To study the role of mean arterial pressure, urine calcium creatinine ratio and uterine artery Doppler between 20 -24 weeks of gestation in predicting preeclampsia

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Abstract

Introduction: Pre-eclampsia affects 3–5% of all pregnancies[1-9] and is a leading cause of maternal morbidity and mortality (12% of all maternal deaths) and also leads to perinatal consequences. The initial pathological changes of preeclampsia begin in the late first trimester leading to chronic placental insufficiency. Hence prediction of preeclampsia in early gestation is of great interest, as early therapeutical intervention such as aspirin[3-6] might reduce the risk of preeclampsia. So in our study, we aim to ascertain the role of mean arterial pressure (clinical), urine calcium creatinine ratio (biochemical) and uterine artery Doppler (radiological) parameters in predicting preeclampsia.

Aims and Objectives: To study mean arterial pressure, spot urine calcium creatinine ratio, Doppler of uterine artery between 20-24 weeks of gestational age as predictor of preeclampsia and to know the effectiveness of combination of above parameters in predicting preeclampsia

Materials and Methods: It was a prospective study involving 100 low risk pregnant women of any parity with gestational age of 20-24 weeks. All study individuals were followed till term and the end point of the study was considered to be the development of preeclampsia as per the ACOG criteria 2013.

Results: All parameters (mean arterial pressure, urine calcium creatinine ratio and uterine artery Doppler) were individually found to be statistically significant predictor. Doppler of uterine artery was found to be a better predictor of preeclampsia when compared to mean arterial pressure and urine calcium creatinine ratio individually. Combination of all three parameters was found to be the better predictor than individual parameter.

Keywords: Preeclampsia, Mean arterial pressure, Urine calcium creatinine ratio and uterine artery Doppler.

Introduction

Preeclampsia is characterized by new-onset hypertension and proteinuria at $\geq$ 20 weeks of gestation.[1-6] In the absence of proteinuria, diagnosis requires the presence of hypertension together with evidence of systemic disease (such as thrombocytopenia, elevated levels of liver transaminases, renal insufficiency, pulmonary oedema and visual or cerebral disturbances).[7,8] Thus proteinuria is not mandatory as per the recent ACOG (American College of Obstetrics & Gynaecology) 2013 criteria.

This gestation specific syndrome affects 3–5% of all pregnancies[1-9] which is a leading cause of maternal morbidity and mortality (12% of all maternal deaths) and also leads to perinatal consequences.

Though the clinical manifestations of preeclampsia can appear anytime from the second trimester to the first few weeks postpartum, the initial pathological changes begin in the late first trimester and consist of abnormal remodelling of the spiral arteries leading to chronic placental insufficiency. This causes generalized endothelial dysfunction[10,11] affecting various organs including kidney and blood vessels, thus manifests as proteinuria and hypertension respectively.

Hence prediction of preeclampsia in early gestation is of great interest, as early therapeutical intervention such as aspirin[3-6] might reduce the risk of preeclampsia. There are lot of predictors tested for routine use; however they are not validated in large population especially in south Indian women and also not so cost effective.

The characteristics of ideal predictors are simple, rapid, non-invasive, in-expensive, easy to perform, and should not expose the patient to discomfort or risk with high sensitivity and specificity to diagnose. It should appear before clinical manifestations and can modify care to prevent complications and death.

So in our study, we aim to ascertain the role of mean arterial pressure (clinical), urine calcium creatinine ratio (biochemical) and uterine artery Doppler (radiological) in predicting preeclampsia. The above parameters are chosen because of affordable cost, easy availability and can be effectively done even in low resource setting.

Aims and Objectives

1. To study mean arterial pressure, Doppler of uterine artery and spot urine calcium creatinine ratio between 20-24 weeks of gestational age as predictor of preeclampsia and to know the effectiveness of combination of above parameters in predicting preeclampsia.

Materials and Methods

The present prospective cross sectional study was conducted after approval from Institutional Ethical committee with the informed consent from the participants in Public health centre, West Mambalam, Chennai. The study period was 1 year, from May 2015 to April 2016.

Sample Size: 100 numbers of women meeting inclusion criteria during one year study period.

Inclusion Criteria:
1. All pregnant women of 20-24 weeks gestational age attending antenatal check-up in public health centre were included.

Exclusion Criteria:
1. Past history of preeclampsia
2. Chronic hypertension
3. Patient on drugs which modify BP
4. Twins
5. Diabetes/GDM
6. Genitourinary tract diseases
7. Patients with chronic illness
8. Major foetal anomaly which are incompatible with life
9. Not consenting

Methodology

It was a prospective study involving 100 pregnant women with gestational age of 20-24 weeks. After getting the informed written consent, a preliminary data was collected to include.
1. Patient demographics, gestational age and detailed history to know any high risk factors associated with the pregnancy.
2. Clinical examination including height, weight, fundal height.
3. Routine haematological investigations and dipstick urine albumin.
4. Checking Systolic, Diastolic & Mean arterial pressures, uterine artery Doppler and Urine calcium creatinine ratio for the study purpose.

All patients were emphasised on imminent symptoms of preeclampsia like leg swelling, giddiness, headache, blurring of vision, epigastric pain, reduced urine output and were advised to review with us if presence of any above. All study individuals were followed once in a month till 28 weeks, then once in fortnight till 36 weeks and subsequently once in a week till term. The end point was considered to be the development of preeclampsia as per ACOG 2013 criteria.

Mean Arterial Pressure: The woman was made to rest in sitting position with back and arm supported for 5 minutes prior to BP measurement. The arm should be supported at heart level and the legs uncrossed. Appropriate cuff size was used. (The length of the bladder (inside the cuff) should be at least 80% of the circumference of the bare arm, and the width should cover 33-50% of the adult's upper arm). The cuff was applied directly to the bare arm on the woman's upper arm 2-3 cm above the brachial artery. Systolic blood pressure was taken as pressure at which the first Korotkoff sound was heard and the diastolic blood pressure was the pressure at which the fifth Korotkoff sound (i.e. silence) was noted. Then MAP was calculated =(systolic BP +2 diastolic BP)/3

In our study, Mean Arterial Pressure ≥ 90 mm Hg was considered to be high which was used for predicting preeclampsia.
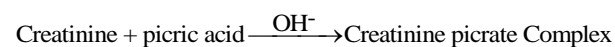
Urine Calcium Creatinine Ratio: The spot urine sample (10 ml volume) from all patients was collected in calcium free vials. 0.2 ml of hydrochloric acid (HCl) was added to 10 ml of urine to prevent calcium salt precipitation. Calcium and creatinine levels were estimated in the collected samples.

a) Estimation of urinary calcium by ortho-cresolphthalein complexone method:

Principle: In alkaline solution, the metal complexing dye cresolphthalein complexone forms a red chromophore with calcium, which is measured at 570 nm. Calcium forms both 1:1 and 2:1 complexes with cresolphthalein complexone with the 1:1 complex predominating at lower concentrations. The sample was diluted with acid to release protein-bound and complexed calcium.

b) Estimation of urinary creatinine by Jaffe's reaction (End point method):

Principle: Diluted urine sample was used for analysis. Creatinine reacts directly with picric acid under alkaline condition to form janovski complex, with an absorbance peak at 520 nm and compared with that of standard.

$$\text{Creatinine + picric acid} \xrightarrow{\text{OH}^-} \text{Creatinine picrate Complex}$$

Those patients whose spot urine calcium creatinine ratio less than or equal to 0.05 were considered to have hypocalciuria and studied for their predictability of preeclampsia.

Doppler Ultrasonography: At 20-24 weeks of gestation, along with anomaly ultrasonography, a Doppler ultrasound was performed transabdominally by experienced sonographer using duplex pulsed wave Doppler ultrasound scanner (ALOKA SSD-650) with a 3.5 MHZ convex transducer, by measuring waveforms in both uterine arteries. The transducer was placed in the lower lateral quadrant, angled medially, and colour Doppler was used to identify the common iliac bifurcation into the internal and external iliac artery. The internal iliac artery was followed medially until close to the lateral edge of the uterus until the main branch entering the uterus was identified and insonated as it entered the uterus and 1 cm distal to its apparent crossing of the external iliac artery. Gate, gain, and

scale were optimized to obtain the waveform. Peak systolic velocity (PSV), end-diastolic velocity (EDV) and time-averaged maximum velocity from the MVE (Maximum velocity envelope) were estimated to calculate the pulsatility index (PI). Pulsatility index PI (systolic end diastolic peak velocity/time averaged maximum velocity) shows a linear correlation with vascular resistance as opposed to both systolic/diastolic (S/D) ratio and Resistance index (RI), which show a parabolic relationship with increasing vascular resistance. Additionally, PI does not approach infinity when there are absent or reversed diastolic values. Hence pulsatility index (PI) is the most commonly used index in current practice.

Hence this study was done by measuring PI index which was taken as abnormal if more than 95th percentile for gestational age. And subsequently they were studied for their predictability of preeclampsia.

Data Analysis

Data analysis was done using SPSS software 22.0 Version (Original Statistical Package for the Social Sciences later modified to read Statistical Product &Service Solution). The sensitivity, specificity, positive and negative predictive value was calculated for each individual parameter and for combination of parameters.To describe about the data descriptive statistics, frequency analysis, percentage analysis were used for categorical variables and for continuous variables the mean and S.D were used. Chi-square test was done to find out any significant statistical relation between the variables. In the above statistical tool the probability value $p<0.05$ was considered to be significant study.

Results

This prospective observational study was done in 100 patients attending antenatal clinic in our hospital. Mean arterial pressure (MAP), spot urine calcium creatinine ratio (Ca: Cr ratio) and Doppler pulsatility index of uterine artery (PI) was calculated and were followed as mentioned in the methodology till term to evaluate their role in predicting preeclampsia. The end point of the study was considered to be the development of preeclampsia as per the ACOG criteria 2013.

Mean age of study population 25.6± 4.0 years. Majority of patients who developed preeclampsia were in the age group of 21 to 25 years which contributes to 61% of study population. 13% (n = 13) of study population developed preeclampsia. 17% (n = 17) of study individuals showed high MAP of which 9 individuals (69%) developed preeclampsia. Mean arterial pressure showed sensitivity of 69%, specificity of 91%, positive predictive value of 53% and negative predictive value of 95% in predicting preeclampsia. High mean arterial pressure was found to be a significant predictor (p-value was found to be 0.001) of preeclampsia using Chi-square test.

16% (n = 16) of population had hypocalciuria (using ROC cut-off value of urine calcium creatinine ratio was chosen as ≤0.05 for prediction) of which 9 people (69%) developed preeclampsia. Urine calcium to creatinine ratio of ≤0.05 yielded sensitivity of 69%, specificity of 92%, positive and negative predictive value of 56% and 95%, respectively in predicting preeclampsia. Hypocalciuria was found to be a significant predictor (p-value was found to be <0.001) of preeclampsia using Chi-square test.

14% of study group showed abnormal pulsatility index of which 10 individuals (77%) developed preeclampsia. Doppler showed sensitivity of 77%, specificity of 95%, positive predictive value of 71% and negative predictive value of 97% in predicting preeclampsia. Abnormal Doppler study was found to be a significant predictor (p-value was found to be <0.001) of preeclampsia using Chi-square test.

Combination of mean arterial pressure, urine calcium creatinine ratio and uterine Doppler showed sensitivity of 100%, specificity of 83%, positive predictive value of 46% and negative predictive value of 100% in predicting preeclampsia, thereby increasing the sensitivity and negative predictive value.

Area under ROC curve (mean (95% CI)) for mean arterial pressure was found to be 0.800 (0.646 – 0.954). Area under ROC curve for urine calcium creatinine ratio was found to be 0.862 (0.723–1.000) and for Doppler was 0.806 (0.652–0.960). Area under ROC curve for combination of all three parameters showed a higher value of about 0.914 (0.859-0.969) when compared to individual parameter.

Table 1: Baselines characteristics of study population

Number of study population	100($\pm$SD/%)
Mean age of study population (in years)	25.6±4.0
Number of patients developed preeclampsia	13
Number of patients with high MAP (≥90 mmHg)	17
Number of patients with low urine Ca:Cr ratio (≤0.05)	16
Number of patients with abnormal Doppler (PI >95 percentile)	14
Number of patients with high MAP developed preeclampsia	9
Number of patients with low urine Ca: Cr ratio developed preeclampsia	9
Number of patients with abnormal Doppler developed preeclampsia	10

Number of patients with combination of high MAP and low urine Ca: Cr ratio developed preeclampsia	12
Number of patients with combining low urine Ca:Cr ratio and Doppler developed preeclampsia	11
Number of patients with combining high MAP and Doppler developed preeclampsia	13
Number of patients with combining high MAP, low urine Ca:Cr ratio and Doppler developed preeclampsia	13
Number of patients with preeclampsia developed IUGR	3

Table 2: Prediction of preeclampsia using mean arterial pressure

Mean arterial pressure	Preeclampsia			
	Absent		Present	
	No.	Percentage (%)	No.	Percentage (%)
Normal <90mmHg(n=83)	79	91	4	31
High ≥90mmHg(n=17)	8	9	**9**	**69**
Total	87	100	13	100
p-Value	**0.001**			
Sensitivity	69%			
Specificity	91%			
PPV	53%			
NPV	95%			

Table 3: Predictive value of urine calcium creatinine ratio in preeclampsia

Urine calcium creatinine ratio	Preeclampsia			
	Absent		Present	
	No.	Percentage (%)	No.	Percentage (%)
Normal >0.05(n=84)	80	92	4	31
Low≤0.05(n=16)	7	8	**9**	69
Total	87	100	13	100
p-Value	**<0.001**			
Sensitivity	69%			
Specificity	92%			
PPV	56%			
NPV	95%			

Table 4: Prediction of preeclampsia using Doppler

Doppler	Preeclampsia			
	Absent		Present	
	No.	Percentage (%)	No.	Percentage (%)
Normal (n=86)	83	95	3	23
Abnormal (PI> 95percentile) (n=14)	4	5	10	77
Total	87	100	13	100
p-Value	**<0.001**			
Sensitivity	77%			
Specificity	95%			
PPV	71%			
NPV	97%			

Table 5: Prediction of preeclampsia using combination of mean arterial pressure, urine calcium creatinine ratio and Doppler

Combination of all Markers (MAP, Urine Ca: Cr Ratio and Doppler)	Preeclampsia			
	Absent		Present	
	No.	Percentage (%)	No.	Percentage (%)
Normal	72	83%	0	0%

Abnormal(n=28)	15	17%	**13**	**100%**
Total	87		13	
p-Value	**<0.001**			
Sensitivity	100%			
Specificity	83%			
PPV	46%			
NPV	100%			

Table 6: Comparison of the performance of individual screening tests and their combination for predicting preeclampsia

Screening test	Area under ROC curve (mean (95% CI))	p-value
Mean arterial pressure (MAP)	0.800 (0.646 – 0.954)	0.001
Doppler	0.862 (0.723 – 1.000)	<0.001
Urine calcium creatinine (Ca/Cr)ratio	0.806 (0.652 – 0.960)	<0.001
Combined all three parameters	0.914 (0.859 – 0.969)	<0.001

Discussion

In the present study, sensitivity and specificity of MAP in predicting preeclampsia was 69% and 91% respectively which was comparable with the study done by Jelstie Cnossen et al[10] in which pooled sensitivity and specificity was 62% and 82% respectively.

In the present study, sensitivity, specificity, positive predictive value and negative predictive value of urine calcium creatinine ratio in predicting preeclampsia were 69%, 98%,85%, 95% respectively which was comparable with the study done by Sheela CN et al[11] in which sensitivity, specificity, PPV and NPV were 69%, 98%, 85% and 95% respectively. In another study done by Rodriguez et al[12] sensitivity and specificity was 70% and 95% respectively. Sanchez-Ramos et al[13] did a similar study in which sensitivity and specificity was 85% and 91%.

In the present study, the following sensitivity, specificity, positive predictive value &negative predictive value of Doppler in predicting preeclampsia were 77%, 95%, 71% & 97% respectively which was comparable with the study done by Papageorghiou et al[14] in which respective values were 69%, 95%, 7% & 99% and also comparable with study done by Sugamgupta et al[15] and Padmalatha et al[16] in which sensitivity, specificity, PPV & NPV were 70%, 94%, 53% & 97% and 60%, 92%, 16% & 99% respectively.

Area under ROC with mean 95% confidence interval for MAP was 0.800(0.646-0.954) in present study and in Jelstie Cnossen et al metaanalysis[10] value was 0.760 (0.700 to 0.820). Area under ROC with mean 95% confidence interval was 0.862 (0.723-1.000) in present study and in study done by N. Onwudive et al value[17] was 0.983 (0.978 to 0.988).

Conclusion

Prediction of preeclampsia should be done in all pregnant women as early intervention reduces both maternal and foetal morbidity and mortality. All the three parameters [mean arterial pressure (clinical), urine calcium creatinine ratio (biochemical) and uterine artery Doppler (radiological)] were found to be simple, inexpensive and easily available method and hence can be recommended in all antenatal patients. Among three parameters, Doppler of uterine artery was found to be a better predictor of preeclampsia when compared to mean arterial pressure and urine calcium creatinine ratio individually. Combination of all three parameters (mean arterial pressure, urine calcium creatinine ratio and uterine artery Doppler) was found to be the better predictor than individual parameter. Large multi-centric studies are still needed for further validation of the above combination of predictors (Mean arterial pressure, Urine calcium creatinine ratio and Doppler of uterine artery) in prediction of preeclampsia.

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