Renal functions in pregnancy induced hypertension, preeclampsia, and eclampsia

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Abstract

Background and Objective: A Hypertensive disorder of pregnancy is an important cause of maternal mortality and Eclamptic conditions including renal dysfunctions. The present study is aimed at evaluating and comparing the urinary protein, creatinine and their ratio during Pregnancy Induced Hypertension, Preeclampsia and Eclampsia.

Materials and Methods: Defined groups of Pregnancy Induced Hypertension, Pre-eclampsia and eclampsia patients were selected with written informed consent with fifty subjects in each group. The urine was collected and used for the estimation the urinary protein, creatinine and their ratio in normal and experimental groups. The data were expressed as Mean ± SD. Comparison between patients and controls was performed using unpaired’ test. P value less than 0.05 was considered significant.

Results: The mean SBP and DBP was significantly higher (p<0.001) in all the experimental groups as compared to normal subjects. The mean urinary protein and creatinine in PIH cases, Preeclampsia and Eclampsia was significantly higher (p<0.001) as compared to normal group. The protein creatinine ratio was also significantly higher (p<0.001) in all the experimental groups as compared to normal subjects.

Conclusion: The significant elevation in urinary protein, creatinine and their ratio in the present study suggesting the fact that, the anti-angiogenic factors emanating from the placenta in PIH, Preeclampsia and Eclampsia contribute to glomerular endotheliosis, proteinuria, and hypertension.

Keywords: Pregnancy Induced Hypertension, Pre-eclampsia, Eclampsia, Urinary Protein, Creatinine and Urinary Protein/ Creatinine ratio.

1. Introduction

Hypertensive disorders of pregnancy is an important cause of maternal mortality and morality and preeclampsia accounts for more than 40% of iatrogenic premature deliveries. Despite the high cost to families and health service resources, there is no effective management strategy other than elective deliveries and no therapeutic interventions have been proven to prevent or delay the onset of this disease.

The effects of high blood pressure during pregnancy vary depending on the disorder and other factors. According to the National High Blood Pressure Education Program (NHBPEP), preeclampsias do not in general increase a woman's risk for developing chronic hypertension or other heart-related problems. The NHBPEP also reports that in women with normal blood pressure who develop preeclampsia after the 20th week of their first pregnancy, short-term complications--including increased blood pressure--usually go away within about 6 weeks after delivery.

Some women, however, may be more likely to develop high blood pressure or other heart disease later in life. Even
though high blood pressure and related disorders during pregnancy can be serious, most women with high blood pressure and those who develop preeclampsia have successful pregnancies. Preeclampsia is a condition that typically starts after the 20th week of pregnancy and is related to increased blood pressure and protein in the mother's urine as a result of kidney problems. Preeclampsia affects the placenta, and it can affect the mother's kidney, liver, and brain. When preeclampsia causes seizures, the condition is known as eclampsia—the second leading cause of maternal death in the U.S.² Preeclampsia is also a leading cause of foetal complications, which include low birth weight, premature birth, and stillbirth. There is no proven way to prevent preeclampsia. Most women who develop signs of preeclampsia, however, are closely monitored to lessen or avoid related problems. Hence, obtaining early and regular prenatal care is one of the most important aspects.

Systemic vascular resistance is reduced in pregnancy. Instead of a 40% increase in cardiac output during the second trimester, blood pressure falls (usually to 100/70mmHg or lower). Vasodilatations in uterine, renal and cutaneous beds, vasodilator prostaglandins released from the uteroplacental unit and a decrease in arteriolar sensitivity to angiotensin II all play a role in the decline of blood pressure during pregnancy. Although a modest rise may occur during the last month of normal pregnancy, an increase in systolic pressure of 30mmHg or in a diastolic pressure of 15mmHg at any time during gestation is abnormal.³,⁶

The minimum criteria for the diagnosis of preeclampsia are hypertension plus minimal proteinuria. The more severe the hypertension or proteinuria, the more certain is the diagnosis of preeclampsia. Similarly abnormal laboratory findings in tests of renal, hepatic and haematological functions increase the certainty of preeclampsia. Persistent premonitory symptoms of eclampsia such as headache, epigastric pain, nausea and vomiting also increase the certainty of preeclampsia.

Proteinuria is an important sign of preeclampsia, and Chesley (1985) rightfully concluded that the diagnosis is questionable in its absence.⁷ Proteinuria is described as a 300mg or more of urinary protein per 24 hours or persistent 30mg/dl (1+dipstick) in random urine samples. Perinatal mortality increases with blood pressure levels that would be normal in non-pregnant women. For example, when mean arterial blood pressure (Diastolic +1/3 pulse pressure) is 90mmHg or higher during the second trimester, there is a greater risk for still birth fetal growth retardation and preeclampsia.⁸

Preeclampsia is a pregnancy specific syndrome of reduced organ perfusion secondary to vasospasm and endothelial activation.⁹ It is associated with hepatic, neurological, haematological and renal involvement. Rapid development of edema, particularly of the face and hands, along with a rise in blood pressure, often signals the onset of this condition. Jaundice and abnormal liver functions may be present.¹⁰ Therefore, renal functions during normal and complicated pregnancy are necessary. Hence, in the present study, the renal functions in pregnancy induced hypertension, preeclampsia, and eclampsia was studied.

2. Materials and Methods

The patients for the present study were obtained from the outpatient ward and eclampsia room in the institute of Maternal and Child Health, Medical College, Calicut. The study was approved by institutional ethics committee. Defined groups of pregnancy induced hypertension; Pre-eclampsia and eclampsia were selected with prior written informed consent.

The total study group was divided into Normal Pregnancy (3rd trimester), PIH, Pre-eclampsia and Eclampsia with fifty subjects in each group. Blood samples were collected by venous puncture using disposable syringes and needles and transferred into clear dry centrifugation at 3000 rpm for 15 minutes. For the assessment of renal function in pregnant women instead of a 24 hr urine collection to determine creatinine clearance and proteinuria, protein creatinine ratio of a single random urine sample can be taken as a simpler method.

Qualitative urinary protein estimation was done on spot urine specimen by dipstick which was graded from negative to 4+ve. Quantitative measurement of protein in the urine was carried out by a method based on the formation of a red complex of protein with pyrogallol red in acid medium on Micro lab 200 (Merck, Germany). Estimation of creatinine was done on Selectra -2 (Merck, Germany) by Jaffe's reaction. In this reaction creatinine reacts with alkaline picrate forming a red complex. Coefficient of variation of creatinine and urinary protein assay were 4.5 and 3.2%. In modified Jaffe's method¹¹ creatinine forms a orange-red colored complex in an alkaline picate solution. The difference in absorbance at fixed times during conversion is proportional to the concentration of creatinine in the sample. Mixed well and incubated for 30 seconds at 370C, then read the absorbance A1. After exactly 60 sec. further absorbance A2 was read at 505 nm.

3. Result

In the present study, the incidence of eclampsia is found to be associated with diastolic Blood pressure (Table-1).
The mean diastolic Blood pressure in the eclampsia cases was 107 mmHg. Similarly, in preeclampsia and PIH also the mean diastolic Blood pressure was significantly higher (p<0.001) than the mean diastolic Blood pressure in normal group. The mean Systolic Blood pressure was also significantly higher (p<0.001) in all the experimental groups as compared to normal subjects.

### Table-1: Comparison of Systolic and Diastolic Blood Pressure between normal and Pregnancy Induced Hypertension, Preeclampsia, And Eclampsia. N=50 in each group.

| Groups       | SBP     |   | DBP     |   |
|--------------|---------|---|---------|---|
|              | Mean    | S.D  | Mean    | S.D |
| NORMAL       | 95      | 4.72 | 70.27   | 0.11|
| PIH          | 137.2   | 4.72 | 91.67   | 3.33|
| PREECLAMPSIA | 145.15  | 6.18 | 100.85  | 5.16|
| ECLAMPSIA    | 157.50  | 7.16 | 107.0   | 8.12|
| P-Value      | 0       | 0   | 0       | 0   |

The mean urinary protein and creatinine in PIH cases was significantly higher (p<0.001) as compared to normal group (Table-2). The protein creatinine ratio was also significantly higher (p<0.001) in PIH as compared to normal subjects. The mean urinary protein and creatinine in preeclampsia cases was significantly higher (p<0.001) as compared to normal group (Table-3). The protein creatinine ratio was also significantly higher (p<0.001) in preeclampsia as compared to normal subjects.

The mean urinary protein and creatinine in Eclampsia cases was significantly higher (p<0.001) as compared to normal group (Table-3). The protein creatinine ratio was also significantly higher (p<0.001) in Eclampsia as compared to normal subjects.

### Table-2: Comparison of Total Protein, Creatinine and its ratio between normal and Pregnancy Induced Hypertension. N=50 in each group.

| Groups       | Normal     |   | PIH         |   | P value |
|--------------|------------|---|-------------|---|---------|
|              | Mean       | S.D  | Mean       | S.D |         |
| Urinary Protein (mg/L) | 144.07     | 42.12 | 877.02     | 99.32 | <0.001 |
| Creatinine (mg/L)    | 1256.68    | 99.34 | 1163.12    | 93.98 | <0.001 |
| Pr/ Cr ratio (%)     | 0.126      | 0.02  | 0.79       | 0.02  | <0.001 |

### Table-3: Comparison of Total Protein, Creatinine and its ratio between normal and Pre-eclampsia patients. N=50 in each group.

| Groups       | Normal     |   | PRE-ECLAMPSIA |   | P value |
|--------------|------------|---|---------------|---|---------|
|              | Mean       | S.D  | Mean         | S.D |         |
| Urinary Protein (mg/L) | 144.07     | 42.12 | 1458.74      | 97.96 | <0.001 |
| Creatinine (mg/L)    | 1256.68    | 99.34 | 881.34       | 78.52 | <0.001 |
| Pr/ Cr ratio (%)     | 0.126      | 0.02  | 1.779        | 0.13  | <0.001 |

### Table-4: Comparison of Total Protein, Creatinine and its ratio between normal and Eclampsia patients. N=50 in each group.

| Groups       | Normal     |   | ECLAMPSIA    |   | P value |
|--------------|------------|---|--------------|---|---------|
|              | Mean       | S.D  | Mean         | S.D |         |
| Urinary Protein (mg/L) | 144.07     | 42.12 | 2227.71      | 89.81 | <0.001 |
| Creatinine (mg/L)    | 1256.68    | 99.34 | 937.57       | 95.34 | <0.001 |
| Pr/ Cr ratio (%)     | 0.126      | 0.02  | 2.34         | 0.98  | <0.001 |
4. Discussion

Renal function is reset at a higher level during normal pregnancy. Renal plasma flow and glomerular filtration rate both increase by 30 to 50%. Therefore serum creatinine levels above 70umol/L (0.8mg/dl) or blood urea nitrogen levels above 4-6mmol/L (13mg/dL) are abnormal in pregnant women and should be investigated.12

Proteinuria indicates renal involvement and is one of the hallmarks of preeclampsia. Since the glomerular filtration rate increases by about 50% in normal gestation, a reduction in glomerular filtration rate heralds the onset of preeclampsia. Indeed a blood urea nitrogen of 6.4mmol/L (18mg/dl) or creatinine level of 90 µmol/L(1mg/dL) during pregnancy may reflect a 50% decline in glomerular filtration rate in preeclampsia, urate clearance decreases, because of increased proximal tubular reabsorption of urate, which in turn is probably due to the reduction of vascular volume. Hyperuricemia usually precedes the rise in serum creatinine and blood urea nitrogen; infect plasma uric acid level above 270umol/L (4.5mg/dl) in hypertensive women suggests preeclampsia.13 In pure preeclampsia (i.e., not superimposed on previously existing hypertensive renal disease) the primary sites of pathology are the glomerular endothelial cells. These cells show marked swelling due to an increase in cytoplasm volume with vacuolization (endotheliosis) and encroach on the vascular lumen rendering the enlarged glomeruli ischemic. For the assessment of renal function in pregnant women instead of a 24 hr urine collection to determine creatinine clearance and proteinuria, protein creatinine ratio of a single random urine sample can be taken as a simpler method. A rise in the ratio of urinary albumin to creatinine may demonstrate impaired glomerular permeability.14 The literature says this ratio method is accurate and avoids 24hr urine collections. It has been proved by various investigators like Ginsberg et al15, Allen B Shaw et al16, Robert M et al17, Ramos JG et al18 that this ratio method is equally significant.

When blood pressure rises appreciably during latter half of pregnancy, it is dangerous (especially to the foetus)-not to take action simply because proteinuria has not yet developed.

The diagnosis of gestational hypertension is made in women whose blood pressure reaches 140/90mm Hg or greater for the first time during pregnancy, but in whom proteinuria has not developed Gestational hypertensions termed transient hypertension if preeclampsia does not develop and the blood pressure has returned to normal by 12 weeks postpartum. In this classification the final diagnosis that the woman does not have preeclampsia is made only postpartum. Thus gestational hypertension is a diagnosis of exclusion. Importantly however, women with gestational hypertension may develop other signs associated with preeclampsia.19

In the present study, the urine protein creatinine ratios in random urine samples were calculated in all the four groups. Comparison of protein creatinine ratio in PIH, preeclampsia and eclampsia with normal was in agreement with the previous studies. There was a significant increase in this ratio in the three groups compared to the control.

The determination of protein creatinine ratio in random urine specimens may be a simple method for quantitation of proteinuria in hypertensive disorders of pregnancy. Random protein creatinine ratio can be used to assess the severity of renal in hypertensive in hypertensive disorders.20 Renal injury in preeclampsia may also be due to oxidative stress.

Glomerular filtration rate and renal plasma flow increase by 40 to 65 and 50 to 85%, respectively, during normal pregnancy in women. Studies using the gravid rat as a model have greatly enhanced our understanding of mechanisms underlying these remarkable changes in the renal circulation during gestation. Hyper filtration is largely due to increased renal plasma flow, the latter attributable to profound reductions in both the renal afferent and efferent arteriolar resistances. The ovarian hormone, relaxin, mediates renal vasodilatation during pregnancy. Relaxin increases vascular gelatinase activity, thereby converting big ET to ET(1-32), which leads to renal vasodilatation, hyper filtration and reduced myogenic reactivity of small renal arteries via the endothelial ET(B) receptor and nitric oxide. Serum concentration of uric acid falls during normal pregnancy as a consequence of increased GFR and/or reduced proximal tubular reabsorption.21 The elevated urinary excretion of protein during pregnancy is secondary to increased GFR, reduced proximal tubular reabsorption, and perhaps alteration in the electrostatic charge of the glomerular filter. In most women with preeclampsia, renal plasma flow and glomerular filtration rate are at most only modestly decreased as a consequence of increased afferent arteriolar resistance and/or reduced ultrafiltration coefficient. Serum uric acid concentrations are increased mainly as a consequence of reduced renal clearance. Reduced GFR leads to decreased filtered load of uric acid, and plasma volume contraction contributes to increased proximal tubular reabsorption coupled to sodium. The increase in urinary protein excretion in preeclampsia occurs secondary to alterations in the size and/or charge selectivity of the glomerular filter, possible increases in glomerular capillary pressure, and compromise of proximal tubular reabsorption. The renal histological lesion characteristic of preeclampsia is termed glomerular endotheliosis.

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5. Conclusion

The significant elevation in urinary protein, creatinine and their ratio in the present study suggesting the fact that, the anti-angiogenic factors emanating from the placenta in PIH, Preeclampsia and Eclampsia contribute to glomerular endotheliosis, proteinuria, and hypertension.

References

1. Mark A. Zamorski, M.D., M.H.S.A., And Lee A. Green, M.D., M.P.H., Nhbp ep Report on High Blood Pressure in Pregnancy: A Summary for Family Physicians. Am Fam Physician. 2001 Jul 15; 64(2):263-271.
2. Camille E. Powe, Richard J. Levine, S. Ananthakarunamachi. Preeclampsia, a Disease of the Maternal Endothelium. The Role of Antiangiogenic Factors and Implications for Later Cardiovascular Disease. Circulation. 2011; 123: 2856-2869.
3. Fauci, Braunwald, Isselbacher, Wilson, Martin, Kasper, Hasuer, Longo. Harrison’s principles of internal medicine. 14th edn. Pages 25, 1561.
4. Fitzgerald DJ, Entman SS, Mully K, Fitzgerald GA. Decreased prostacyclin biosynthesei preceding the clinical manifestation of pregnancy-induced hypertension. Circulation 1987; 75: 956.
5. Fitzgerald DJ. Rocki W. Murray R, Mayo G, Fitzgerald GA. ThromtoxaneA\textsubscript{2} synthesis in pregnancy-induced hypertension. Lancet 1990; 335: 751.
6. Friedman SA, Lindheimer MD. Prediction and differential diagnosis. Chesley’s hypertensive disorders in pregnancy 2nd edn. CT, Appleton & Lange. 1999; P.201.
7. Chesley LC. Diagnosis of preeclampsia. Obstet Gynecol 1985: 65; 423.
8. Ginsberg JM, Chang B, Marrarese R, Garella S. Use of single voided urine samples to estimate Quantitative proteinuria. N Engl J Med 1983; 309:1543-6.
9. Gratacos E, Casals E, Deulofeu R, Carach V, Alonso PL, Forurty A Lipid peroxide and vitamin E patients in pregnant women with different types of hypertension in pregnancy. Am J Obstet Gynecol 1998; 178:1072-6.
10. Greer IA, Leask R, Hodson BA, Dawes J, Kilpatrick DC, Liston WA, Endothelin, elastase, and endothelial dysfunction in preeclampsia. Lancet 1991; 337:228.
11. Thomas L. Clinical Laboratory Diagnostics. 1st edition, Frankfurt: TH-Books, 1998.
12. Huble CA Oxidative stress in pathogenesis of preeclampsia. Proc. Soc Exp Biol Med 1999; 222: 222-235.
13. Hego E Aebi. Catalase estimation. Bergmeyer H. V edn. Metros of enzymatic analysis 2nd Edn Vol.III. verlag chemic werietin 1974;673-684.
14. Igarro LJ. Biological actions and properties of endothelium-derived nitric oxide formed and released from artery and vein. Cric Res 1989; 65:1.
15. Ginsberg JM, Chang B, Marrarese R, Garella S. Use of single voided urine samples to estimate Quantitative proteinuria. N Engl J Med 1983, 309:1543-6.
16. Allen B Shaw, Paul R, Judith D Lewis- Jackson. Protein creatinine index and Albustix in assessment of proteinuria. Br. M. J 1983 Oct; 287: 929-32.
17. Robert M, Sepandi F, Liston RM, Dooley KC. Random protein-creatinine ratio for the quantitation of proteinuria in pregnancy. Obstet Gynecol 1997 Dec; 90(6): 893-5.
18. Ramos JG, Marthins-Costa SH, Mathias MM, Guerin YL, Barros EG Urinary protein/creatinine ratio in hypertensive pregnant women. Hypertens Pregnancy. 1999; 18(3): 209-18.
19. Rodrigueze- Thompson DR, Lieberman ES. Use of a random urinary protein-to-creatinine ratio for the diagnosis of significant proteinuria during pregnancy. Am J Obstet Gynecol 2001; 185: 808-11.
20. Shaarawy M, Aref A, Salem ME, Sheiba M. Radical-scavenging antioxidants in pre-eclampsia and eclampsia. Int J Gynaecol Obstet 1998 Feb; 60(2):123-8.
21. Sibai BM. Prevention of preeclampsia: a big disappointment. Am J Obstet Gynecol 1998; 179: 1275-78.