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Research Paper

Evaluation of the diagnostic importance of serum, urinary Creatinine and Calcium in early detection of pre-eclampsia

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***Aim**: To evaluate the diagnostic importance of serum, urinary Creatinine and Calcium in early detection of pre-eclampsia.*
***Material and method**: Pregnant females diagnosed for pre-eclampsia visiting the Out-patient Department of Obstetrics and Gynecology of Mahatma Gandhi Medical College & Hospital fulfilling the inclusion criteria were enrolled for the study. Age matched normotensive pregnant females contributed the control group. The study was conducted for healthy females for approval from the Institutional ethics committee (IEC) vide letter no. MGMCH/IEC/JPR/2017/309 dated 6/04/2017. Written and informed consent was obtained from all participants before enrollment for the study.100 females were considered for the diagnosed for PE.100 healthy individuals of the same age were considered as controls. Blood samples after overnight fasting were collected by standard aseptic techniques.*
***Results**: Mean serum calcium levels in control group which is 9.05±0.90mg/dl while in subject group is 7.74±1.19mg/dl. Mean urinary calcium levels in control and case group was 9.15±3.44 and 7.99±1.94 respectively with statistically significant difference. Mean urinary creatinine levels in control and case group was 135.71±15.52 and 216.21±61.95 respectively with statistically significant difference. Statistical analysis showed that both group was CCR ≤ 0.4 and CCR > 0.4 with chi-square test 34.949 and P- value is <0.01.*
***Conclusion**: The study suggests inclusion of urine CCR as a marker for screening of PE in pregnant females. Further, monitoring of serum calcium levels during antenatal period may be helpful in minimizing the risk of development of PE.*
***Keywords**: Pre-eclampsia, creatinine, calcium*

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I. INTRODUCTION:

Two important complications of pregnancy are Hypertension and proteinuria. The hypertensive disorders of pregnancy such as pre-eclampsia (PE) and pregnancy induced hypertension (PIH) are a major cause of maternal morbidity. It estimates about 2-8% pregnancies and PE occurs in 2-5% of pregnancies. In developing countries, maternal mortality rate varies from 4-40 per 1 lakh live births in cases of eclampsia. [2] The clinical findings of PE can manifest as either a maternal syndrome (hypertension and proteinuria with or without other multi-organ involvement) or fetal syndrome (fetal growth restriction, abnormal umbilical artery Doppler findings and reduced placental growth with infarctions). Despite advances in perinatal care, the incidence of gestational hypertension (GH)--PE has not been changed. [3]

In India about 20-30% pregnancies belong to high risk category. High risk pregnancy contributes to 80% of maternal mortality due to severe bleeding/ hemorrhage (25%), infections (15%), unsafe abortions (13%), eclampsia (12%), obstructed labour (8%) & other direct causes. Indirect causes such as malaria, HIV/AIDS and cardiovascular diseases account for 20%. [4]

Women with severe PE may have sign and symptoms such as renal insufficiency, reduced urinary volume, raised serum creatinine Cr, liver disease (upper abdominal pain, elevated liver enzymes), neurological disturbances (headache, visual disturbances, exaggerated tendon reflexes, convulsions), hematological disturbances (thrombocytopenia, disseminated intravascular coagulation, hemolysis). Therefore, it's a disorder of the second half of pregnancy which regresses after delivery. [5] Reducing maternal mortality by 75% between 1990 and 2015 has been considered as a part of the millennium development goals of the WHO Nations.

Due to absence of epidemiological information in many low and middle income countries, the exact prevalence of PE and associated morbidity and mortality from low and middle income countries is unknown. [6] Various laboratory parameters including serum creatinine, urinary creatinine, serum calcium (Ca+2), urinary calcium and renal biopsy have been suggested as markers of PE.

Plasma Creatinine and urea concentration decrease during pregnancy and in eases in 24 hrcreatinine clearance (paralleling the increase in GFR) becomes apparent 4weeks after conception. Maximum increase in creatinine clearance occurs at 9-11weeks after conception. The present study was planned to evaluate the serum Ca+2, serum Creatinine, urinary Ca+2 and urinary Creatinine levels in normotensive and PE females. The results may help in the better management of patients with PIH.

II. MATERIAL AND METHOD:

Pregnant females diagnosed for pre-eclampsia visiting the Out-patient Department of Obstetrics and Gynecology of Mahatma Gandhi Medical College & Hospital fulfilling the inclusion criteria were enrolled for the study. Age matched normotensive pregnant females contributed the control group. The study was conducted for healthy females for approval from the Institutional ethics committee (IEC) vide letter no. **MGMCH/IEC/JPR/2017/309 dated 6/04/2017**. Written and informed consent was obtained from all participants before enrollment for the study. The patients diagnosed with PE based on urine analysis and B.P recording in the second and third trimesters was included. In Mild PE, B.P of at least 140/90mm Hg measured on two occasions each 6 hours apart, proteinuria of at least 300mg per 24 hours or at least 1+ on dipstick testing. In severe PE, B.P of at least 160/110mmHg measured on two occasions 6 hours apart, proteinuria of at least 5g per 24 hours or at least 3+ on dipstick testing. Women with multiple gestations and chronic hypertension, mixed parity (nulliparous and multiparous women), bad obstetric history and recurrent abortions and thyroid disorders were excluded from the study.

100 females were considered for the diagnosed for PE.100 healthy individuals of the same age were considered as controls. Blood samples after overnight fasting were collected by standard aseptic techniques. The samples collected were subjected to following investigations:

Sample was collected to analyses renal functional tests such as serum urea, serum creatinine, serum uric acid, serum calcium, urinary calcium and creatinine (Using Vitros 4600- Dry Chemistry Analyzer). No special patient preparation is necessary. Special Precautions Urine specimens must be pretreated prior to processing. Refer to "Specimen Pretreatment" for instructions.

Statistical analysis: Total 100 pregnant females diagnosed for PE and 100 normotensive pregnant females were enrolled for the study. Serum Ca^{+2}, serum Creatinine, urinary Ca^{+2} and Creatinine were compared between the PE and normotensive pregnant females by applying student's t-test. The results obtained were presented as mean ± SD. A P value ≤ 0.05 was considered as statistically significant.

III. RESULTS:

The mean age of control group is 25.65 ± 3.94 years while that of PE group is 26.44±3.58.Table 1 represents the mean serum calcium levels in control group which is 9.05±0.90mg/dl while in subject group is 7.74±1.19mg/dl. Statistical analysis showed that the mean serum calcium levels of subjects group were significantly lower than control group (P-value = <0.01). Mean urinary calcium levels in control and case group was 9.15±3.44 and 7.99±1.94 respectively with statistically significant difference.

Mean serum creatinine level in control group was 0.79 ± 0.24mg/dl and in subject group was 0.95 ± 0.25mg/dl. Mean urinary creatinine levels in control and case group was 135.71±15.52 and 216.21±61.95 respectively with statistically significant difference (table 2).

Table 3 represents the mean calcium: creatinine ratio in control group which is 0.07 ± 0.05 and in subject group is 0.04 ± 0.02. Statistical analysis showed that the mean calcium: creatinine ratio of subjects group were significantly lower than control group (P=<0.01).

Table 4 represents the comparison of CCR between control and subject groups using chi-square test. Statistical analysis showed that both group was CCR $\leq$ 0.4 and CCR > 0.4 with chi-square test 34.949 and P-value is <0.01.

IV. DISCUSSION:

Pregnancy refers to the fertilization and development of one or more offspring known as a fetus or embryo in a woman's uterus. Childbirth usually occurs about 38 weeks after conception. In women who have a menstrual cycle length of four weeks this is approximately 40 weeks from the start of the last normal menstrual period. [7] Hypertension complicates 10-15% of all pregnancies. Among them, 10-20% develops proteinuria. HDP and PIH are the common medical disorders in pregnancy. It has an adverse effect on both expectant mother and foetus. [8].

In this study, mean serum calcium levels in control group which is 9.05 ± 0.90mg/dl while in subject group is 7.74 ± 1.19mg/dl. In normal pregnancy there is physiological hypercalciuria due to an increased GFR, however the fall in Ca+2 excretions in PE females is independent of the glomerulopathy and altered filtration rate. The changes in urinary Ca+2 levels are thus basically a reflection of the alterations in the calcium homeostasis at the cellular level. Normotensive pregnant women and PE women exert distinct changes on cellular Ca+2 metabolism in normal VSMC. [9] According to Punthumapol C et al., 2008 [10] low serum Ca+2 levels may also increase B.P by stimulating parathyroid hormone and renin release which in turn increases intracellular Ca+2 in smooth muscles leading to vasoconstriction, increased vascular resistance and a rise in B.P in pre-eclamptic mother. Hovdenak et al., 2000 [11] has reported Ca+2 deficiency associated with PE and IUGR. It has also been reported that this effect is exaggerated in PE due to a significant increase in the membranous Ca+2 content. Vural et al., 2000 [12] reported that in PE alterations in renal function, electrolytes and water metabolism occurs and PE was associated with hypocalciuria but there was no correlation between parameters of renal function and Ca+2 or phosphate excretion.

Mean urinary calcium levels in control group which is 9.15 ± 3.44 and in subject group is 7.99 ± 1.94 in the present study. Similarly Sirohiwal et al., 2009 [13] reported that compared to normotensive women, the hypertensive women had significantly lower urinary Ca+2 excretion which tells the efficacy of measurement of 24 hour urinary protein and Ca+2 for the prediction of PE in second trimester. Dasgupta et al., 2008 [14] have reported the changes in Ca+2 excretion in PE, eclampsia and their role as a predictor and concluded that hypocalciuria was a good tool for prediction of hypertensive disorder of pregnancy which was independent of renal function.

Serum Creatinine levels are elevated in PE females with renal malfunction especially with the significant decrease in GFR. Vasodilation of the renal vessels in pregnancy causes 50–80% increase in plasma flow and change in GFR which further complicates the use of serum Creatinine as a marker of GFR in pregnancy. [15] In our study; mean serum creatinine levels in control group which is 0.79 ± 0.24mg/dl while in subject group is 0.95 ± 0.25mg/dl. According to Shah, DM et al., 2005 [16] Increase in serum Creatinine and reduction in creatinine clearance was observed in PE females these differences was significant as compared to normotensive pregnant women because PE is associated with a reduction in plasma rennin activity (PRA) and plasma rennin concentration (PRC).

In our study, mean calcium: creatinine ratio in control group which is 0.07 ± 0.05 and in subject group is 0.04 ± 0.02.In the study of Rodriguestz et al., 1988 [17] 83% patients with low CCR develops PE as compared to normotensive women. Ozcan et al., 1995 [18] who investigated the predictive value of decreasing CCR in a spot urine sample reported that it is an effective marker for PE. The mean level of Urinary CCR was significantly decreased in PE cases as compared to control group.

The present study suggests that during PE, urine output decreases which leads to low output of Ca+2 and Creatinine. As a result the urinary CCR decreases. CCR ≤ 0.04 can be considered as cut off of PE. The study recommends inclusion of estimation of urinary CCR for screening of pregnant females.

V. CONCLUSION:

PE is more commonly reported in primary pregnancy. Besides hypertension and proteinuria, PE is also characterized by decreased GFR with retention of salt and water by the kidneys, weight gain, development of oedema, compromised placenta perfusion, increased central nervous system irritability and ureters muscle stretch (ischemia). If unattended, PE may further lead to complications such as eclampsia, HELLP, acute renal failure, cerebrovascular accidents etc. Findings of the present study suggest that during PE renal functions are affected which increases serum Creatinine and decreases serum Ca+2. The study suggests inclusion of urine CCR as a marker for screening of PE in pregnant females. Further, monitoring of serum calcium levels during antenatal period may be helpful in minimizing the risk of development of PE.

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Table 1: Comparison of Serum Calcium and creatinine between Normotensive and Pre-eclamptic Females

Groups	No. of cases (n)	Serum Calcium (mg/dl) (Mean ± SD)	t-value	P-value
Normal pregnant Women	100	9.05 ± 0.90	8.78	<0.01*
Pre- eclamptic Women	100	7.74 ± 1.19		
Groups	**No. of cases (n)**	**Serum Creatinine (mg/dl) (Mean ± SD)**		
Normal pregnant Women	100	0.79 ± 0.24	-4.617	<0.01*
Pre-eclamptic Women	100	0.95 ± 0.25		

*: statistically significant

Table 2: Comparison of Urinary Calcium and Creatinine between Normotensive and Pre-eclamptic Females

Groups	No. of cases (n)	Urinary Calcium (mg/dl) (Mean ± SD)	t-value	P-value
Normal pregnant Women	100	9.15 ± 3.44	2.937	0.004*
Pre-eclamptic Women	100	7.99 ± 1.94		
Groups	**No. of cases (n)**	**Urinary Creatinine (mg/dl) (Mean ± SD)**	**t-value**	**P-value**
Normal pregnant Women	100	135.71 ± 15.52	-12.590	<0.01*
Pre-eclamptic Women	100	216.21 ± 61.95		

*: statistically significant

Table 3: Comparison of Calcium-Creatinine Ratio between Normotensive and Pre-eclamptic Females

Groups	No. of cases (n)	Calcium:Creatinine Ratio (mg/dl) (Mean ± SD)	t-value	P-value

Normal pregnant Women	100	0.07 ± 0.05	5.571	<0.01*
Pre-eclamptic Women	100	0.04 ± 0.02		

*: statistically significant

Table 4: Distribution of subjects according to Urinary Calcium-Creatinine Ratio (CCR)

Groups	**Normal pregnant women (n)**	**Pre-eclamptic women (n)**	**Chi- square test (χ^2)**	**P-value**
CCR ≤ 0.04	12%	52%	34.949	<0.01*
CCR > 0.04	88%	48%		

*: statistically significant