

MICROALBUMINURIA IN WOMEN WITH GESTATIONAL HYPERTENSION

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ABSTRACT

Background: Gestational hypertension (BP $\geq$ 140/90 mm of Hg without proteinuria) is classified under hypertensive disorders of pregnancy (HDP). HDP causes widespread endothelial dysfunction leading to hypertension and damage to vital organs such as liver, kidney, brain etc. Damage to kidney may lead to elevation in urinary excretion of albumin which can be used for predicting severity of the disease.

Aims & Objective: This study was done to detect presence of microalbuminuria and to evaluate role of its estimation among women with gestational hypertension and normal pregnancy.

Material and Methods: Case control study was done taking 40 women with gestational hypertension as cases and 40 age matched healthy pregnant women as controls. Urinary concentration of albumin was measured using immuturbidimetry kit. Statistical analysis was done using SPSS 17.0.

Results: Urinary excretion of albumin was significantly increased in women with gestational hypertension compared with controls. Its level significantly positively correlated with systolic and diastolic blood pressure.

Conclusion: Urinary albumin excretion gradually increases as the disease severity increases. Early & regular monitoring for microalbuminuria in women with gestational hypertension may give a clue of disease severity and associated organ damage.

KEY-WORDS: Gestational Hypertension; Albuminuria; Glomerular Dysfunction; Kidney Damage; Prognosis

Introduction

Definition of gestational hypertension was given by working group of National High Blood Pressure Education Programme (NHBPEP 2000). According to it, any pregnant female of ≥ 20 weeks of gestation with blood pressure $\geq 140/90$ mm of Hg noted first time during pregnancy on ≥ 2 occasions at least 6 hours apart without any visible proteinuria was considered as having gestational hypertension. It is also known as pregnancy induced hypertension (PIH). Here blood pressure returns to normal prepregnant level within 12 weeks of delivery so it is also known as transient hypertension.^[1]

Overall incidence of PIH is 6-7% of all pregnancies. The risk of its progression to preeclampsia is 15-26%. When PIH develops after 36 weeks of gestation, the risk of its progression to preeclampsia falls to 10%.^[2] An estimated 50,000 women die annually from preeclampsia world-wide. It contributes to death of a woman

every 3 minutes world-wide.^[3] Hypertensive disorders of pregnancy (HDP) are one of the most common causes of prematurity accounting for 25% of all very low birth weight infants with birth weight less than 1500 grams.^[2]

HDP are known since very ancient time. Eclampsia was first noted in the Hippocratic writings in 430 – 330 BC. In coan prognosis it was stated that headache accompanied by heaviness and convulsion during pregnancy should be considered as a bad sign.^[4] Since then many researchers have postulated various theories for the pathogenesis of the disease but still the exact mechanism is not known. Impaired trophoblast invasion leading to atherosclerotic lesions in placenta is implicated as a causal factor in pathogenesis of the disease.^[5] Many other theories such as immunological intolerance between maternal and foetal tissue, genetic predisposition, nutritional imbalance, oxidative stress etc. are also postulated.^[1,6]

This impaired trophoblast invasion causes narrowing of uterine spiral arterioles leading to placental ischemia. Placental ischemia leads to alteration in expression of various factors that affect the endothelial function. It leads to reduced expression of vascular endothelial growth factor (VEGF), placental growth factor (PlGF), prostacyclin (PGI₂), nitric oxide (NO) etc. from vascular endothelium. On the other side, there is increased expression of antiangiogenic factors such as tumour necrosis factor- α (TNF α), interleukins (ILs), soluble Fms like tyrosine kinase 1 (sFlt 1), Angiotensin 1 receptor autoantibody (AT1-AA), endothelin-1 (ET-1), thromboxane A₂ (TxA₂) etc. This angiogenic imbalance leads to wide spread endothelial dysfunction all over the body.^[7,8]

Because of wide spread endothelial dysfunction, extensive changes are found to occur in the renal system in PIH. As a part of the “end organ pathology” glomeruli undergo structural changes with pronounced endothelial vacuolization and hypertrophy of the cytoplasmic organelles which is defined as “glomerular endotheliosis”. The net effects are reduced renal blood flow and GFR, impaired tubular reabsorption or secretory function.^[4,9]

A normal adult excretes about 300mg/24hours of non-dialysable material of which about 140mg/24hour is protein. Plasma proteins only represent some 25mg/24hours or 17mg/L of which about half is albumin and the remaining proteins are of renal origin, Tamm-Horsfall glycoprotein being the major contributor.^[10]

Proteinuria has been recognized as one of the cardinal signs of renal disease and it is used for the diagnosis and management of patients with nephropathy. Chemical methods have limitation in sensitivity of detection of proteinuria, below that level it cannot detect. This limitation has overcome by more sensitive immunological methods that can detect very minute quantity of protein in biological fluids. Albuminuria below detection limit of chemical urine protein method is now described as microalbuminuria. Microalbuminuria can be defined as albumin excretion rate of approximately 20-200 μ g/min or 30-300mg/24 hours.^[10]

Studies have confirmed that the microalbuminuria is not only associated with cardiovascular disease but also with acute inflammatory condition, and is a reflection of systemic vascular endothelial function. In some conditions microalbuminuria is reversible in response to vascular protecting interventions.^[11]

Thus, data suggests that, microalbuminuria is present in condition with endothelial dysfunction and renal damage. Endothelial dysfunction has come out as basic underlying pathology behind PIH. Therefore, this study was undertaken to detect the presence of microalbuminuria in women with gestational hypertension.

Materials and Methods

A case control study was conducted taking women with gestational hypertension as cases and healthy pregnant women as controls. The study subjects were selected from Bapuji Hospital and Chigateri Hospital, Davangere (both these hospitals are attached to teaching institute, JJM Medical College, Davangere).

Selection of Study Subjects

Based on inclusion and exclusion criteria a total number of 80 subjects (40 cases and 40 controls) were selected for the present study.

Inclusion Criteria

Cases: It included 40 diagnosed cases of gestational hypertension in age group of 20-45 years. Women with gestational hypertension were selected on the bases of definitions given by National high blood pressure education program (NHBPEP 2000).^[11] Pregnant female of ≥ 20 weeks of gestation with blood pressure $\geq 140/90$ mm of Hg noted first time during pregnancy on ≥ 2 occasions at least 6 hours apart without proteinuria was considered as having gestational hypertension.

Controls: It included 40 age matched healthy pregnant women of ≥ 20 weeks of gestation without any major illness and who are not on any medication.

Exclusion Criteria

The women with history of chronic hypertension, renal diseases, diabetes mellitus, drugs intake, smoking, alcoholism, liver or cardiac diseases or any other major illness were excluded from the study.

Based on the inclusion and exclusion criteria, age matched cases and controls were included in the present study after obtaining informed consent. A proforma was used to record relevant information and patient's data.

Collection & Analysis of Urine Samples

The early morning first urine sample from all subjects was collected for the estimation of microalbumin. Approximately 10ml of urine was collected in a clean plastic container free from detergents and even traces of protein. Sample was tested within 24hrs of collection. If urine was turbid then it was centrifuged at 2000rpm for 10min, and clear supernatant was used for testing. Concentration of urinary microalbumin was analyzed by turbidimetric Immunoassay kit from AGAPEE Company in semi-autoanalyzer (CHEM-5 Plus V₂, Erba Mannheim).

Statistical Analysis

Values were calculated as Mean $\pm$ SD and the statistical analysis was done using SPSS 17.0 software. Student's unpaired t-test was used for comparison between two groups. Pearson's correlation coefficient was used to see the correlation of systolic & diastolic blood pressure with microalbuminuria. The p-value of less than 0.05 was considered as statistically significant.

Results

As shown in Table-1, significantly elevated levels of urine microalbumin were noted in women with PIH when compared with normal healthy pregnant women ($p < 0.001$). The mean systolic BP was elevated by 27% and the mean diastolic BP was elevated by 26% in cases over the mean systolic and diastolic BP in controls. This elevation was statistically significant ($p < 0.001$). No significant difference was found in period of gestation (POG) and age of mother in both the study groups ($p > 0.05$).

Table-2 and figure-1 show that urine microalbumin concentration in subjects is significantly positively correlated with systolic & diastolic blood pressure of the study subjects ($p < 0.001$).

Table-1: Comparison of Parameters among Study Groups

Parameters	Gestational Hypertension (Cases) ^a	Normal Pregnant Women (Controls) ^a	t test (p-value) ^b
POG (weeks)	24.90 $\pm$ 2.17	24.75 $\pm$ 2.11	0.755
Age of mother (years)	22.88 $\pm$ 2.45	23.18 $\pm$ 2.5	0.589
Systolic BP (mm of Hg)	144.65 $\pm$ 11.38	113.5 $\pm$ 9.49	< 0.001**
Diastolic BP (mm of Hg)	95.95 $\pm$ 7.32	75.9 $\pm$ 5.22	< 0.001**
Urine Microalbumin (mg/L)	127.43 $\pm$ 37.75	24.93 $\pm$ 9.74	< 0.001**

^a Values are shown as Mean $\pm$ S.D. ^b p-value of unpaired student's t-test between cases and controls. POG – Period of Gestation; BP- Blood Pressure; ** Highly Significant

Table-2: Pearson's correlation of Systolic & Diastolic BP with Urine Microalbumin

	Pearson Correlation Coefficient (r)	p value
Systolic BP	+ 0.646**	< 0.001**
Diastolic BP	+ 0.502**	< 0.001**

** Highly Significant

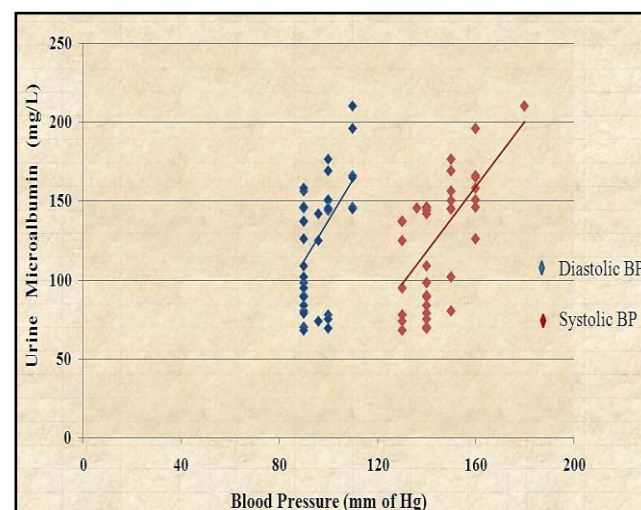


Figure-1: Correlation of Systolic & Diastolic Blood Pressure with Urine Microalbumin Levels in Cases

Discussion

In our study, subjects of case & control groups were matched for age of mother and period of gestation. There was no significant difference in mean age of mother and POG in both groups. Matching for POG & age of mother was done to

reduce the bias occurring due to physiological changes in different trimesters of pregnancy and age related factors.

In our study, we found increased excretion of albumin in urine in women with PIH when compared with normotensive healthy pregnant women. This finding is in accordance with the studies done by Zhang SJ and Li J et al.^[12,13] In a case-control study, Zhang SJ found that serum Beta 2 microglobulin level was also increased along with urine albumin in women with PIH when compared to normal healthy pregnant women.^[12] Li J et al noted increased urinary excretion of IgA & IgG along with increased excretion of albumin in urine.^[13]

In cohort studies done by Misiani R et al, Sirohiwal D et al and Bouton E et al concluded that increased urinary albumin excretion early in the gestation can be considered as a good predictor for occurrence of hypertensive disorders in normotensive pregnant women.^[14-16] Misiani R et al performed an additional urinary albumin measurement at 24 weeks postpartum. They found increased urinary albumin levels persisted long after blood pressure had returned to normal levels in women who developed PIH.^[14] This shows that some pathological changes in renal glomeruli tend to persist for a long time.

Bouton E et al stated that there should not be any microalbuminuria in normal pregnancy. If microalbuminuria develops during course of pregnancy, it should be considered as an important risk factor for development of HDP.^[16]

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 HDP with the sensitivity, specificity, positive and negative predictive values of 88.9%, 67.9%, 22.2% and 98.3% respectively.^[17] Lara González AL and co-workers also found microalbuminuria as a sensitive predictor and risk factor for HDP but of low positive predictive value.^[18]

Glasscock R suggested that microalbuminuria should be considered as a manifestation of a diffuse endothelial injury and thereby ongoing

collateral kidney damage.^[19] Due to glomerular endotheliosis, there may be increased leakiness of the glomerular filtration membrane and also there is reduced renal blood flow and tubular function. All these factor leads to increased filtration and reduced reabsorption of smaller plasma protein such as albumin leading to microalbuminuria initially. If the damage continues to progress, it may land up in gross proteinuria. Therefore, presence of microalbuminuria should be taken as a signal for impending serious renal damage. Microalbuminuria can be found long before the manifestations such as edema, hypertension, renal failure etc. sets in.

We found significant positive correlation of urine microalbumin level with systolic & diastolic blood pressure. This indirectly indicates that amount of albumin excretion in urine can correlate with the disease severity.

Nisell H et al followed up women with HDP for 7 years and looked for occurrence of chronic hypertension and renal dysfunction. They noted that women with a history of pregnancy induced hypertension or preeclampsia had an increased risk for development of chronic hypertension and microalbuminuria at follow up for 7 years.^[20]

Thus, there is a presence of microalbuminuria in women with PIH. Amount of albumin excretion may give a clue of severity of renal damage and disease progression.

Limitation and Future Scope of Study

In this case-control study, we had taken cases that were already diagnosed for having PIH. A prospective study can be done taking normotensive pregnant women as cohort and women with microalbuminuria can be followed up for the outcome of the pregnancy and development of cardiovascular & renal diseases in later life.

Conclusion

Presence of microalbuminuria early in the gestation can be useful for detection of ongoing renal damage in women with PIH. 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.

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