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RESEARCH ARTICLE

SERUM AND URINARY CALCIUM AND CREATININE LEVELS IN THE 3RD TRIMESTER OF NORMAL PREGNANT AND PRE-ECLAMPTIC FEMALES

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ABSTRACT

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Key words:

Preeclampsia, serum creatinine, Urine Calcium, Urine Creatinine, Urinary calcium, Calcium/Creatinine Ratio. Aim: The objective of the study is to detect predictive value of serum and urinary calcium and creatinine levels in the 3rd trimester of normal pregnant and pre-eclamptic females. Materials And Methods: The present study was conducted in the Departments of Biochemistry and Obstetrics & Gynaecology, Government Medical College and hospital, Amritsar. The study included total 40 asymptomatic pregnant women at 20-28 weeks of gestation and aged between 21-35 years. In the present study, special biochemical investigations including serum calcium, urinary calcium, serum creatinine and urinary creatinine were carried out in the both groups (normal pregnant female and pre-eclamptic females both in their third trimester of pregnancy). Calcium clearance and creatinine clearances were also calculated. An effort was made to find out the correlation between these parameters on the basis of present findings and also with respect to the comparable and contrasting reports of other workers. Results: The mean serum calcium values in pre-eclamptic pregnant females were significantly lower (mean± S.E 8.3±0.19, t=3.3, p<0.01) as compare to normal pregnant females (mean± S.E 9.3± 0.233). Similar findings were observed in urinary calcium levels of pre-eclamptic pregnant females (mean±S.E 7.4±0.36, t=4.417, p<0.001) and in normal pregnant females in their 3^{rd} trimester of pregnancy (mean±S.E 9.8± 0.398). The mean serum creatinine values in pre-eclamptic pregnant females were significantly higher(mean± S.E 1.1± 0.041, t=8.70, p<0.001) as compared to the mean serum creatinine values in normal pregnant females in their 3rd trimester of pregnancy(mean± S.E 0.64± 0.033).Similar findings were observed in urinary creatinine levels of pre-eclamptic pregnant females (mean±S.E 249.8±14.4,t=4.19,p<0.001) when compared to that of normal pregnant females in their 3^{rd} trimester of pregnancy (mean±S.E 179.6± 8.466). The mean calcium clearance value in pre-eclamptic pregnant females were significantly lower (mean± S.E 0.43±0.024, t=10.6, p<0.001) than mean calcium clearance values in normal pregnant females (mean± S.E 0.86 ± 0.033). The mean creatinine clearance value in pre-eclamptic pregnant females were significantly lower (mean± S.E 111.5 ± 7.06, t=5.8, p<0.001) than in normal pregnant females (mean± S.E 247± 21.96). The mean urinary calcium/urinary creatinine ratio in pre-eclamptic pregnant females were significantly lower (mean± S.E 0.03 ± 0.001, t=4.97, p<0.001) as compared to the calcium/urinary creatinine values in normal pregnant females (mean \pm S.E 0.05 \pm 0.003). Conclusion: This study evaluates the serum calcium, urinary calcium, serum creatinine and urinary creatinine, Calcium clearance and creatinine clearances along with calcium/Creatinine Ratio which may be an effective parameter for detecting women at greater risk.

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INTRODUCTION

The word "Eclampsia" is probably derived from the Greek work "Eclampsus" (lightening). It was Mauriceau, a French physician who distinguished eclamptic seizures from epilepsy in 1668. It was then recognized that the generalized convulsions or fits prone to occur in pregnant or recently delivered women. Those due to epilepsy were not limited to pregnancy and were rarely fatal; whereas those associated only with pregnancy were frequently fatal. The latter type was attributed by Ahifieid in 1894 to blood poisoning or toxemia caused by a poisonous substance derived from pregnancy.

Dr. R. Bright (1827) recognized that dropsy and albuminuria also contributed to toxemia of pregnancy. The exact nature of the primary event causing pre-eclampsia is not known. The evidence accumulated in the past 20 years indicates that abnormla placentation is one of the initial events in this disease. The main feature of abnormal placentation is inadequate trophoblastic invasion of the maternal spiral arterioles. In normal pregnancy the wall of the spiral arteries is invaded by trophoblastic cells and transformed into large, tortuous channels that carry a large amount of blood to the

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intravillous space and are resistant to the effects of vasomotor agents. These physiological changes are restricted in patient with pre-eclampsia with resulting decreased ulteroplacental perfusion. The anatomic and physiological disruption of normal placentation is thought to lead to altered endothelial cell function and multiple organ damage by a mechanism that is unknown. The evidence indicating that endothelial cell dysfunction is responsible for the most significant biochemical changes and wide spectrum of clinical presentation that characterizes pre-eclampsia is increasing rapidly. A search for the factor (s) released by the inadequately perfused trophoblast which is responsible for endothelial cell damage and trials of medications potentially capable of modifying endothelial cell dysfunction probably will dominate the research in this subject in the next few years.

Pre-eclampsia is a common complication of pregnancy and occurs in about 5-10% of all pregnancy. It is a syndrome characterized by the development of hypertension to the extent of 140/90 mm Hg or more with oedema or proteinuria or both induced by pregnancy after the 20th week of pregnancy. Thus it is a variant of PIH associated with oedema and proteinuria. The toxemic features may appear even before the 20th week as in cases of hydatidiform mole and acute hydraminios. The term toxemia is an unfortunate misnomer as there is no proof of its toxic origin but is being used as a common usage. Pre-eclampsia is a disorder of the second half of pregnancy which regresses after delivery [1, 2].

Women with mild pre-eclampsia generally have no symptoms. However, women with severe pre-eclampsia may have sign and symptoms such as renal insuffiency (reduced urinary volume, raised serum creatinine), liver disease (upper abdominal pain, elevated liver enzymes),neurological disturbances(headache, visual disturbances, exaggerated tendon reflexes, convulsions), haematological disturbances (thrombocytopenia, disseminated intravascular coagulation, haemolysis) and disturbances in bone –mineral metabolism [3,4,5].So many decades have passed still this toxic syndrome has not yet been prevented. Besides medical reasons, low socioeconomic status, poverty, lack of antenatal care, unavailability of transport with deep coma and pulmonary odema is a deadly combination leading to maternal mortality [6]

In an attempt to solve this problem, help has been sought from laboratory parameters. Various laboratory parameters that have been studied by various workers include blood uric acid, blood urea nitrogen, blood lactic acid, serum creatinine, urinary creatinine, serum calcium, urinary calcium, altered liver function test, coagulation studies and renal biopsy. An overlap in values of all these parameters of pre-eclamptic patients has been observed.

Many similar studies had been conducted to evaluate the cause of this disorder. Malt *et al* 1993, in his study, concluded that pre-eclampsia is associated with a significant decrease in urinary calcium excretion. This hypocalciuria is due to increased tubular reabsorption of calcium rather than decreased glomerular filtration rate. Ca/Cr are useful clinical tools in distinguishing pre-eclampsia from chronic hypertension in the

third trimester. The urinary rather than serum calcium/creatinine ratio is a better predictor of preeclampsia[7].Ye et al (1995) during their study at Quingdao Medical College concluded low urinary calcium excretion as a valuable marker for prediction of pregnancy induced hypertension. Twenty four hour urinary calcium excretion and urinary calcium/creatinine (Ca/Cr) ratio were determined with pregnancy induced hypertension. The result was Ca/Cr ratio in pregnancy induced hypertension groups were significantly lower than that in normal pregnant group. Ratio of 0.04 of Ca/Cr was chosen as predictive threshold for refrigerator at a temperature below 4 C for estimation of calcium and creatinine [8]. Some of the researchers emphasized on spot urine sample for the Ca/Cr ratio as predictor in the first trimester of pregnancy [9, 10, 11, 12, 13, 14]. In the light of above facts the present study was conducted to assess the role of serum and urinary calcium, serum and urinary creatinine levels and the ratio of urinary calcium to urinary creatinine in diagnosing the pre-eclampsia of pregnancy for proper patient care.

MATERIAL AND METHODS

Selection of cases

In the present study 40 subjects were studied. It was categorized into two categories. 40 subjects were meeting strictly the clinical criteria of pre-eclampsia in their III trimester of pregnancy and 40 normal healthy females of third trimester of pregnancy(control)in the age group of 20-30 years were selected from amongst the pregnant mothers attending the outpatient department of obstetrics and gynaecology, S.G.T.B. Hospital, Amritsar. A detailed history was taken which was correlated with the clinical criteria of pre-eclampsia in their III trimester of pregnancy.

Method of study

The patients were examined in the antenatal clinic for detection of any rise of blood pressure; appearance of urinary albumin and appearance of oedema with gain in body weight. 5 ml blood sample was withdrawn and serum separated for the estimation of calcium and creatinine .24 hrs urine samples were collected for estimation of urinary calcium and creatinine. Serum and urinary creatinine was estimated by the alkaline picrate method calorimeterically(Jaffe's method,1886). Serum and urinary calcium was estimated by OCPC KIT method using Seac CH-100 semi auto-analyzer (Sshwartzenbach, 1956).The urine **was** diluted 1 in 50 ml. Values are expressed as mean \pm S.D .Statistical analysis between three groups was done using student's t- test.

RESULTS

Pregnant hypertension syndrome is associated with hypocalciuria probably due to increased tubular reabsorption of calcium. Low levels of serum calcium were found as early as 28 weeks and can therefore be used for early diagnosis of preeclampsia. The urinary rather than serum calcium/creatinine ratio is a better predictor of pre-eclampsia.

 Table1 Serum calcium/Urinary calcium in normal pregnant females and pre-eclamptic pregnant females in their 3rd trimester of pregnancy

N. 20		Serum Calcium (mg %)			Urinary Calcium (mg %)		
S.No	N=20	Range	mean± S.E		Range	mean± S.E	
1.	Normal Pregnant females	8.1-12.0	9.3 ± 0.233		6.8-13.2	9.8 ± 0.398	
				t=3.3 P < 0.01			t=4.417 p<0.001
2.	Pre-eclamptic pregnant female	6.6-10.6	8.3±0.19		3.3-10.1	7.4±0.36	

- 1. The data presented in the table 1, indicates that the mean serum calcium values in pre-eclamptic ppregnant females in their 3^{rd} trimester of pregnancy were significantly lower(mean \pm S.E 8.3 \pm 0.19, t=3.3, p<0.01) when compared to the mean serum calcium values in normal pregnant females in their 3^{rd} trimester of pregnancy(mean \pm S.E 9.3 \pm 0.233).Similar findings were observed when urinary calcium levels of pre-eclamptic pregnant females in their 3^{rd} trimesterofpregnancy (mean \pm S.E7.4 \pm 0.36,t=4.417,p<0.001) were compared to that of normal pregnant females in their 3^{rd} trimester of pregnancy (mean \pm S.E 9.8 \pm 0.398).
- 4. The data presented in the table 4, indicates that the mean creatinine clearance value in pre-eclamptic pregnant females in their III trimester of pregnancy were significantly lower (mean \pm S.E 111.5 \pm 7.06, t=5.8, p<0.001) when compared to the mean creatinine clearance values in normal pregnant females in their 3rd trimester of pregnancy (mean \pm S.E 247 \pm 21.96).
- 5. The table 5, indicates that the mean urinary calcium/urinary creatinine ratio in pre-eclamptic pregnant females in their III trimester of pregnancy were significantly lower (mean \pm S.E 0.03 \pm 0.001, t=4.97, p<0.001) when compared to

Table 2 Serum creatinine/Urinary creatinine in normal pregnant females and pre-eclamptic pregnant females in their 3rd trimester of pregnancy.

N=20	Serum Creatinine (mg %)		Urinary Creatinine (mg %)			
	Range	mean S.E		Range	Mean±S.E	
Normal Pregnant females	0.4-0.85	0.64±0.033	t=8.70 p<0.001	166-274	179.6±8.466	t=4.19 p<0.001
Pre-eclamptic pregnant female	0.83-1.4	1.1±0.041		183-416	249.8±14.4	

2. The above table 2, indicates that the mean serum creatinine values in pre-eclamptic pregnant females in their 3^{rd} trimester of pregnancy were significantly higher(mean \pm S.E $1.1\pm$ 0.041, t=8.70, p<0.001) when compared to the mean serum creatinine values in normal pregnant females in their 3^{rd} trimester of pregnancy(mean \pm S.E $0.64\pm$ 0.033).Similar findings were observed when urinary creatinine levels of pre-eclamptic pregnant females in their 3^{rd} trimester of pregnancy(mean \pm S.E 249.8 ± 14.4 ,t=4.19,p<0.001) were compared to that of normal pregnant females in their 3^{rd} trimester of pregnancy (mean \pm S.E $179.6\pm$ 8.466).

 Table 3
 Calcium Clearance of Normal Pregnant Females

 and Pre-Eclamptic Pregnant
 Females In their III trimester

No. of cases, n=20	Range	M		
	(ml/mt)	Mean ±5.D	±S.E	
Normal Pregnant females	0.73-1.04	0.86±0.149	±0.033	t=10.6, p<0.001
Pre-Eclamptic females	0.37-0.55	0.43 ± 0.016	±0.024	•

3. The above table 3, indicates that the mean calcium clearance value in pre-eclamptic pregnant females in their 3rd trimester of pregnancy were significantly lower (mean± S.E 0.43±0.024, t=10.6, p<0.001) when compared to the mean calcium clearance values in normal pregnant females in their 3rd trimester of pregnancy (mean± S.E 0.86± 0.033).

Table 4Creatinine Clearance of Normal Pregnant Femalesand Pre-Eclamptic Pregnant Females In their III trimester

No. of cases, n=20	Range (ml/mt)	Mean ±S.D	±S.E	
Normal Pregnant females	138-462	247±98.20	±21.96	t=5.8,
Pre-Eclamptic females	59.2-169.7	111.5±31.56	±7.06	p<0.001

the mean urinary calcium/urinary creatinine values in normal pregnant females in their 3^{rd} trimester of pregnancy (mean \pm S.E 0.05 \pm 0.003).

Table 5 Urinary Calcium/Urinary Creatinine Ratio ofNormalPregnant Females and Pre-Eclamptic PregnantFemales In their III trimester.

No. of cases=20	Range (ml/mt) Mean ±S.D +S.E			
Normal Pregnant females	0.02-0.10	0.05±0.016	±0.033	t=4.97,p<0.001
Pre-Eclamptic females	0.02-0.04	0.03±0.007	+0.001	

DISCUSSION

Pre-eclampsia as assessed by clinical criteria of hypertension, oedema and proteinuria has been shown to have many technical errors and variability depending on several factors. It is not primarily a hypertensive disease and its cause is not fully known but must lie within the gravid uterus (Chesely, 1974). The raised blood pressure and other maternal signs by which it is recognized are secondary features and are more often the reflections of intrauterine problem. Foetus is invariably involved and may suffer its own morbidity and mortality.

In the present study, special biochemical investigations including serum calcium, urinary calcium, serum creatinine and urinary creatinine were carried out in the both groups (normal pregnant female and pre-eclamptic females both in their third trimester of pregnancy). Calcium clearance and creatinine clearances were also calculated. An effort was made to find out the correlation between these parameters on the basis of present findings and also with respect to the comparable and contrasting reports of other workers.

In the present study, the serum calcium levels in normal pregnant females were found to range 8.1-12.0 mg% with a mean \pm S.E 9.3 \pm 0.233 mg%, table 1 figure falling within the defines normal range 8.6-11.5mg% with a mean10.0mg%[15] for non pregnant females. In pre-eclamptic pregnant females the serum calcium was found to range 6.6-10.6mg% with a mean \pm S.E 8.3 \pm 0.194mg%(Table 1).The mean serum calcium in pre-eclamptic pregnant females was found to be close to lower normal limits of non-pregnant females but it was found to be significantly lower, t=3.3, p<0.01 (Table 1) than that of age matched normal pregnant females in the third trimester of pregnancy. These findings are consistent with those of Hasan *et al*, 1991, Malt *et al* in 1993 and Mandira *et al* in 2006 [17, 7, 14].

Urinary calcium values in case of normal pregnant females were found to range from 6.8-13.2 mg% with a mean \pm S.E 9.8 ± 0.398 mg% (table1). These urinary values were found to be close the figures obtained in case of normal non-pregnant females (Range 6.6-16.6 mg%, mean=11.6mg%)[13]. Despite the fact that pregnant normal females were regularly taking calcium orally, their calcium excretion was not affected much because the excessively absorbed calcium from the intestine was regularly being taken up by the growing foetus, through placenta and hence probably not left in the blood for being filtered out in the urine through the kidney. This again supports our serum findings stating serum calcium levels are not much affected in normal females pregnancies when compared to that of normal non pregnant. Urinary calcium excretion in preeclamptic pregnant females was observed to range from 3.3-10.1 mg% with mean \pm S.E 7.4 \pm 0.36mg% (Table 1). The data is suggestive of the fact that in pre-eclamptic pregnant females, a relatively less intestinal absorption of calcium as predicted by low serum calcium levels may be responsible for its significantly less excretion in urine when compared to that of either normal pregnant females in their trimester of pregnant (t=4.417,p<0.001, table 1) and non pregnant females. This hypocalciuria in pre-eclamptic pregnant female is due to decreased in GFR increased tubular reabsorption has been suggested by a number of workers [16, 18, 19, 20].

A decrease in serum calcium, urinary calcium and urine volume (glomerular filtration rate) in pre-eclampsia lead to decreased calcium clearance (range from 0.37-0.55 ml/mt, with a mean ±S.E 0.43 ± 0.024 ml/mt, table 3) when compared to that of normal pregnant females where the calcium clearance was found to range from 0.73-1.04 ml/mt with a mean±S.E 0.864 ± 0.033 ml/mt (Table 3). Luis *et al* 1991, suggested hypocalciuria may be due to increased reabsorption of calcium at the level of renal tubules. But our present findings go more in favour of decreased intestinal absorption of calcium. Serum calcium levels were also significantly lowered in pre-eclampsia as compared to that observed in normal pregnancies [18, 19].

The serum creatinine level in normal pregnant females in their third trimester were found to range from 0.4-0.85 mg% with mean \pm S.E 0.64 ± 0.033 mg% (Table 2) a value significantly

lower t=8.70,p<0.001 than that observed in case of normal nonpregnant females with a range from 0.69-1.29 mg% and mean of 0.99 mg%[12] and in pre-eclamptic females(range 0.83-1.4 mg%) with a mean \pm S.E 1.1 \pm 0.041 mg%(Table 2).A significantly decreased level of serum creatinine in normal pregnancies when compared to that of either age matched preeclamptic females or normal non-pregnant females could be attributed to its more excretion in urine as a result of increased glomerular filtration rate in normal pregnancies and decreased glomerular filtration rate in pre-eclamptic [21].

Urinary creatinine levels in normal pregnant females were found to range from 166 - 274 mg% with a mean \pm S.E 179.6 \pm 8.466 mg% (Table 2), a value significantly higher than that observed in case of normal non pregnant females (range 80 -180 mg%) with a mean of 120 mg% [15].Pre-eclamptic pregnant females, the urinary creatinine excretion was found to range from 183-416 mg% with a mean \pm S.E. 249.8 \pm 14.4 mg% (Table 2), a value significantly higher t = 4.19. p < 0.001 (Table 2) than that observed in case of either normal pregnant females in third trimester of pregnancy or normal non-pregnant females. There is significantly increased excretion of creatinine in pre-eclamptic females as compared to that of normal pregnant females and normal non pregnant females could be attributed to significantly less amount of urine formed in preeclamptics. Slightly increased (but close to normal values) serum creatinine and significantly increased urinary creatinine but decreased amount of urine forms is due to decreased glomerular filtration rate in pre-eclampsia. These parameters were responsible for decreased creatinine clearance (range 59.2-169.7 ml/mt, mean± S.E. 111.5± 7.06 ml/mt)(Table 4) as compared to that of age matched normal pregnant females in their third trimester of pregnancy(range 138-462 ml/mt, mean \pm S.E.247± 21.96 ml/mt(table 4) and normal non-pregnant females (Range 85-125ml/mt, mean=100ml/mt)[13]. These findings are consistent to those of Leuis et al, 1991[19].

Hypocalciuria accompanied by hypercreatinurea are the features responsible for decreased urinary calcium/creatinine ratio in pre-eclamptic females < 0.04 (Table 5) as compared to that of age matches normal pregnant females (0.05, Table 5). This study i.e Calcium/creatinine ratio has a support of many findings [14,22,23,24,25] .This parameter is a good predictor of pre-eclampsia. But 24hrs collection of urine sample is not so easy for all pre-eclamptic patients. So collecting only spot urine can indicate risk, it can be a good parameter. In a past as well recent study found, Spot Urinary Calcium/Creatinine Ratio may be an effective marker for detecting women at greater risk. The study by shilpa et al also concluded to detect predictive value of Calcium/Creatinine Ratio in spot urine sample in preeclampsia and an afford it to introduce spot urine test in ANC profile [26].NICE Guidelines i.e. a clinical guideline offers evidence-based advice on the care and treatment of women who have or are at risk of developing hypertension (high blood pressure) in pregnancy. It contains advice on the diagnosis and management of hypertension during pregnancy, birth and the postnatal period. It also includes advice for women with chronic hypertension who wish to conceive and for women who have had a pregnancy complicated by hypertension. Some other

antihypertensive treatment should be discussed with the healthcare professional responsible for managing their hypertension, if they are planning pregnancy. NICE guidelines [CG107] had been published on August 2010; review revision was in 2013and next review is in sept, 2014[27]. So preventive measures at all levels can minimize this syndrome which is fatal for a neonate and mother itself. Latest , according to the American College of Nurse-Midwives symptoms of severe preeclampsia are same as that of preeclampsia, with some exceptions(proteinuria not required), some features included, systolic BP 160 mmHg, measured twice at least 15 min apart, Diastolic BP 110 mmHg, measured twice at least 15 min apart, Impaired liver function: AST or ALT > 70 units/L or twice the normal concentration, Renal insufficiency: serum creatinine > 1.1 mg/dl or doubled from baseline values, pulmonary edema, Symptoms indicating possible cerebral or neurologic involvement: headache or visual changes.

CONCLUSION

Serum and urinary calcium and creatinine levels were estimated in normal pregnant females and pre-eclamptic pregnant females in their III trimester of pregnancy. A comparative study was conducted and following conclusions were drawn.

- 1. Serum calcium levels in normal pregnant females remained close to normal serum calcium levels in the aged matched non-pregnant females.
- 2. Serum calcium levels in pre-eclamptic females were found to be lower than the values observed in case of normal pregnant females in their III trimester of pregnancy and also the non-pregnant normal females.
- 3. Decrease in serum calcium in pre-eclamptic pregnant females could be due to either defective intestinal absorption or decreased renal tubular reabsorption.
- 4. Urinary calcium levels in normal pregnant females were observed to be close to the urinary calcium excretion in normal non-pregnant females.
- 5. Urinary calcium excretion in pre-eclamptic females was significantly lower than that observed in case of age matched normal pregnant females and normal non pregnant females.
- 6. Decreased urinary excretion of calcium in pre-eclampsia rules out the possibility of decreased resorption of calcium at the level of renal tubules.
- 7. Hence ,decreased calcium excretion along with decreased serum calcium levels are probably due to defective, intestinal absorption of calcium that may be associated with decreased production of 1,25 dihydroxycholecalciferol (Vitamin D₃) in pre-eclamptic females as compared to that observed in case of normal pregnancies.
- 8. Decreased serum calcium, urinary calcium and urine volume (because of decreased GFR) in pre-eclamptic females contributed to significantly decreased calcium clearance values when compared to that of normal pregnant females.
- 9. Serum creatinine levels in normal pregnant females were found to be relatively lowered when compared to that of normal non-pregnant females which may be

probably be because of increased GFR observed in case of normal pregnancies.

- 10. Serum creatinine levels in pre-eclamptic females were found to be raised when compared to that of normal pregnant females or normal non- pregnant females which could probably be because of lowered GFR observed in case of pre-eclamptic females.
- 11. Urinary creatinine excretion in normal pregnant females was found to be more than that observed in case of normal non-pregnant females.
- 12. More urinary excretion of creatinine in normal pregnancies could be because of increased GFR. More excretion of creatinine in urine has been reflected as decreased serum creatinine in normal pregnancies.
- 13. Urinary excretion of creatinine in pre- eclamptic pregnant females was significantly more than that observed in case of normal pregnant females or normal non-pregnant females. This could be attributed to significantly decreased volume of urine formed in pre-eclamptic females as compared to that of normal pregnant females.
- 14. Significantly raised urinary and serum creatinine levels and decreased urine volume (because of decreased GFR) in pre-eclamptic pregnant females were found to be responsible for decreased creatinine clearance when compared to that of normal pregnant females in their third trimester of pregnancy.
- 15. Both, decrease in urinary calcium and urinary creatinine concentration in pre-eclampsia were responsible for the decreased urinary calcium: urinary creatinine ratio when compared to that of normal pregnancies.

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