, preeclampsia without severe features was seen in 14.4%, severe pre-eclampsia in 11.1% and eclampsia in 2.2%. Among 70 multiparous women, 4.3% had pre-eclampsia without severe features, 15.7% had severe pre-eclampsia and 1.4% had eclampsia.

Body mass index

Among the study subjects who were overweight 14.6% had pre-eclampsia without severe features, 2.4% had Severe pre-eclampsia. Among obese I subjects 17.5% had pre-eclampsia without severe features, 22.5 % had severe pre-eclampsia and 5% had eclampsia. Among obese II subjects 14.3% had pre-eclampsia without severe features, 71.4 % had severe pre-eclampsia and 14.3% had eclampsia. The association of BMI and severity of pre-eclampsia was statistically significant.

Severity of pregnancy induced hypertension

Among 160 patients, 16 (10%) had pre-eclampsia without severe features, 21 (13.1%) had pre-eclampsia with severe features, and 3 (1.9%) of them developed eclampsia. Nearly 120 (75%) did not develop any signs and symptoms of pre-eclampsia in our study.

Distribution of study subjects based on the severity of pre-eclampsia (Table 2).

Table 2: Severity of pregnancy induced hypertension.

		n	%
Severity of pre-eclampsia	Pre-eclampsia without severe feature	16	10.0
	Pre-eclampsia with severe feature	21	13.1
	Eclampsia	3	1.9
	Normotensive	120	75.0

Gestational age at delivery

Table 3 shows that in our study, majority of patients developed pre-eclampsia at term. Among subjects who delivered before 36 weeks of gestation 6.2% had mild, 31.2% had severe and 18.8% had imminent and 6.2% had eclampsia. Among those who delivered between 36 to 37 weeks 42.9% of them were in severe pre- eclampsia. Among those delivered between 37 to 38 weeks 14.8%

had mild, 3.7% had severe, 1.9% had imminent eclampsia and 3.7% had eclampsia. Those who delivered between 38 to 39 weeks, 8.3% were mild, 8.3% had severe, 2.1% had imminent eclampsia. Those who delivered between 39 to 40 weeks, 8.6% were mild, 2.9% had severe and 2.9% had imminent eclampsia. Overall, it was found that the delivery weeks and the severity of pre-eclampsia was found to be statistically significant. Distribution of study subjects based on the weeks when pre-eclampsia was diagnosed.

Table 3: Gestational age at development of pre-eclampsia.

		N	%
Preeclampsia diagnosed at	Less than 30 weeks	2	1.2
	Between 30 to 34 weeks	10	6.2
	Between 34 to 36 weeks	3	1.9
	More than 36 weeks	25	15.7

Mode of delivery

The study showed that, among patients who underwent vaginal delivery, none of them had eclampsia. The rate of caesarean delivery is higher in patients who had increased severity of pre-eclampsia.

In the present study, who underwent LSCS. 4.3% had pre-eclampsia without severe features, 29% had severe eclampsia and 4.3 % had eclampsia. Among the subjects who underwent normal delivery 14.3% had pre-eclampsia without severe features and 1.1% of severe pre-eclampsia, none of them developed eclampsia.

Table 4 shows the mean values of serum PlGF levels and uterine artery pulsatility index with development of pre-eclampsia.

Table 4: Serum placental growth factor levels and uterine artery doppler P.I value and their association with development of pre-eclampsia.

		PlGF levels(pg/ml)		PI Value	
		Mean	**Standard Deviation**	**Mean**	**Standard deviation**
Pre-eclampsia	Present	25.09	11.29	2.02	0.61
	Absent	65.05	16.69	1.39	0.34

For the PIGF value of 40.33 the sensitivity was found to be 97.5 % and specificity was found to be 98.3% based on the Yoden index (Figure 1).

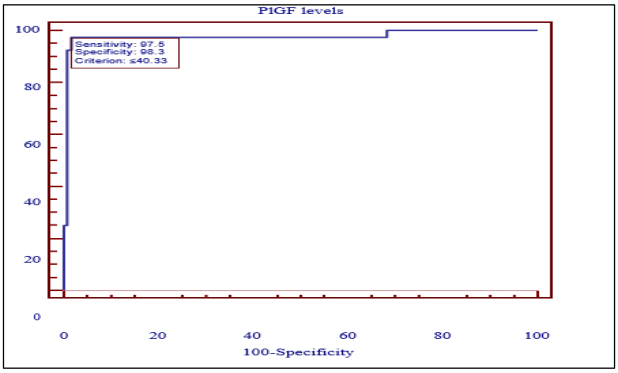

Figure 1: Diagnostic value of PIGF value with severity of pre-eclampsia.

For the PI value of 1.85 the sensitivity was found to be 74.4% and specific was found to be 92.5% based on the Yoden index (Figure 2). It was observed in Figure 3 that there was negative correlation among uterine artery doppler mean P.I and serum PlGF levels.

On performing Correlation test it was found that the PI Value and PIGF value among the subjects with pre-eclampsia was negatively co related with p value around 0.16.

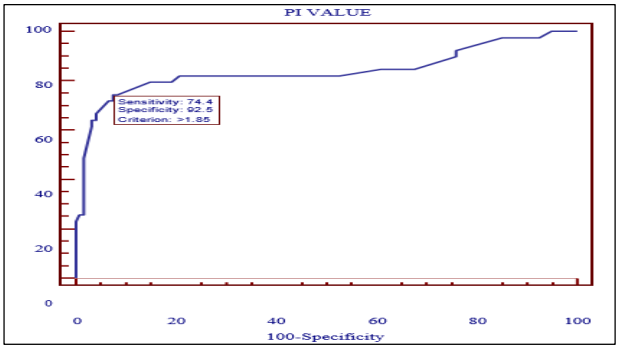

Figure 2: Diagnostic value of PI value with severity of pre-eclampsia.

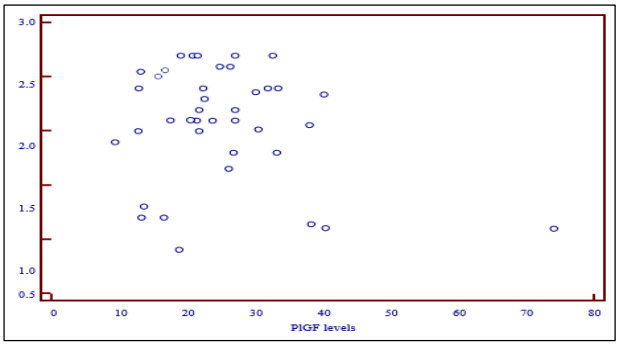

Figure 3: Correlation between PI value and PIGF value among the subjects with pre-eclampsia.

Table 5 shows the relation between the severity of pre-eclampsia and values of mean uterine artery P.I value and serum PlGF levels, as the severity increases P.I value increases and PlGF levels decreases.

Table 5: Serum placental growth factor levels and uterine artery doppler P.I and their association with severity of pre-eclampsia.

		PlGF levels (pg/ml)		P.I value	
		Mean	**Standard deviation**	**Mean**	**Standard deviation**
Severity of pre-eclampsia	Pre-eclampsia without severe feature	23.71	7.35	1.77	0.68
	Pre-eclampsia with severe feature	26.07	14.20	2.14	0.52
	Eclampsia	25.51	6.02	2.57	0.23
	Normotensive	65.05	16.69	1.39	0.34

DISCUSSION

Pre-eclampsia is more common in extremes of age group. Pregnant women below 20 years and above 35 years are at an increased risk, and in the latter group pre-eclampsia superimposed on chronic hypertension is seen.

Preeclampsia is more common in nulliparous due to the exposure of the trophoblastic tissue for the first time. Women with high BMI in pregnancy are more likely to become hypertensive compared with lower BMI.

Conditions associated with increased chances of pre-eclampsia include diabetes mellitus, thyroid disorders, systemic diseases like auto-immune disorders, chronic renal disorders, PCOS, anemia, associated obstetric conditions including multiple pregnancy, cholestasis of pregnancy.

In our study, majority of the cases who developed pre-eclampsia had no other co-morbidities, among patients who developed pre-eclampsia without severe features, obstetric cholestasis was associated in 1(6.2%), GDM in 1 (6.2%) and 14 patients (87.4) were not associated with any other co-morbidities. In patients who developed severe eclampsia, 2 (9.5%) had GDM, 2 (9.5%) had hypothyroidism, 2 (9.5%) had seizures, 1 (4.8%) had adult polycystic kidney disease. Patients who developed eclampsia, 1 (33.3%) had hypothyroidism. Predictive value of uterine artery P.I at 11 to 13 weeks 6 days.

It is the most commonly used index, levels above 95th percentile or a PI >2.3 appears to be appropriate. Performance at 11-13weeks 6 days gestation is a reasonable approach. In their study by Andrew et al, performing uterine artery P.I in first trimester had the sensitivity of 25% whereas specificity was 96.05%.[6] Papageorgiou et al, in their study of 16806 women attending antenatal care, concluded that combining risk factors from history such as race, parity, BMI, smoking, past history of preeclampsia, and family history of hypertension, along with uterine artery Doppler would recognize the patient's specific risk for preeclampsia development.[8] In a study by Gomez et al, uterine artery doppler values were taken at 11 and 34 weeks and further at 41 weeks. There was a significant reduction in the mean UtA-PI between 11 weeks (mean PI, 1.79) and 34 weeks (mean PI, 0.70). It then became stable until 41 weeks (mean PI, 0.65).[9]

In our study when the predictive value of the test was evaluated, the sensitivity and specificity were 74.4% and 92.5% using PI>1.85 as the abnormal Doppler study criteria which was similar to the studies by Andrew et al.[6] The positive and negative predictive value in our study was 76.32% and 90.98% respectively, compared to study by Lopez et al where positive and negative predictive value was 90% and 39.1% respectively and other study by Andrew et al, where PPV was 25% and NPV being 96.05% and the positive and negative likelihood ratios were 9.67 and 0.30, compared to other studies by Cnossen JS et al, where PLR was 21 and NLR was 0.82%.[5,6,10]

Our study also gives the higher sensitivity and specificity compared to other studies indicating the higher predictive value of Doppler studies in prediction of preeclampsia.

Predictive value of serum placental growth factor levels at 11 to 13weeks 6 days.

In our study when the predictive value of the test was evaluated, the sensitivity and specificity were 97.5% and 98.3% at mean of 40.33pg/ml of serum placental growth factor levels which was comparable to the studies by Necmiye et al, with 61.5% sensitivity and 82.2% specificity.[11] PIGF levels less than 62.5 pg/ml increases the risk of developing preeclampsia and studies by Nahib et al, with the mean PlGF levels of 39.02pg/ml below which there are high chances of developing pre-eclampsia, with the sensitivity and specificity being 57% and 77.5% respectively.[12] The positive and negative predictive values in our study being 95.12% and 99.16% respectively, when compared to studies by Nahib et al, where PPV was 71% and NPV was 64%, and in the study by Mccarthy et al, PPV being 41.1% and NPV and 95.9%.[12] The positive and negative likelihood ratios in our study is 58.50 and 0.03 respectively, when compared to the study by Mccarthy et al, where positive and negative likelihood ratios were 3.95 and 0.24.[13]

Our study also gives the higher sensitivity and specificity compared to other studies indicating the higher predictive value of serum placental growth factor levels in early prediction of preeclampsia. Various studies have proved a higher predictive value of serum placental growth factor levels at different periods of gestation as seen in the present study also.

This study has some limitations. As this is a small study, the usefulness of the uterine artery Doppler study and serum placental growth factor levels has to be evaluated using a large cohort.

CONCLUSION

Incidence of pre-eclampsia was around 25% in this study. Early recognition of women will help initiation of prophylactic measures and enhanced surveillance. Abnormal uterine artery Doppler studies and decreased biochemical marker i.e., placental growth factor levels have been associated with subsequent adverse pregnancy outcomes including preeclampsia and its complications.

First trimester uterine artery Doppler velocimetry and placental growth factor levels together with maternal characteristics can be used as a reliable screening test for the prediction of preeclampsia and it helps to reduce maternal and fetal complications by planning delivery in a well-equipped set up. However, the prediction is of not much use as there are no effective preventive strategies for preeclampsia and other complications.

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