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Angiogenic factors and uterine artery Doppler in predicting preeclampsia and associated adverse outcomes in a tertiary hospital in south India

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1. Introduction

Preeclampsia is a pregnancy associated disorder that is characterized by hypertension and proteinuria that develops after 20 weeks of gestation. Hypertensive disorders of pregnancy are estimated to account for 12.9% and 14% of maternal deaths in developed and developing countries respectively [1]. Pre-eclampsia is a leading cause of maternal and perinatal morbidity and mortality and complicates up to 10% of pregnancies worldwide [2]. The maternal causes of death are due to pulmonary edema, eclampsia, HELLP syndrome, cerebral hemorrhage, renal or hepatic failure. The fetal and neonatal risks involved are intrauterine growth restriction, preterm delivery, still birth and neonatal death.

The prediction of preeclampsia has been the dream of obstetricians for decades. Reliable prediction of preeclampsia would allow closer prenatal monitoring, early diagnosis and timely intervention with steroids to enhance lung maturity, magnesium for seizure prophylaxis, antihypertensive medications and when indicated expeditious delivery. An ideal test for predicting preeclampsia should be simple, rapid, noninvasive, inexpensive, easy to perform and comfortable to the patient [3]. The technology should be widely available and the results reproducible and reliable, with a high sensitivity and positive predictive value. A robust biomarker would also enable targeted studies of therapy and preventive strategies so that intervention can be carried out to prevent the development of the disease and thus improve the maternal and fetal outcome [4].

A number of biologic, biochemical and biophysical markers involved in the pathophysiology of preeclampsia have been proposed to predict its development [5–9]. As per ACOG the best and only recommended approach to screen for preeclampsia is a detailed medical history. Current predictive tests for preeclampsia have low positive predictive value (PPV) and they may harm more women than they benefit [10]. A combination of tests, some yet to be adequately evaluated may be promising. Future screening tests will need to have sensitivities and PPVs high enough to accurately identify women who will develop preeclampsia.

The pathogenesis of preeclampsia involves an imbalance between angiogenic factors such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) and factors inhibiting angiogenesis such as soluble fms like tyrosine kinase (sFlt-1) and soluble endoglin (s-Eng). Many studies have shown a marked increase in sFlt-1 and decrease in PlGF weeks before the onset of preeclampsia [11–14].

The basic pathology in preeclampsia is impaired placentation due to inadequate trophoblastic invasion of spiral arterioles that prevents their

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conversion into distended utero-placental arteries [15]. Abnormally high resistance persists in uterine vessels is seen as notching and high resistive index (RI) and pulsatility index (PI) in Doppler velocimetry studies [16]. Hence Doppler velocimetry has been used to predict preeclampsia. However the sensitivity of Doppler studies in predicting preeclampsia is low [17].

These tests individually have low sensitivity to predict pre-eclampsia. Hence a combination of tests might improve the sensitivity and positive predictive value. None of these tests have been adequately evaluated in Indian women. Hence a prospective cohort study was planned to determine whether the combination of soluble fms like tyrosine kinase-1, placental growth factor and uterine artery Doppler velocimetry in second trimester of pregnancy in women at risk of pre-eclampsia improves the prediction of preeclampsia in Indian women.

2. Materials and methods

The Institutional Review Board and ethic committee of Christian Medical College, Vellore, India approved this study in August 2009 [IRB No.6911 dated 19-08-2009]. This study was funded by the Institutional Fluid Research Grant No. 22X432. Antenatal women attending the prenatal care clinic of our hospital from December 30, 2009 to May 02, 2014, who are at high risk of developing preeclampsia, were recruited in the study between 24 and 30 weeks of gestation after obtaining a written informed consent. The inclusion criteria were history of chronic hypertension, maternal age < 18 years or > 35 years, pre-gestational and gestational diabetes mellitus, chronic kidney disease, systemic lupus erythromatosis, antiphospholipid antibody syndrome, history of preeclampsia in previous pregnancy or family history of preeclampsia in a first degree relative. Women with multifetal pregnancy, pregnancies with fetal congenital anomalies and women who were not planning to deliver in CMC were excluded.

Assuming the sensitivity of maternal angiogenic markers and uterine artery Doppler velocimetry as 90%, with a precision of 10 and with a prevalence of preeclampsia in high risk women being 10%, the sample size required was 360.

For each participant, measurement of height, weight, blood pressure and uterine artery PI, RI and presence of notch were checked and blood samples were taken. Sonologists participating in the study were trained senior operators. Pulsed wave Doppler with an abdominal probe was used and Doppler velocimetry of bilateral uterine arteries was done to obtain two consecutive waveforms of satisfactory quality. Mean PI, mean RI and presence of unilateral or bilateral uterine artery notch was noted. On the same day a blood sample of 6 ml was collected in clotted tubes from patients by peripheral venipuncture. Serum was separated by centrifugation at 2500g for 10 min and frozen at −20 degrees Celsius until assayed. All samples were assayed within 2 months. Levels of sFlt-1 and PlGF were measured with a commercially available highly sensitive electro-chemiluminescence immunoassay (Roche Diagnostics GmbH, D-69298 Mannheim)

Women underwent standard antenatal care. Details of pregnancy, Doppler statistics and biomarkers were collected and analyzed after delivery.

The primary outcome assessed was preeclampsia defined as systolic blood pressure of more than or equal to 140 mmHg and diastolic blood pressure of more than or equal to 90 mm Hg or urine proteinuria of 1 + by dipstick after 20 weeks of gestation [18]. Dipstick analysis was used as it is readily available and is also semi quantitative and it overcomes the time constraints involved in obtaining the 24 h urine protein value and urine protein creatinine ratio thereby avoiding the delay in initiating treatment.

Secondary outcomes were eclampsia, preeclampsia superimposed on chronic hypertension and intrauterine growth restriction. Eclampsia was defined as seizure that cannot be attributed to other causes in a woman with preeclampsia [18]. Preeclampsia superimposed on chronic hypertension was defined as new onset proteinuria assessed by urine dipstick of 1 + or more in a woman with hypertension and no proteinuria before 20 weeks of gestation or a sudden increase in proteinuria (doubling of baseline) or increase in blood pressure (> 30 mm Hg of systolic BP , > 15 mmHg of Diastolic BP) or Thrombocytopenia (platelet count < 100,000 per μl), elevated liver transaminases (two times the upper limit of normal concentration), new onset and worsening renal insufficiency (S. Creatinine more than or equal to 1.1 mg/dl or doubling of previous value), right upper quadrant pain, pulmonary edema or persistent cerebral or visual disturbances in women with hypertension and proteinuria before 20 weeks of gestation [18]. Small for gestational age was defined as birth weight of < 10th centile for gestational age [19].

Statistical analysis was performed using IBM SPSS Statistics 21.0 software. Results are expressed as mean, or as median (interquartile range, IQR) when data were not normally distributed. The descriptive statistics of all measurements were studied. Women with a primary outcome and combined outcome (preeclampsia, eclampsia, chronic hypertension with superimposed preeclampsia and intrauterine growth restriction) were compared with unaffected women using uterine artery Doppler studies and biomarkers by Mann Whitney *U* test.

3. Results

A total of 393 patients were recruited in the study. 35 patients were lost to follow up who did not deliver in our hospital. Uterine artery Doppler study reports were unavailable for 21 patients. Serum biomarkers were either not sent or reports were unavailable for 77 patients, resulting in a study cohort of 270 patients. Consort figure (Fig. 1).

Of the 270 high risk patients followed up till delivery, 197 were Primigravida, 91 patients were obese with BMI > 25 kg/m^2. 19 of our patients were teenage mothers while 16 patients were above 35 years of age. The average age of the patients was 26 years (16–40 years). 16 patients had chronic hypertension, 20 had previous history of pre-eclampsia, 41 patients had gestational diabetes and 4 had Pregestational diabetes. The mean gestational age at recruitment was 26.8 weeks (24–30 weeks).The average MAP (mean arterial pressure) at

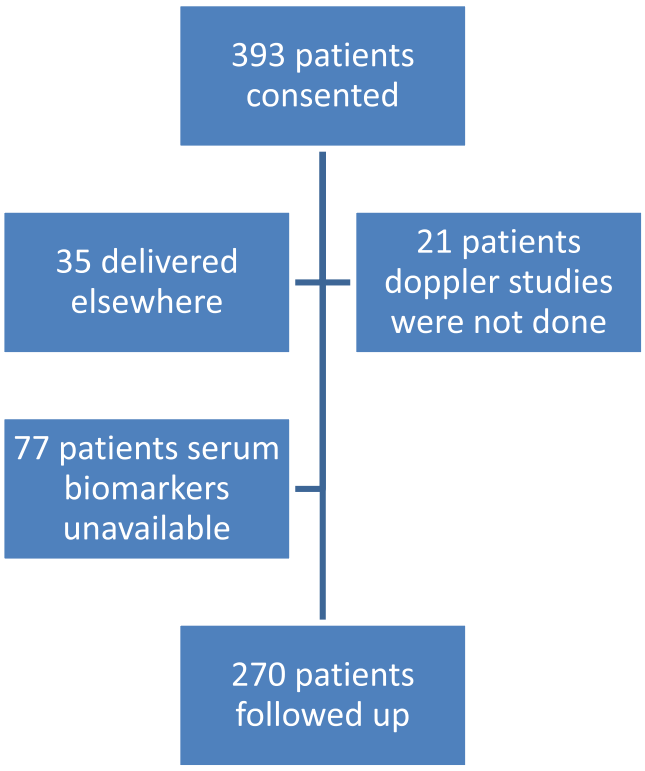

Fig. 1. Consort flowchart.

Table 1
Population clinical characteristics.

Characteristics	Women with outcomes n = 52	Women without Outcomes n = 218
Maternal age (years)[a]	26.7 ± 4.9	25.3 ± 4.7
Body mass index (kg/m2)[a]	21.9 ± 10.2	20.5 ± 9.0
Gestational age at recruitment (weeks)[a]	26.6 ± 1.9	26.8 ± 2.0
Systolic blood pressure at recruitment (mm Hg)[a]	111.6 ± 12.9	109.7 ± 11.9
Diastolic blood pressure at recruitment (mm Hg)[a]	71.1 ± 9.3	69.3 ± 7.8
MAP	84.6 ± 9.5	82.8 ± 8.1
Primigravida [b]	35 (67.3)	162 (74.3)
Diabetes in pregnancy [b]	9 (17.3)	32 (14.7)
Chronic Hypertension [b]	7 (13.4)	9 (4.1)
Previous history of preeclampsia [b]	5 (9.6)	15 (6.9)
Pregestational diabetics [b]	1 (1.9)	3 (1.4)
Gestational age at delivery (weeks)[a]	37.4 ± 2.6	38.4 ± 1.7
Systolic blood pressure at delivery (mm Hg)[a]	124.9 ± 19.4	116.6 ± 10.6
Diastolic blood pressure at delivery (mm Hg)[a]	81.8 ± 14.5	74.5 ± 7.3
Birth weight (kg)[a]	2.3 ± 0.5	3.0 ± 0.4

[a] mean ± SD.
[b] n(%).

recruitment was 83.1 mm Hg. The average gestational age at delivery was 38 weeks. Table 1 shows the clinical characteristics of the patients with any outcome and those without the outcome.

Table 2 shows the spectrum of primary and secondary outcomes among the study population. Table 3 shows the distribution of pre-eclampsia as per gestational age and type.

52 patients had one or more of the outcomes and 218 patients had neither of those outcomes. The average gestational age at delivery among the women with preeclampsia was 35.4 weeks

18 patients with one of the outcomes had indicated preterm delivery of whom 4 were delivered for early onset severe preeclampsia and 4 were delivered between 34 and 37 weeks for preeclampsia (2 for mild preeclampsia and 2 for severe preeclampsia).

2 of the 3 patients with chronic hypertension and superimposed preeclampsia were delivered between 34 and 37 weeks of gestation. 1 patient with eclampsia had delivered before 34 weeks. The remaining indicated preterm deliveries were for intrauterine growth restriction.

The levels of serum biomarkers PlGF, sFlt-1, ratio of sFlt-1/PlGF and the uterine artery PI, RI and notch were compared between the patients who had the outcome and those without the outcome. Among the studied cohort of patients, the mean PI and mean RI of uterine artery was 0.7 ± 0.3 and 0.5 ± 0.1respectively.

In women who developed preeclampsia, the mean PI and mean RI were significantly higher (P = 0.007; P = 0.006 respectively), serum PlGF levels were significantly lower (P < 0.001) and the ratio of sflt-1/PlGF levels was also significantly elevated (p = 0.015) compared with those who did not have any outcome (Table 4)

There was no statistically significant difference in plasma sFlt-1 levels between women who developed preeclampsia and those who did not (P = 0.405).

When women with the combined outcomes were compared with those without any adverse outcome it was found that the mean PI and mean RI were significantly elevated (P= < 0.001, P < 0.001 respectively) and the PlGF levels were significantly less (P = 0.017) (Table 5)

Table 2
Preeclampsia and related adverse outcomes.

Outcome	Number	Percentage
Preeclampsia	11	4
Eclampsia	3	1
Chronic hypertension with superimposed preeclampsia	3	1
IUGR	40	14.8

Table 3
Distribution of preeclampsia as per gestational age and type.

Gestational age at delivery	Mild preeclampsia (n = 3)	Severe preeclampsia (n = 9)
< 34 weeks	–	4
34–37 weeks	2	2
> 37 weeks	1	3

Table 4
Univariate analysis for predicting preeclampsia with biomarkers and uterine artery velocimetry.

	Women with Pre-eclampsia N = 11	Women without any outcomes N = 218	p value
Biomarkers			
PlGF (pg/ml) [a]	518.47 ± 360.05	1387.86 ± 1021.50	< 0.001
sFlt-1 (pg/ml) [a]	3122.30 ± 3877.40	1663.47 ± 1835.25	0.405
RatiosFlt1/PlGF [a]	27.36 ± 69.19	2.52 ± 10.23	0.015
Uterine artery dopplers			
Mean PI [a]	0.98 ± 0.36	0.67 ± 0.24	0.007
Mean RI [a]	0.58 ± 0.15	0.45 ± 0.12	0.006
Notch (n = 261)[b]	1(9.1)	21 (9.6)	1.000

[a] Continuous variable, results in Mean ± SD.
[b] Categorical variable, results in n(%).

Table 5
Univariate analysis for predicting combined outcomes with biomarkers and uterine artery velocimetry.

	Women with outcomes N = 52	Women without outcomes N = 218	*P* value
Biomarkers			
PlGF (pg/ml) [a]	1094.5 ± 924.5	1387.9 ± 1021.5	0.017
sFlt-1 (pg/ml) [a]	1835.0 ± 2103.0	1663.5 ± 1835.3	0.903
RatiosFlt1/PlGF [a]	7.85 ± 32.74	2.52 ± 10.23	0.238
Uterine artery dopplers			
Mean PI [a]	0.9 ± 0.3	0.7 ± 0.2	< 0.001
Mean RI [a]	0.5 ± 0.2	0.5 ± 0.1	< 0.001
Notch (n = 261)[b]	12 (23.0)	21 (9.63)	

[a] Continuous variable, results in Median (IQR).
[b] Categorical variable, results in n(%).

4. Discussion

Though the manifestations of preeclampsia are more obvious in the third trimester, the changes that lead to it start very early in pregnancy. Early detection of patients who are prone to develop this spectrum of hypertension related illnesses in pregnancy, will benefit by close supervision through pregnancy and early intervention.

Angiogenic factors play an important role in the pathogenesis of preeclampsia. No single biomarker is likely to be predictive of the disorder [20]. A combined screening that involves uterine artery Doppler and biomarkers exhibits a good predictive ability for early onset preeclampsia [21].

The aim of this study was to evaluate whether the uterine artery Doppler and serum biomarkers like sFlt-1 and PlGF performed together at 24–30 weeks of gestation were useful in predicting preeclampsia.

Our study has shown that PlGF levels and ratio of slFlt-1/PlGF measurement in second trimester were significantly altered in patients who developed preeclampsia which is consistent with previously reported studies where mid trimester placental growth factor had the highest predictive value for preeclampsia [22]. Preeclampsia is associated with reduced placental production of PlGF and several studies reported that during the clinical phase of PE, the maternal serum PlGF concentration is reduced. These reduced levels of serum PlGF precede the clinical onset of disease and are evident in both first and second trimesters of pregnancy [23–27].

Studies have been published which show that a sFlt-1/PlGF ratio of 38 has a high sensitivity and specificity of predicting the onset of preeclampsia within a week to 4 weeks [22,28,29]. Among the 11 patients who developed preeclampsia one patient had a high sFlt-1/PlGF ratio of 234 while the remaining 10 patients had a value below 24. Therefore we did not identify the cut-off value of 38 as significant.

Uterine artery mean PI is an important predictor of preeclampsia. Consistent with literature we showed an increased uterine artery mean pulsatility index and resistive index during late second trimester in patients who developed preeclampsia [13,21,30]. We also did not find any correlation between the biomarkers and Doppler.

The limitation of this study is that it was a prospective observational study and not an interventional trial. Most of the patients were followed up but less than one third of the patients were lost to follow up. The use of urine dipstick to classify women as preeclampsia is not a standard test and it lacks sensitivity suggesting that there would have been more true positives who would have been detected had we used urine protein creatinine ratio.

Another major limitation in this study is a low prevalence of preeclampsia as well as the other adverse outcomes among the cohort of high risk women. This can be explained by the fact that our high risk patients who are booked with us and follow up in our antenatal clinic till delivery are monitored closely by frequent antenatal checkups and home BP monitoring and are advised to return to the facility if BP readings are > 140/90 mm Hg or if signs and symptoms ensue. Intervention like initiation of anti-hypertensive medications and early induction of labor is undertaken even before they develop features of preeclampsia. Also patients who are at high risk for preeclampsia are initiated on low dose Aspirin from the confirmation of pregnancy which could be the reason for less number of patients with adverse outcomes even though the population selected was at a high risk. They are also closely watched for development of fetal growth restriction. To overcome this we would suggest studies with larger numbers.

5. Conclusion

Serum placental growth factor, ratio of sflt-1/PlGF and uterine artery mean PI and RI may be used for the prediction of preeclampsia in second trimester.

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Declaration of interest

None.

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