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EVALUATION OF GLOMERULAR FUNCTION IN WOMEN WITH PREECLAMPSIA.

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ABSTRACT

Introduction: Preeclampsia is defined as elevation of BP ≥140/90 mm of Hg after 20 weeks of gestation and proteinuria of ≥300mg/24hours or ≥1+ by dipstick method in a random urine sample. Preeclampsia causes widespread endothelial dysfunction leading to hypertension. It is associated with high occurrence of damage to kidney glomeruli. Damage to kidney may lead to elevated serum creatinine levels & reduced Glomerular Filtration Rate (GFR) which can be used for evaluation of glomerular function. **Objectives:** To compare and to evaluate role of serum creatinine level & GFR among women with preeclampsia & normal pregnancy. **Materials and methods:** Case control study was done taking 35 women with preeclampsia as cases and 35 women with normal pregnancy as controls. Serum creatinine was measured using Jaffe's Kinetic method. GFR was calculated using Cockcroft-Gault formula & MDRD formula. Statistical analysis was done using SPSS 17.0. **Results:** Serum creatinine was significantly increased in cases when compared with controls ($p<0.001$). GFR was significantly low in cases when compared with controls ($p<0.001$). **Conclusions:** Presence of glomerular damage leads to elevated serum creatinine & reduced GFR. GFR gradually decreases as the disease

severity increases. Regular monitoring of GFR in women with preeclampsia may give a clue of associated kidney damage.

KEYWORDS: *Cockcroft-Gault formula, glomerular filtratition rate, MDRD formula, preeclampsia, serum creatinine.*

Evaluation of glomerular function in women with preeclampsia.

INTRODUCTION

Definition of preeclampsia was given by working group of National High Blood Pressure Education Programme (NHBPEP 2000). Preeclampsia is defined as elevation of BP ≥140/90 mm of Hg after 20 weeks of gestation and proteinuria of ≥300mg/24hours or ≥1+ by dipstick method in a random urine sample.[1]

Preeclampsia and their complications are one of the major causes of maternal mortality and morbidity in the world.[2] Its incidence is approximately 6-8% of all pregnancies and 10% of first pregnancies. It is even more common in women with a history of chronic hypertension.[3] An estimated 50,000 women die annually from preeclampsia world-wide. It contributes to death of a woman every 3 minutes world-wide.[4] Presence of preeclampsia in mother is strongly associated with fetal growth retardation and prematurity. These are one of the major causes of perinatal mortality and morbidity.[5]

Impaired invasion of trophoblast leads to narrowing of uterine spiral arterioles in placenta. This is implicated as a causal factor in pathogenesis of the disease.[6] Placental ischemia caused by narrowing of uterine spiral arterioles leads to alteration in expression of various factors affecting the endothelial function. Reduced expression of vascular endothelial growth factor (VEGF), placental growth factor (PlGF), prostacyclin (PGI_2), nitric oxide (NO) from vascular endothelium and increased expression of antiangiogenic factors such as tumour necrosis factor-α (TNFα), interleukins (ILs), soluble Fms like tyrosine kinase 1 (sFlt 1), etc causes scenario of angiogenic imbalance. This angiogenic imbalance is a causative factor for spreading of endothelial dysfunction all over the body.[7,8]

These circulating antiangiogenic substances deprive the glomerular endothelium of essential growth factors & lead to glomerular injury. A distinctive glomerular appearance known as "Glomerular endotheliosis" is seen in microscopic study of preeclamptic kidney. The glomeruli seem enlarged and solidified due to narrowed or occluded capillary lumen as a

result of swelling of the endothelial cells and mesangial cells surrounding them. These changes lead to compromise of glomerular function & decline of GFR.[9] It is seen that serum creatinine & BUN level are often normal in patients with preeclampsia despite significant decrease in GFR.[10]

This study was undertaken to evaluate glomerular function in women with preeclampsia & compare it with normal pregnant women.

MATERIALS & METHOD

A cross sectional study was conducted taking women with preeclampsia as cases and healthy pregnant women as controls. The study cases & controls were selected from Bapuji Hospital and Chigateri Hospital, Davangere (both these hospitals are attached to teaching institute, J.J.M. Medical College, Davangere). Each participant gave an informed consent and this study was approved by the ethical and research committee of J.J.M. Medical College, Davangere to use human subjects in the research study. A proforma was used to record relevant information and patient's data.

Cases- It included 35 diagnosed cases of preeclampsia in age group of 20-45 years.
Pregnant female of ≥20 weeks of gestation with blood pressure ≥140/90 mm of Hg noted first time during pregnancy on ≥2 occasions at least 6 hours apart with proteinuria of ≥1+ (≥30mg/dl) by dipstick method in a random urine sample was considered as having preeclampsia.[1]

Controls- It included 35 age & gestational period 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, diabetes mellitus, drugs intake, smoking, alcoholism, liver, cardiac or renal diseases or any other major illness were excluded from the study. Women with molar pregnancy, twins or multiple fetuses were also excluded from the study.

Collection & analysis of serum samples

About 3 ml of blood was drawn under aseptic precautions from selected subjects in a plain vial for serum. Serum was separated by centrifugation and used for estimation of serum levels of creatinine. Concentration of serum creatinine was analyzed by kit based on Jaffe's

method [11] from ERBA Diagnostics Mannheim GmbH in semi-autoanaylzer (CHEM-5 Plus V_2, Erba Mannheim). Creatinine clearance (CCr) and calculated GFR (eGFR) was calculated using Cockcroft-Gault's (CG) formula and Modification of Diet in Renal Diseases study (MDRD) formula respectively.

As per CG formula, CCr = {140-age x body weight (kg)} / {72 x serum creatinine (mg/dl)}. The final value should be multiplied by 0.85 for females.[12]

As per MDRD formula, eGFR = 186 x $(SCr)^{-1.154}$ x $(age)^{-0.203}$. The final value should be multiplied by 0.742 for females and 1.21 for African American patients.[13]

Values were calculated as mean±SD and the statistical analysis was done using SPSS 17.0 software. Student's unpaired t-test was used for comparison between two groups. The p-value of less than 0.05 was considered as statistically significant.

RESULTS

Table-1 shows that the mean value of calculated GFR was significantly lower in cases when compared with controls ($p<0.001$). The mean levels of serum creatinine were significantly higher in cases when compared with controls ($p<0.001$). No significant difference was found in period of gestation and age of mother in all the study groups.

Table 1: comparison of parameters among cases & controls.

	Controls (Mean±S.D.)	Cases (Mean±S.D.)	p value of unpaired student's t test
Period of Gestation (Weeks)	34.36 ± 1.69	34.03 ± 3.46	0.57
Age (years)	23.51 ± 2.68	23.77 ± 2.55	0.68
Serum Creatinine (mg/dL)	0.61 ± 0.12	0.82 ± 0.16	< 0.001
CCr as per CG formula (mL/min/1.73m^2)	135.06 ± 29.30	103.35 ± 20.59	< 0.001
eGFR as per MDRD formula (mL/min/1.73m^2)	125.56± 31.37	89.45 ± 21.09	< 0.001

DISCUSSION

Hypertensive disorders of pregnancy are known since ancient time.[14] Preeclampsia affects virtually in all organ systems, most notably the renal, cardiovascular, brain, hematologic and immunologic systems. These disorders are associated with increased mortality and morbidity both in mother as well as in fetus.[1,15]

This study was done to compare changes in glomerular function in preeclampsia & in normal pregnancy. Age is one of the major factors affecting GFR [16], therefore age matched cases & controls are selected to remove the bias. GFR increases along with advancement of pregnancy [17], therefore cases & controls are also matched for period of gestation.

In our study, serum creatinine levels were significantly higher in cases when compared with controls. The findings are in accordance with Manjareeka M et al[18] & Bernheim J et al[19]. Mean serum creatinine levels in both the groups are within normal range. Sonagra AD et al reported that GFR may be significantly lower in some patients evenif serum creatinine is within normal limits. In order to detect such cases, GFR should be estimated.[20]

Direct measurement of GFR can be done by clearance of exogenously administered markers such as inulin, iohexol, iothalmate, Cr51-EDTA etc. But these procedures are costly so they cannot be prescribed frequently for the regular follow up. Creatinine or urea clearance can also give idea about actual GFR but it requires timely collected urine specimen which makes these methods cumbersome. Cockcroft-Gault's formula and Modification of Diet in Renal Diseases study (MDRD) formula can overcome these limitations. They are used to find creatinine clearance (CCr) and calculated GFR (eGFR) from serum creatinine value & patient's anthropometric details.[21]

In our study, CCr & eGFR were significantly lower in preeclamptics when compared with normal pregnant women. Such decline in GFR can be attributed to renal damage caused by preeclampsia. Glomerular endotheliosis leads to impairment of permeability of glomerular capillary walls. This is likely to be the predominant cause of hypofiltration in preeclampsia.[22] There is also reduction in renal plasma flow & presence of proteinuria in preeclampsia which also suggest severe damaging tendency of this disease.[23]

Untreated preeclampsia can lead to severe deterioration of renal function & progress to acute renal failure. Such cases may require admission to intensive care unit (ICU) and dialysis support to sustain life. In such severe cases, maternal as well as fetal mortality & morbidity drastically increases.[24] Regular follow up and work up can ensure early diagnosis of the disease and assessment of ongoing organ damage. Timely therapeutic intervention can reduce amount of renal and other organ damage.[25]

Recent studies have shown that women with preeclamptic pregnancy are at higher risk of developing end stage renal disease in later age.[26] Such women are also prone to develop chronic hypertension, diabetes mellitus, ischemic heart disease, cerebrovascular disease, thromboembolism, hypothyroidism, and even impaired memory in later life.[27]

CONCLUSION

Preeclampsia leads to severe glomerular injury associated with elevated serum creatinine & decline in GFR. Regular evaluation of GFR can give idea about ongoing renal damage. Timely diagnosis, assessment & treatment can reduce the complications related to disease.

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