

Comparison of Urine Microalbuminuria and Uterine Artery Resistance Index as a Predictors of Hypertensive Disorders In Pregnancy As Alone And In Combination

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Abstract: Hypertensive disorders in pregnancy complicate 1 in 10 pregnancies, often associated with maternal and neonatal mortality and morbidity. It accounts for nearly one fifth of all maternal deaths. The only treatment for preeclampsia is delivery, which may lead to premature death. Despite the last two decades of research into this condition, the ability of clinicians to predict gestational hypertension/preeclampsia prior to the onset of symptoms has not improved remarkably. The purpose of this study is to Compare the efficacy of urine microalbuminuria and uterine artery Doppler resistance index in prediction of gestational hypertension/preeclampsia with sensitivity, specificity, positive predictive value and negative predictive value.

KEYWORDS: Gestational hypertension, urine microalbuminuria, uterine artery Doppler.

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I. Introduction

Hypertensive disorders of pregnancy remain a major cause of maternal as well as perinatal morbidity and mortality despite recent advances in antenatal care¹. Preeclampsia is diagnosed when the blood pressure at or above 140/90 mmHg occurring on two occasions at least 6 hours apart, associated with proteinuria greater than 300mg/24 hours or greater than 1 gm/l in a random sample, after 20 weeks of gestation². Hypertension in pregnancy is also responsible for fetal and infant mortality as well as 46% of infants born small for gestation³. Similarly it was estimated that 3-10% of infants are growth restricted. Fetal growth restriction is associated with substantive perinatal morbidity and mortality^{4,5}. This is true for both preterm and term infants⁶.

Early screening for preeclampsia may allow vigilant antenatal surveillance and appropriate timing of fetal delivery in order to avoid serious sequelae. Various haemodynamic and biochemical measures have been found to have limited accuracy as a screening measures for this condition^{7,8}. Preeclampsia is characterised by an imbalance between prostacycline and thromboxane A2 production as well as failure of the second wave trophoblastic invasion of the endometrio-myometrial vasculature. The result is abnormal uteroplacental blood flow and this lead an idea of using Doppler assessment of uterine artery velocimetry waveforms as the method of screening for this antenatal complication⁹.

Doppler is a non-invasive method for evaluation of feto-placental circulation without any disturbance to human pregnancy¹⁰. A high Resistance Index, Pulsatility Index and persistent uterine artery notching in uterine artery Doppler wave form has shown as the best screening test³ thus, we have conducted this study to find out the predictive value of transabdominal uterine artery resistance index Doppler at 18-20 week of gestation for the prediction of preeclampsia and sub-sequent perinatal out come.

Proteinuria has classically been an important finding in the diagnosis of preeclampsia/eclampsia. Persistent microalbuminuria indicates a high probability of damage of the glomerular filtration capacity of the kidney and is of great diagnostic relevance in pregnancy as a possible predictor of developing PE. However, customary dipstick methods for detecting proteinuria fail to detect minimal elevations in urinary excretion of albumin that may be present earlier than other clinical signs and symptoms of preeclampsia. With radioimmunoassay and other sensitive methodology for detection of microalbuminuria, it is now possible to detect minimal elevations in albumin excretion that have gone unnoticed in the past.

Micoalbuminuria refers to subclinical elevation of urinary albumin excretion¹¹. It has been shown to precede the development of chronic renal failure in patients with insulin-dependent diabetes mellitus, and may be evidence of renal involvement in hypertension¹². Healthy pregnant women may not excrete albumin in amounts, needed to detect by the conventional dipstick screening test in the presence of micro-albumin should be an important clinical finding in pregnant women. So, here my attempt was to detect the predictive value of urinary albumin levels in pregnant women who are free from symptoms of preelampsia.

II. Materials And Methods

This study was conducted in compliance with the protocol; The Institutional Ethics Committee (IEC) clearance was taken. Informed consent was obtained from all study participants and ICH/GCP guidelines was followed. The purpose of this study is to estimate microalbuminuria 2 times in the antenatal period and uterine artery resistance index in the second trimester as a predictor of gestational hypertension/ pre-eclampsia. This study is a prospective study which involves a group of 200 women who attend the antenatal clinic of Sree Balaji Medical College and Hospital.

- **Inclusion criteria:** Women at 14 wks of GA, Age of 18 -35 yrs, Singleton pregnancy.
- **Exclusion criteria:**
- Women who are diagnosed with Hypertension, renal diseases, diabetes mellitus
- Women with overt Proteinuria
- Women with acute urinary tract infection

METHODOLOGY-All women who meet the inclusion and exclusion criteria were taken into the study after signing an informed written consent. Detailed history was taken and thorough general physical examination was done at the onset of the study.

MICROALBUMINURIA

This procedure is simple, rapid, noninvasive, inexpensive and easy to perform. Measurement of microalbuminuria was done in the laboratory of Sree Balaji Medical College and Hospital by immunoturbidimetry method. All subjects were admitted for a day at 14 to 16 weeks and 24 hour urine Sample was collected for testing of micro albuminuria in the urine sample. The 24 hour urine microalbuminuria was tested again at 22 to 24 weeks. Criteria for microalbuminuria in 24 hour urine sample: Lower limit – 30mg albumin/24 hours and upper limit – 300mg albmin/24 hours.

DOPPLER STUDY

Trans-abdominal Doppler Ultrasonography is performed in the Department of Radiology of Sree Balaji Medical College & Hospital, Chennai. All subjects underwent a Trans-abdominal Doppler ultrasonography for the measurement of Resistance Index at 18 to 22 weeks of gestation. RI value of 0.58 was taken as the cut-off value. The results were documented. Subsequently they were followed up at 2 weekly intervals until 36wks & weekly thereafter until 6 weeks after delivery. At each visit blood pressure were recorded. The primary outcome is the development of gestational hypertension or pre-eclampsia. Gestational hypertension will be diagnosed in the presence systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on at least two occasions, 6 hours apart. Those subjects who develop gestational hypertension were subjected to estimation of urinary protein. If proteinuria is present (≥ 300 mg in a 24-hour urine collection or 1 dipstick measurement $\geq 2+$) they will be diagnosed as pre-eclampsia. If gestational hypertension or pre-eclampsia is diagnosed, the subject is directed to appropriate management. Data was statistically analysed and results were discussed at the end of the study.

III. Results

Table 1 : Incidence of Hypertensive Disorders

Incidence of HTN	No of cases	Percentage
Normal	171	85.5%
Hypertensive	29	14.5%
Total	200	100

This table shows , 85.5% (n=171) patients in normotensive group, remaining 14.5% (n=29) patients are in hypertensive group. Hence, the incidence of hypertensive disorders is 14.5% (n=29).

Table 2: Distribution of Cases in to Various Groups

Categories of HTN Disorders	No of cases	Percentage
Gestational hypertension	9	31.04%
Mild Pre Eclampsia	8	27.58%
Severe Pre Eclampsia	10	34.48%
Eclampsia	1	3.44%
HELLP Syndrome	1	3.44 %
Total	29	100%

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In this table about 34.48% (n=9) of women developed severe preeclampsia, 27.58% (n=8) of women developed mild preeclampsia, 31.04% (n=10) developed gestational hypertension, 3.44% (n=1) of women categorised into eclampsia, remaining 3.44% (n=1) developed HELLP syndrome.

Table-3 Age Distribution in Years

Age (in years)	Normal	Percentage	Hypertensive	Percentage
18-20	15	8.77	3	10.35
21-25	94	54.97	8	27.59
26-29	41	23.98	9	31.03
30-35	21	12.28	9	31.03
Total	171	100	29	100

Groups	N	Mean ± SD	t value	p value	Inference
Normal	171	23.4128 ± 12.233	23.345	0.0231	Highly significant
HTN	29	28.4910 ± 17.327			

This table shows, the mean age of women in this study group was 23.34 years. Majority of women were under the age group 21-25 years in normotensive patients. Where as in hypertensive group, majority of the patients were under 26-29 yrs & 30-35 yrs age group and the same is statistically significant (p=0.0231).

Table 4 : Parity

Parity	Normal	Percentage	Hypertensive	Percentage
Primigravida	111	64.91	21	72.41
Multigravida	60	35.09	8	27.59
Total	171	100	29	100

Groups	N	χ ² value	p value	Inference
Normal	171	5.4328	0.0190	Highly significant
HTN	29			

In this table, when compared to the parity between normotensive & hypertensive patients, majority of them were primigravida in both the groups (64.91% & 72.41%).

Table 5 :Body Mass Index

BMI	Normal	Percentage	Hypertensive	Percentage
<18.5	20	11.70	3	10.34
18.5-24.99	65	38.01	7	24.14
25-29.99	57	33.33	10	34.48
>30	29	16.96	9	31.04
Total	171	100	29	100

Groups	N	Mean ± SD	t value	p value	Inference
Normal	171	22.918 ± 5.4380	12.4390	0.0000	Highly significant
HTN	29	32.438 ± 10.139			

This table shows, hypertensive patients most of them were under 25-29.99 BMI classification, when compared to normotensive patients.

Table 6 : Socioeconomic Class

SOCIOECONOMIC STATUS	Normal	percentage	Hypertensive	Percentage
Upper class	24	14.03	3	10.34
Upper middle class	59	34.50	7	24.14
Lower middle class	66	38.60	14	48.28
Upper lower class	14	8.19	4	13.79
Lower class	8	4.68	1	3.45
Total	171	100	29	100

Groups	N	χ ² value	p value	Inference
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Normal	171	9.7585	0.0190	Highly significant
HTN	29			

In this table, majority of patients belong to lower middle class in both the normotensive & hypertensive group patients (38.60% & 48.28%).

Table 7: Onset of Hypertension

Onset of HTN Disorders	No of cases	Percentage
20-24	1	3.45%
24-28	5	17.24%
28-34	14	48.28%
>34	9	31.03%
Total	29	100%

In this table, 48.28% (n=14) of patients developed hypertension around 28-34 weeks of gestation, About 31.03% (n=9) of women were developed hypertension in more than 34 weeks, 17.24% (n=5) of patients developed at 24-28 weeks and remaining 3.45% (n=1) patient developed at 20-24 weeks.

Table 8 : Positive Predictors

Positive Predictors	No of Cases	Percentage
Urine Micro Albumin	21	10.5%
Uterine Artery Resistance Index	37	18.5%
Both 1 & 2	14	7%
None	156	78%

This table shows, Out of 200 women, 10.5% (n=21) subjects with urine microalbuminuria and 18.5% (n=37) with increased uterine artery resistance index, 7% (n=14) both urine microalbuminuria and uterine artery resistance index. The remaining 78% (n=156) of women were negative for predictors.

Table 9: Time of Onset of Microalbumin & Risk of Hypertension

Weeks	No of Cases Detected with Urine Albumin	%	Developed HTN		Not developed HTN		Total %
			No of cases	%	No of cases	%	
14-16wks	14	66.67	9	68.28	5	35.71	100
22-24wks	7	33.33	3	42.85	4	57.14	100
Total	21	100	12	100	9	100	

Groups	N	Mean ± SD	t value	p value	Inference
Developed HTN	12	0.2789 ± 0.012	26.1390	0.0023	Highly significant
Not Developed HTN	09	208.679 ± 12.768			

This table 9 shows about 66.67% (n=14) patients were positive at 14-16 weeks gestation, 68.28% (n=9) patients developed hypertension earlier & about 33.33% (n=7) patients were positive at 22-24 weeks, in which 42.85% (n=3) patients developed hypertension. Totally 57.14% (n=12) patients developed hypertension. This association of urine microalbuminuria and hypertension is significant with (p=0.0023).

Table 10: Range of Microalbuminuria & Risk of Hypertension

URINE MICRO ALBUMIN	No. of cases	%	HYPER TENSIVE	%	NORMO TENSIVE	%	Total%
<30	179	89.5	17	9.50	162	90.50	100
30-100	5	3	2	40	3	60	100
100-200	9	4.5	5	55.56	4	44.44	100
200-300	7	3	5	71.43	2	28.57	100
Total	200	100	29	-	171	-	-

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Groups	N	Mean ± SD	t value	p value	Inference
Normotensive	171	27.147 ± 4.5675	17.247	0.013	Highly significant
Hypertensive	29	249.564 ± 16.319			

This table 10 shows, out of 9.50% (n=17) of patients With range less than 30mg/24hrs developed hypertension ,40% (n=2) of women with range 30-100mg/24hrs ,55.56% (n=5) Of women with 100-200mg/24hrs ,71.43% (n=5) of women with range 200-300 mg/24hrs.

Table 11: Uterine Artery Resistance Index At 18-20weeks

Resistance Index	No of cases	%	Developed HTN	%	Normotensive	%	Total %
≤0.58	163	81.5	4	2.45	159	97.55	100
> 0.58	37	18.5	25	67.57	12	32.43	100
Total	200	100	29	-	171	-	-

In this table, 18.5% (n=37) subjects were positive for uterine artery Doppler resistance index at 18-20 weeks of gestation.

Groups	N	Mean ± SD	t value	p value	Inference
Normal	171	0.4219 ± 0.0021	3.3289	0.0041	Highly significant
HTN	29	0.6740 ± 1.113			

This table 11 shows, 67.57% (n=25) patients developed hypertension. This association of uterine artery resistance index and hypertension is significant with p=0.0041.

Table 12: Urine Microalbuminuria as A Predictor

Predictors	Developed HTN	Not developed HTN	Total
Urine albumin Positive	12 True + (a)	9 False + (b)	21 (a+b)
Urine albumin Negative	17 False - (c)	162 True - (d)	179 (c+d)
Total	29 (a+c)	171 (b+d)	200 (a+b+c+d)

Factor	Formula	Percentage
Sensitivity	$a/(a+c)*100$	41.38%
Specificity	$d/(b+d)*100$	94.74%
Positive predictive value	$a/(a+b)*100$	57.14%
Negative predictive value	$d/(c+d)*100$	90.50%
Diagnostic accuracy	$(a+d)/(a+b+c+d)*100$	87%

Groups	N	χ ² value	P value	Inference
Developed HTN	29	6.588	0.021	Highly significant
Not Developed HTN	171			

Table 12 shows urine microalbuminuria as a predictor of hypertension has sensitivity of 41.38%, specificity of 94.74%, positive predictive value of 57.14%, negative predictive value of 90.50% and diagnostic accuracy was 87%.This association is highly significant with p value(p=0.021).

Table 13: Uterine Artery Resistance Index as a Predictor

Predictors	Developed HTN	Not developed HTN	Total
Resistance Index positive	25 True + (a)	12 False + (b)	37 (a+b)
Resistance Index Negative	4 False - (c)	159 True - (d)	163 (c+d)
Total	29 (a+c)	171 (b+d)	200 (a+b+c+d)

Factor	Formula	Percentage
Sensitivity	$a/(a+c)*100$	86.21%
Specificity	$d/(b+d)*100$	92.98%
Positive predictive value	$a/(a+b)*100$	67.57%
Negative predictive value	$d/(c+d)*100$	97.55%
Diagnostic accuracy	$(a+d)/(a+b+c+d)*100$	92%

Groups	N	χ^2 value	P value	Inference
Developed HTN	29	2.153	0.0142	Highly significant
Not Developed HTN	171			

Table 13 shows, Uterine artery resistance index as a predictor of hypertension has sensitivity of 86.21%, specificity of 92.98%, positive predictive value of 67.57%, negative predictive value of 97.55% and diagnostic accuracy was 92%. This association is highly significant with p value ($p=0.0142$).

Table-14 Both as a Predictors

Predictions	Developed HTN	%	Not Developed HTN	%	TOTAL
Both +ve	10	71	04	29	14
Urine Albumin +ve	12	57	09	43	21
Resistance Index +ve	25	68	12	32	37

Groups	N	χ^2 value	P value	Inference
Developed HTN	47	17.396	0.002	Highly significant
Not Developed HTN	25			

When compared with tests done in alone, the test done in combination as high predictive value of 71% and this is also statistically significant with p value ($p=0.002$).

IV. Discussion

In this study, 200 singleton pregnant women attending the antenatal OPD of Sree Balaji Medical College & Hospital, Chrompet, Chennai, who met the inclusion and exclusion criteria were studied over three years.

In present study, the mean age of women in this study group was 23.34 years. Majority of women were under the age group 21-25 years in normotensive patients. Whereas in hypertensive group, majority of the patients were under 26-29 yrs & 30-35 yrs age group. When compared to the parity between normotensive & hypertensive patients, majority of them were primigravida in both the groups (64.91% & 72.41%). Among hypertensive patients most of them were under 25-29.99 BMI classification. The increase in BMI will cause increased risk of hypertension in pregnancy. The p value was 0.0000 which is less than 0.05 and hence it is highly significant.

In our study majority of patients belong to lower middle class in both the normotensive & hypertensive group patients (38.60% & 48.28%).

In our study, the incidence of hypertension is 14.5% ($n=29$). This corroborates with national incidence of 5 to 15%. Salako et al¹³ had incidence of 15.1% of the patients developed hypertension in his study. On further differentiation of hypertension into various categories of hypertension in our study, about 34.48% ($n=10$) of women developed severe preeclampsia, 27.58% ($n=8$) of women developed mild preeclampsia, 31.04% ($n=9$) developed gestational hypertension, 3.44% ($n=1$) of women categorised into eclampsia, where this eclamptic patient had both urine microalbuminuria and uterine artery resistance index positive, remaining 3.44% ($n=1$) developed HELLP syndrome.

In this study, 48.28% ($n=14$) of patients developed hypertension around 28-34 weeks of gestation, About 31.03% ($n=9$) of women were developed hypertension in more than 34 weeks, 17.24% ($n=5$) of patients developed at 24-28 weeks and remaining 3.45% ($n=1$) patient developed at 20-24 weeks.

Out of 200 women, 10.5% ($n=21$) subjects with urine microalbuminuria and 18.5% ($n=37$) with increased uterine artery resistance index, 7% ($n=14$) both urine microalbuminuria and uterine artery resistance index. The remaining 78% ($n=156$) of women were negative for predictors.

In present study, Out of 10.5% ($n=21$) subjects who were positive for urine microalbuminuria, 57.14% ($n=12$) patients developed hypertension. This association of urine microalbuminuria and hypertension is significant with ($p=0.0023$). Amit Sonagra et al. 2012, Significantly increased levels of urine microalbumin were noted in women with PIH when compared with normal healthy pregnant women ($p<0.001$). Salako et al¹³ found

that, Out of 93 patients, 23.7% (n=22) were positive for microalbuminuria. There was an increased incidence of preeclampsia with an increase in albumin excretion and this was significant ($p < 0.05$).

Out of the people who developed hypertension, 40% (n=2) of women with range 30-100mg/24hrs, 55.56% (n=5) of women with 100-200mg/24hrs, 71.43% (n=5) of women with range 200-300 mg/24hrs. Patients who had increased albumin excretion range of 200-300mg/24hrs are at more risk of developing hypertension. About 66.67% (n=14) patients were positive at 14-16 weeks gestation, 68.28% (n=9) patients developed hypertension & about 33.33% (n=7) patients were positive at 22-24 weeks, 42.85% (n=3) patients developed hypertension. Hence it is suggestive to do at the earlier weeks, so that we can detect the patients who are under high risk at earlier weeks of gestation. Chhabra S et al, found that at 16-22 weeks, 5.89 percent were microalbuminuria positive, 60 percent of them and out of microalbuminuria negative, 20 percent developed hypertensive disorder. By 29-34 weeks of gestation 97.06 percent were microalbuminuria positive, 22.5 percent of them and 20 percent of microalbumin negative also developed hypertensive disorder by term., the mean microalbumin excretion in those who remained normotensive was 0.49mg/dl, 237 mg/dl, 4.37mg/dl at 16-22 weeks, 23-28 weeks and 29-34 weeks of gestation respectively compared to 1.33mg/dl, 3.62mg/dl and 6.44mg/dl in those who developed hypertensive disorder. Microalbuminuria estimation at earlier weeks of gestation is more effective to detect hypertension.

Out of 18.5% (n=37) subjects were positive for uterine artery Doppler resistance index at 18-20 weeks of gestation, 67.57% (n=25) patients developed hypertension. This association of uterine artery resistance index and hypertension is significant with $p = 0.0041$. Katie M Groom et al¹⁴ described the changes in mean uterine artery resistance index and bilateral uterine artery notches between 20 and 24 weeks of gestation and its outcome was done, concluded that 20 weeks is the most appropriate gestation in second trimester to perform uterine artery Doppler. Martin et al also found that high resistance index was associated with development of preeclampsia..

In present study, urine microalbuminuria as a predictor of hypertension has sensitivity of 41.38%, specificity of 94.74%, positive predictive value of 57.14%, negative predictive value of 90.50% and diagnostic accuracy was 87%. This association is highly significant with p value ($p = 0.021$). Sirohiwal D et al found that microalbuminuria as a predictor of hypertension, in 200 normotensive patients at 20-28 weeks of gestation with sensitivity-86%, specificity-72%, positive predictive value-26% and negative predictive value-98%. Salako B et al found significantly increased incidence of preeclampsia with an increase in albumin excretion. Single urinary microalbumin excretion estimation at time of antenatal booking predicted occurrence of Hypertension in Pregnancy with the sensitivity, specificity, positive and negative predictive values of 88.9%, 67.9%, 22.2% and 98.3% respectively.¹³

Uterine artery resistance index as a predictor of hypertension has sensitivity of 86.21%, specificity of 92.98%, positive predictive value of 67.57%, negative predictive value of 97.55% and diagnostic accuracy was 92%. This association is highly significant with p value ($p = 0.0142$). Bower et al¹⁵ (1993) conducted a cross sectional study on 2430 women between 18-22 weeks to obtain velocity waveforms from both uterine arteries. Their outcome measures were intrauterine death, ante partum hemorrhage and three different degrees of severity of pre-eclampsia and growth retardation. Their sensitivity is 7.5 %, specificity is 86 %, PPV is 12 %, NPV is 99%. Bewley et al¹⁶ (1991) similar to our study, RI $> 95^{\text{th}}$ centile used as predictor of preeclampsia. This study showed 24% of sensitivity, 95% of specificity, PPV is 20% and NPV is 96%. Dugoff et al¹⁷, in this study used mean RI cut off at $\geq 75^{\text{th}}$ centile (0.731) & the 95^{th} centile (0.81). Accordingly at the 75^{th} centile, the sensitivity for detecting preeclampsia & IUGR was 72.3 % & 66.7% with a specificity of 84 % and 75 % respectively. But at 95^{th} centile or greater, a relatively low sensitivity was found which was 22% & 16% with a specificity of 48% and 39% for preeclampsia.

Both urine microalbuminuria and uterine artery resistance index as a predictor of hypertension. When compared with tests done in alone, the test done in combination as high predictive value of 71% and this is also statistically significant with p value ($p = 0.002$).

V. Conclusion

- Hypertensive disorders in pregnancy complicate 1 in 10 pregnancies, often associated with maternal and neonatal mortality and morbidity.
- Second trimester uterine artery Resistance Index and urine Microalbuminuria can be used as a predictor of moderate strength for hypertension in pregnancy.
- Microalbuminuria should be considered as important risk factor for development and progression of preeclampsia and eclampsia even in normotensive pregnant women. Early intervention can be done to retard the progression of disease in such women. Thus, detection of microalbuminuria may prove useful tool to identify the women with high risk of disease progression.
- Present study and review of literature concludes that uterine artery Doppler has a definite place in all antenatal patients to prevent or reduce maternal as well as perinatal morbidity and mortality.

- However it will be still more effective when both the tests are done in combination.

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