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# COMPARATIVE ASSESSMENT OF MICROALBUMINURIA AND EARLY UTERINE ARTERY DOPPLER INDICES AS A PREDICTOR OF DEVELOPING PREECLAMPSIA.

Radiology

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## ABSTRACT

**BACKGROUND :** As we know hypertensive disorders in pregnancy is always a deadly threat to mothers and fetus. Mothers will be in large benefit if we predict it earlier. Easy reproducible non cumbersome screening test are needed for it.

**METHODS:** This is a Prospective longitudinal study. Patients were studied from first trimester to late trimester in the department of g & o for 1 year who fulfilled the inclusion and exclusion criteria. They were observed through out the time period. All the data were studied by chi – square test . A p value of <.05 was considered statistically significant.

**RESULTS :** Out of 150 antenatal mothers 12 developed pre-eclampsia (including 1 eclampsia) among which 8 had microalbuminuria during their antenatal period. 10 mothers had microalbuminuria but did not develop pre-eclampsia, 4 of them developed pre-eclampsia but they did not have microalbuminuria during antenatal period. 128 mothers did not have microalbuminuria and they did not develop pre-eclampsia

When RI of >0.58 was used as cut off value at 18weeks of POG. In our study of 150 antenatal mothers 12 developed pre-eclampsia (including 1 eclampsia) among which 4 had RI of > 0.58 during their antenatal period. 6 of them had RI of >0.58 but did not develop pre-eclampsia, 8 of them developed pre-eclampsia but did not have increased RI value. 132 mothers did not have raised RI value and they did not develop pre-eclampsia.

**CONCLUSION** Both the screening tools are easy to done. Microalbuminuria and early uterine artery doppler indices can be used as predictor of detecting preeclampsia. Mothers with no microalbuminuria and uterine artery RI value of < 0.58 would have less chance of developing pre eclampsia in late pregnancy.

## KEYWORDS

Microalbuminuria , preeclampsia, uterine artery doppler

**BACKGROUND :**

The deadly triad that complicates pregnancy and contribute significantly to maternal morbidity include haemorrhage, infection and hypertensive disorders in pregnancy. According to some studies, hypertensive disorders in pregnancy complicate approximately 7-15% of all pregnancies .[1,2]

As we know hypertensive disorders in pregnancy is always a deadly threat to mothers and fetus. Mothers will be in large benefit if we predict it earlier. Easy reproducible non cumbersome screening test are needed for it.

Pre-eclampsia is defined as development of hypertension ≥140/90mm hg, proteinuria (≥300mg/24hrs) or both after 20weeks of gestation in a woman with previously normal blood pressure. Pre-eclampsia may develop before 20 weeks in patients with extensive hydatiform changes in chorionic villi or in presence of lupus anti-coagulant. The following two types are recognized.[3,12]

1. Pre-eclampsia.
2. Severe pre-eclampsia-One or more of the following features are present:

- BP≥160/110 mm hg
- Proteinuria >5gm/24hrs
- Oliguria-24hrs urine output less than 500ml
- Cerebral or visual disturbances altered consciousness, headache, scotomata, blurred vision.
- Pulmonary oedema or cyanosis
- Epigastric or right upper quadrant pain
- Impaired liver function of unclear etiology
- Thrombocytopenia (<1,00,000 per cumm)
- Intra uterine growth restriction

The exact pathogenesis of pre-eclampsia is unknown. Considering its potential threat to the mother and fetus from time to time there were efforts to develop tests for prediction of its development so that it can be used to discriminate those at risk of developing pre- eclampsia. An accurate predictive test to assess the risk of pre-eclampsia could be a useful tool in targeting studies of new interventions towards those at risk of the disease who might benefit from future potential preventive therapies. Many investigators have focussed at various clinical, bio-physical and biochemical tests in an attempt to form a clinically useful tool to predict the development of pre-eclampsia, with varying degrees of success . The ideal predictive test should be simple, non-invasive, rapid, inexpensive and easy to perform early in pregnancy and reproducible, with high sensitivity and predictive value.

Doppler ultrasound is an invaluable tool in the management of high-risk pregnancies. The clinical value of UA Doppler has been promising (Harrington, Fayyad, Thakur, & Aquilina, 2004, p.50) in the prediction of severe adverse outcomes in patients at high risk for pre-eclampsia (El-Hamedi et al., 2005). Doppler measurements of the uteroplacental vasculature performed in the second trimester or in the late first trimester reportedly could identify women who subsequently develop preeclampsia or intra-uterine growth restriction (IUGR). It was most sensitive identifying women requiring delivery before 32 weeks gestation. The presence of UA notching and a PI > 1.5 during the first trimester were considered indicative of increased vascular resistance in the placental bed. The vascular[32] impedence in the uterine arteries starts to decrease linearly or exponentially with increasing peak systolic velocity as early as 5 and 7weeks.[33]Uterine artery flow increases gradually from 77ml/min at 5th week to 159ml/min at 10th week and there after more rapidly to a level of 665ml/min at 16th week.[34]Apart from changes of vascular impedence , a very important change seen in the uterine artery flow velocity waveform is the disappearance of early diastolic notch during the early second trimester which is believed to be caused by trophoblastic invasion.[35]

The uterine artery flow velocity waveform in early pregnant woman has relatively high pulsatility index as well as an early diastolic notch. The presence of a notch and an elevated RI or PI with advancing gestation is indicators of increased uterine vascular resistance and impaired uterine blood flow.[32,38]

The pathophysiological events resulting in pre-eclampsia begin early in gestation, and precede the onset of the clinical features. One of the early pathophysiological hallmarks is endothelial cell damage. Microalbuminuria is a marker of endothelial dysfunction.

Microalbuminuria might be used as an early marker of endothelial dysfunction in pre-eclampsia, before the onset of the overt syndrome, as it is likely that overt proteinuria is preceded by a microalbuminuric phase.

**METHODS :**

It is a prospective longitudinal study and has been done in the department of obstretics and gynaecology, Calcutta national medical college. The data was collected for 1 year.

Total 150 antenatal mothers attending OPD were studied for this period.

Mothers suffering from urinary tract infection , Epilepsy ,Diabetes ,Chronic hypertension ,Chronic kidney disease were excluded from this study.

Urine for 24 hrs microalbuminuria at 18 weeks of POG and Uterine artery Doppler at 18 weeks of POG were evaluated for those mothers.
Follow up study was done during routine antenatal visit, labour process , post natal period and for any complication during labour or in post natal period.

**STATISTICALANALYSIS :**
The data collected on the basis of above mentioned parameters was first tabulated and analysed by standard statistical methods in consultation with statistician, Dept. of Community Medicine

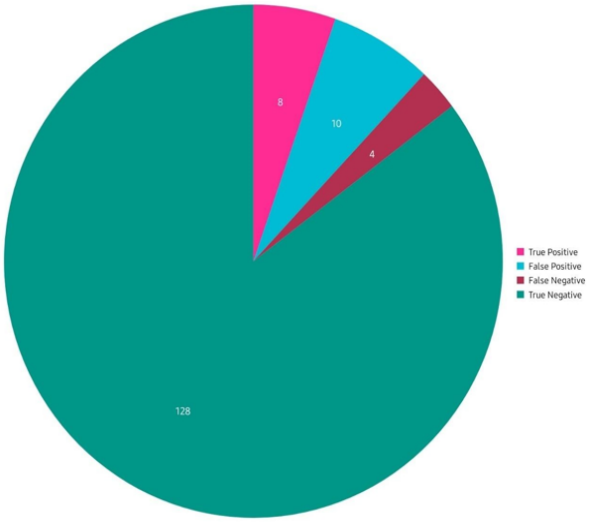
**RESULTS :**
While testing for microalbuminuria the 150 antenatal mothers at 18 weeks of POG and following them for development of pre- eclampsia and till term/delivery the following results were obtained:-

| MICRO-ALBUMINURIA | PRE-ECLAMPSIA DEVELOPED | PRE-ECLAMPSIA NOT DEVELOPED |
|---|---|---|
| PRESENT | 8(TP) | 10(FP) |
| ABSENT | 4(FN) | 128(TN) |
| TOTAL | 12 | 138 |

SENSITIVITY=True positive/ (True positive + False negative) X 100=8/ (8+4)X100 = 66.67%

SPECIFICITY=True negative/ (True negative + False positive) X 100=128/ (128+10) X 100 = 92.75%
PREDICTIVE VALUE OF A POSITIVE TEST=True positive/(True positive + False positive) X100 = 8/ (8+10)X100=44.44%

PREDICTIVE VALUE OF A NEGATIVE TEST=True negative/ (True negative + False negative) X 100 = 128 / (128+4) X 100=96.97%




**STATISTICALANALYSIS**
1 * FINAL OUTCOME Cross tabulation count

| | FINAL OUTCOME | | TOTAL |
|---|---|---|---|
| | PREECCLAMPSIA | NORMAL PREGNANCY | |
| 1 | 4 | 128 | 132 |
| 2 | 8 | 10 | 18 |
| TOTAL | 12 | 138 | 150 |

1-MICROALBUMINURIA ABSENT

2-MICROALBUMINURIA PRESENT

**Chi-Square Tests**

| | Value | df | Asymp. Sig. (2-sided) | Exact Sig. (2-sided) | Exact Sig. (1-sided) |
|---|---|---|---|---|---|
| Pearson Chi- Square | 32.107[a] | 1 | .000 | | |
| Continuity Correction[b] | 27.286 | 1 | .000 | | |
| Likelihood Ratio | 20.985 | 1 | .000 | | |
| Fisher's Exact Test | | | | .000 | .000 |
| N of Valid Cases | 150 | | | | |

a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 1.60.

b. Computed only for a 2x2 table
*P value=0.000(significant)*

***INFERENCE:-***
In our study of 150 antenatal mothers 12 developed pre-eclampsia (including 1 eclampsia) among which 8 had microalbuminuria during their antenatal period. TEN of them had microalbuminuria but did not develop pre-eclampsia, 4 of them developed pre-eclampsia but did not have microalbuminuria during antenatal period. ONE HUNDRED TWENTY EIGHT mothers did not have microalbuminuria and they did not develop pre-eclampsia. The sensitivity was 66.67%, specificity was 92.75% and predictive value of a positive test was 44.44% and predictive value of a negative test was 96.97%. So it might be possible that a phase of microalbuminuria precedes onset of proteinuria and that testing for microalbuminuria might be used a screening test for development of pre-eclampsia in future, as it is a non-invasive test and can be afforded by general population. Since the test had a specificity of 92.75% and predictive value of negative test 96.97%, a woman who does not have microalbuminuria in her antenatal period will have remote chance of developing pre-eclampsia. Since our sample size was small and the previous results of microalbuminuria as a predictor of pre-eclampsia showed a wide range of values it was difficult to compare our study with previous results and so larger studies are needed for evaluation of more accurate predictive value. ***Using microalbuminuria as a potential screening test for pre-eclampsia on a large scale clinical basis may be possible in future as a screening test for pre-eclampsia.***

**Doppler velocimetry was done at 18weeks and the following results emerged:-**

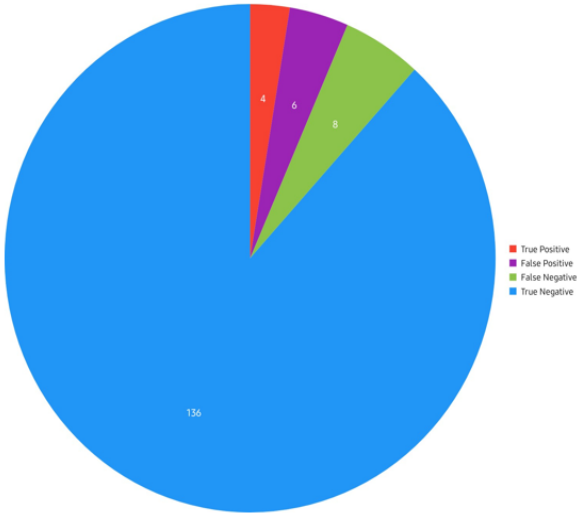
| DOPPLER VELOCIMETRY | PRE-ECLAMPSIA DEVELOPED | PRE-ECLAMPSIA NOT DEVELOPED |
|---|---|---|
| RI VALUES> 0.58 | 4(TP) | 6(FP) |
| RI VALUES < 0.58 | 8(FN) | 132(TN) |
| TOTAL | 12 | 138 |

SENSITIVITY=True positive/ (True positive + False negative) X 100=4/(4+8)X100 = 33.33%

SPECIFICITY=True negative/ (True negative + False positive) X 100=132/(132+6)X100 =95.65%

PREDICTIVE VALUE OF A POSITIVE TEST=True positive/ (True positive + False positive) X100 = 4/ (4+6) X 100=40%

PREDICTIVE VALUE OF A NEGATIVE TEST=True negative/ (True negative + False negative) X100 =132/ (132+8)X100=94.28%



**1 * FINAL OUTCOME Cross-tabulation** Count

| | FINAL_OUTCOME | | Total |
|---|---|---|---|
| | PRE- ECLAMPSIA | NORMAL PREGNANCY | |
| 1 | 4 | 6 | 10 |
| 2 | 8 | 132 | 140 |
| Total | 12 | 138 | 150 |

1-RI VALUE>0.58

2-RI VALUE<0.58

**Chi-Square Tests**

| | Value | df | Asymp. Sig. (2-sided) | Exact Sig. (2- sided) | Exact Sig. (1-sided) |
|---|---|---|---|---|---|
| Pearson Chi-Square | 6.206[a] | 1 | .013 | | |
| Continuity Correction[b] | 4.071 | 1 | .044 | | |
| Likelihood Ratio | 4.554 | 1 | .033 | | |
| Fisher's Exact Test | | | | .033 | .033 |
| N of Valid Cases | 149 | | | | |

a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 1.37.

b. Computed only for a 2x2 table P value=0.033(significant)

**INFERENCE:-**

When RI of >0.58 was used as cut off value at 18weeks the sensitivity was 33.33%, specificity was 95.65%, predictive value of a positive test was 40% and predictive value of a negative test was 94.28% for development of pre-eclampsia. Previous studies by Cambell et al[40] using RI value of >0.58 got sensitivity of 68%,specificity 69%,predictive value of positive test 42%,predictive value of negative test 87%.A study by North et al[44] using RI value >0.56 got sensitivity of 27%,specificity 89%,predictive value of a positive test 8%,predictive value of a negative test 97%.

RI value as predictive marker of pre-eclampsia had high specificity and predictive value of a negative test, antenatal mother who has RI value <0.58 in uterine artery doppler velocimetry will have less chance of developing pre-eclampsia. With the wide spread availability of ultrasonography second trimester uterine artery doppler velocimetry can serve as a potential screening tool in future for pre-eclampsia**.** The test has the advantage of being non invasive and less costlier than estimating microalbuminuria.

| Screening test | Sensitivity | Specificity | Positive predictive value (%) | Negative predictive value (%) |
|---|---|---|---|---|
| Microalbuminuria | 66.67% | 92.75% | 44.44% | 96.97% |
| RI>0.58 | 33.33% | 95.65% | 40% | 94.28% |

**INFERENCE :**

From the above it is seen that among the two tests microalbuminuria had the higher sensitivity and positive predictive value for predicting pre-eclampsia. So it will better detect the "true positives" i.e mothers who can develop pre-eclapmsia in presence of microalbuminuria in their antenatal period. As the predictive value of negative test of microalbuminuria was 96.97% which was more than the predictive value of negative test of RI, therefore it is likely that it will better predict who among the antenatal mothers have lesser chance of developing pre-eclampsia.

The specificity was highest when RI>0.58 in second trimester doppler velocimetry was used as a screening tool for predicting pre-eclampsia. So among the above two tests it has the best potential to detect the "true negatives" i.e. those who are unlikely to develop pre-eclampsia when RI value<0.58 in the second trimester doppler velocimetry.

**DISCUSSION**

In our study we have tried to find out the usefulness of detecting microalbuminuria during antenatal period and RI value >0.58 in second trimester in uterine artery Doppler velocimetry during antenatal period as a screening test for pre-eclampsia. This was done with the rationale that a phase of microalbuminuria might precede the development of overt proteinuria in pregnancy and that detection of microalbuminuria may be used as screening test for pre-eclampsia. Study by Das et al[28] testing with the micral test (a dip stick test for microalbuminuria) found it to have a sensitivity of 68% and specificity of 92%.They also concluded that microalbuminuria testing was a good predictor of pregnancy induced hypertension.

In another study 88 normotensive normal pregnant women between 24 and 34 weeks of gestation were seen at Los Angeles University of Southern California.[29] Pre-eclampsia subsequently developed in 83% of patients with higher level of microalbumin(>11 microgm/ml), conversely 94% of women who did not demonstrate high microalbumin level in urine remained normotensive at the time of delivery. These results suggest that changes in renal function are present in gravid women who are otherwise free of symptoms, in whom pre-eclampsia will eventually develop. This gives the test a sensitivity of 50% and a specificity of 82%, a positive predictive value of 26% and a negative predictive value of 93%.

In a study carried out at Queen Mary's Hospital at King George's Medical College, Lucknow, India,[28] one hundred and thirty pregnant women between 24 and 34 weeks were seen for prenatal care. Once the women extended the study, a first morning urine sample was studied for presence for microalbuminuria. 17% of patients developed microalbuminuria during the antenatal period while none of the non-pregnant women showed microalbuminuria. The test was considered positive when level of albumin in urine was >20ugm/ml, of these 60% developed pregnancy induced hypertension whereas only 5.8% of microalbuminuria negative patients developed pregnancy induced hypertension.Sensitivity of the test was 68.42%, specificity 91.84%, positive predictive value was 56.09% and negative predictive value was 94.40%.

In our study of 150 antenatal mothers, 12 developed pre-eclampsia (including one eclampsia) among which 8 had microalbuminuria during their antenatal period. TEN of them had microalbuminuria but did not develop pre-eclampsia, 4 of them develop pre- eclampsia but did not have microalbuminuria during their antenatal period. ONE HUNDRED AND TWENTY EIGHT mothers did not have microalbuminuria and they did not develop pre-eclampsia. The sensitivity was 66.67%, specificity was 92.75% and predictive value of a positive test was 44.44% and predictive value of a negative test was 96.97%. So it might be possible that a phase of microalbuminuria precedes onset of proteinuria and that testing for microalbuminuria might be used aa a screening test for development of pre-eclampsia in future, as it is a non-invasive test and can be afforded by general population. Since the test had a specificity of 92.75% and predictive value of negative test 96.97%, a woman who does not have microalbuminuria in her antenatal period will have remote chance of developing pre-eclampsia. Since our sample size was small and the previous results of microalbuminuria as a predictor of pre-eclampsia showed a wide range of values it was difficult to compare our study with previous results and so larger studies are needed for evaluation of more accurate predictive value. Using microalbuminuria as a potential screening test for pre-eclampsia on a large scale clinical basis may be possible in future as a screening test for pre-eclampsia.

The other potential tool which may have utility in future as predictive marker is uterine artery doppler velocimetry in the second trimester. When RI of >0.58 was used as cut off value at 18weeks the sensitivity was 33.33%, specificity was 95.65%, predictive value of a positive test was 40% and predictive value of a negative test was 94.28% for development of pre-eclampsia. Previous studies by Cambell et al[40] using RI value of >0.58 got sensitivity of 68%,specificity 69%,predictive value of positive test 42%,predictive value of negative test 87%.A study by North et al[44] using RI value >0.56 got sensitivity of 27%,specificity 89%,predictive value of a positive test 8%,predictive value of a negative test 97%.Since RI value as predictive marker of pre-eclampsia had high specificity and predictive value of a negative test, antenatal mother who has RI value<0.58 in uterine artery velocimetry will have less chance of developing pre-eclampsia. Our sample size was small larger studies are needed for evaluation of more accurate predictive value. With the wide spread availability of ultrasonography second trimester uterine artery doppler velocimetry can serve as a potential screening tool in future for pre-eclampsia. The test has the advantage of being non -invasive and less costlier than estimating microalbuminuria.

These tests might help in identifying women who might need more intensive blood pressure monitoring and the rest may do well with simpler community based antenatal care. The clinical utility of these predictive markers will depend on development of prophylaxis for pre-eclampsia in future. Recent clinical trials are evaluating the role of aspirin, vasodilators (glyceryl trinitrate) and anti-oxidants as potential future prophylactic agents. (48.51)

## CONCLUSION

The ideal predictive test should be simple, reproducible, non-invasive, safe, rapid and inexpensive, easy to perform in pregnancy with high sensitivity and predictive value. No such screening test is currently available which can be applied on a clinical basis for detection of at risk women for development of pre-eclampsia. We have attempted to study the value of detecting microalbuminuria in the antenatal period as a predictor for future development of pre-eclampsia. Our results show that it has got sensitivity - 66.67%, specificity - 92.75%, positive predictive value - 44.44% and negative predictive value- 96.97%. So, our study shows that a woman who does not have microalbuminuria in her antenatal period will have remote chance of developing pre-eclampsia. Our study suggests detecting microalbuminuria may have some utility as screening test for pre-eclampsia. Since our sample size was small larger studies are needed for evaluation of more accurate predictive value.

The other potential tool which may have utility in future as predictive marker is uterine artery doppler velocimetry in the second trimester. Since RI value as predictive marker of pre-eclampsia had high specificity and predictive value of a negative test, antenatal mother who has RI value<0.58 in uterine artery velocimetry will have less chance of developing pre-eclampsia. Our sample size was small larger studies are needed for evaluation of more accurate predictive value. With the wide spread availability of ultrasonography second trimester uterine artery doppler velocimetry can serve as a potential screening tool in future for pre-eclampsia. The test has the advantage of being non-invasive and less costlier than estimating microalbuminuria.

These tests might help in identifying women who might need more intensive blood pressure monitoring and the rest may do well with simpler community based antenatal care. The clinical utility of these predictive markers will depend on development of prophylaxis for pre-eclampsia in future. Recent clinical trials are evaluating the role of aspirin, vasodilators (glyceryl trinitrate) and anti-oxidants as potential future prophylactic agents (48.51)

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