Original Research Article DOI: 10.18231/2394-6377.2018.0057

Estimation of serum uric acid, urinary calcium-creatinine ratio and microalbuminuria in prediction of pre-eclampsia

Lekha Tejaswi Y[1*], Preethi BP[2]

[1]Intern, [2]Associate Professor, Dept. of Biochemistry, J.J.M. Medical College, Davangere, Karnataka, India

***Corresponding Author:**
Email: lekha.tejaswi@gmail.com

Received: 24th January, 2018 **Accepted:** 16th February, 2018

Abstract

Introduction: The present study was aimed at evaluating serum uric acid, urinary calcium to creatinine ratio and microalbuminuria as predictors of pre-eclampsia in asymptomatic pregnant females.

Materials and Methods: 100 asymptomatic pregnant females were screened for uric acid, urinary calcium to creatinine ratio and microalbuminuria between 20-24weeks of their gestation and were followed up till delivery. BP was recorded and proteinuria evaluated by dipstick method. Our observations were subjected to statistical analysis by evaluating diagnostic accuracy and Receiver Operating Characteristic curve of uric acid, urinary calcium to creatinine ratio and microalbuminuria.

Results: Calcium creatinine ratio (94%) and microalbuminuria (89%) turned out to have good specificity, negative predictive value remained high for calcium creatinine ratio (97%), microalbuminuria (95%) and serum uric acid (91%). Area under the curve for calcium creatinine ratio is highest when compared to microalbuminuria and serum uric acid, making it an excellent predictor.

Conclusion: Our study findings suggest that calcium creatinine ratio was an excellent predictor of preeclampsia followed by microalbuminuria which was a good test for preeclampsia and serum uric acid which turned out to be a fair predictor of preeclampsia. We conclude that calcium creatinine ratio and microalbuminuria as early predictors of preeclampsia and can be used for screening purpose.

Keywords: Pre-Eclampsia, Serum Uric Acid, Microalbuminuria, Urinary Calcium-Creatinine Ratio.

Introduction

Hypertensive disorders of pregnancy have been a challenge to obstetricians and researchers since many centuries and remain a major public health problem worldwide. Pre-eclampsia and its complications are frequent causes of maternal and perinatal morbidity and mortality, particularly in developing countries.[1]

Hypertensive disorders complicate approximately 12% to 22% of all pregnancies. Preeclampsia accounts for 70% cases of Gestational hypertension, whereas Chronic hypertension for 30% cases of Gestational hypertension. Worldwide incidence of preeclampsia is around 5% to 8%. Pre-eclampsia complicates 3-5% of first pregnancies and 1% of subsequent pregnancies with 5-10% of cases being severe.

Pregnancy induced hypertension(PIH) occurs when new onset hypertension develops in the second half of pregnancy but in the absence of proteinuria or any other symptoms and signs of pre-eclampsia.

Pre-eclampsia is characterized by a rise in blood pressure of 140/90 mmHg on two different occasions having minimal interval of 4 hours duration, manifesting after the 20th week of pregnancy in a healthy pregnant female. This is accompanied by significant proteinuria (>300mg in 24hours) and resolves completely by 6th postpartum week.

A profound increase in blood pressure more than 160/110mmHg is a characteristic feature of severe preeclampsia. Eclampsia is the end result of a complicated preeclampsia which is characterized by occurrence of convulsions in a preeclamptic pregnant woman. Imminent eclampsia or fulminating pre-eclampsia is the transitional condition characterized by increasing signs and symptoms.

Pre-eclampsia may be asymptomatic, symptoms include headache, visual disturbances or epigastric pain. Signs may include facial and peripheral oedema, hyper reflexia and dull aching pain in right upper quadrant of abdomen.[2]

Pre-eclampsia is a multi-systemic syndrome and far more than simply gestational hypertension and proteinuria. The presentation is very variable and can involve any organ predominantly, but hypertension and proteinuria are two signs most commonly present. In pre-eclampsia, there is total or patchy failure of trophoblastic invasion of myometrial segments of spiral arteries that interferes the foetal growth and oxygenation. Endothelial dysfunction with profound vasospasm involving most of the blood vessels of uterus, uterine bed, renal system and brain has been implicated as the underlying pathological disturbance in preeclampsia. However, the responsible agent for endothelial dysfunction and vasospasm still has not been isolated precisely, but it seems certain to be humoral in origin. There occurs encroachment of endovascular trophoblasts into the walls of spiral arteries of placenta under normal circumstances. These

endovascular trophoblasts progress towards decidual segments during first trimester and further invade myometrial segments during second trimester replacing endothelial lining and muscular arterial wall by fibrous tissue. As a result of these changes, spiral arterioles become tortuous and distended characterized by low resistance, low pressure and high flow system. These endovascular trophoblastic invasion gets affected in preeclampsia thereby reducing blood flow fetoplacental unit.[3]

Risk factors for the development of pre-eclampsia are broadly divided into maternal specific and foetal or pregnancy specific. These may include primigravida, multiple pregnancy, molar pregnancy, diabetes mellitus, chronic hypertension, previous history of pre-eclampsia etc. So there is an immediate need to identify these high risk pregnant women before they develop life threatening complications. Biochemical or hormonal changes are detectable in an early pregnancy that may also clarify pathogenesis of superimposed eclampsia and ultimately lead to more specific mechanistically based prevention and treatment.[2]

Serum uric acid an insoluble purine metabolite excreted from distal tubule is a marker of oxidative stress tissue injury and renal dysfunction. The kidney which is responsible for 2/3rd of total excretion is dependent upon the filtered load and the balance between proximal tubular secretions versus re-absorption. Isotope study have demonstrated that 8-12% of lost uric acid is degraded to carbon dioxide and ammonia which is excreted in feces. Some uric acid excreted in the bile is subjected to degeneration by intestinal flora. The normal serum uric acid level is 3-7.5mg/dl in a non-pregnant females. Uric acid levels are 25-30% lower in normal pregnant females and reaches normalcy during third trimester. Uric acid merely identifies more specific form of eclampsia. Increments in urate level have been associated with development of severe pre-eclamptic changes lesion in renal biopsy, the degree of utero-placental vascular pathology and the poor foetal outcome. Redman et al clearly demonstrated that hyperuricemia was associated with significant increase in perinatal mortality.[4] The result of many studies, but not of others (reviewed by Dekhar and Sibai, 1991), have suggested increase in uric acid before appearance of proteinuric hypertension. In most patients the increase in blood pressure precedes the development of proteinuria stage of the disease. Redman et al demonstrated that for a given blood pressure level, a plasma urate level above 0.35mmol/L (6mg/dl) identified a sub group of pre-eclampsia with a tenfold increase in perinatal mortality. Uric acid is an indicator of disease severity in established pre-eclampsia. But the value in prediction and early diagnosis still not established.[2]

Renal function changes in pre-eclampsia have been documented and several prospective studies indicate that at least some of these changes precede the development of clinical signs and symptoms of pre-eclampsia. Proteinuria has been traditionally used as a reliable clinical sign for diagnosing pre-eclampsia. However, customary dipstick methods for detecting proteinuria fail to detect minimal elevations in urinary excretions of albumin that may be present before other clinical signs and symptoms of pre-eclampsia. With the recent development of the radioimmunoassay for detection of microalbuminuria, it is now possible to detect minimal elevations in albumin excretion that would have gone unnoticed in the past.

Many studies have suggested the association of decreased calcium as a risk factor for preeclampsia. In addition, Taufield et al. have recently demonstrated that pre-eclampsia is associated with hypocalciuria.[5] Many others have evaluated efficacy of decreased calcium-creatinine ratio and microalbuminuria as predictor of preeclampsia, and found it to be useful, whereas others have not found it as useful. This calls for thorough evaluation of these tests as screening tools.

Hence this study was attempted to determine whether presence of hyperuremia or hypocalciuria or microalbuminuria or combination of all three together in pregnant woman who is free of symptoms can predict subsequent development of pre-eclampsia.

Materials and Methods

This prospective study was carried out at the Department of Biochemistry, JJM medical College, Karnataka. Pregnant women visiting the OPD of Chigateri Government Hospital, Davangere, Karnataka were included in the study. A total of 100 asymptomatic pregnant women between 20-24weeks of gestation participated in the study. Those women with blood pressure more than 140/90mmHg, proteinuria positive by dipstick method, pregnant woman with diabetes mellitus and renal disorders were excluded from the study. Patients were explained about the study, consent was taken and their details regarding age, blood group and medical history was obtained.

Specimen Collection: 2ml venous blood was withdrawn under sterile condition from median cubital vein in red coloured vacutainer. Serum obtained after centrifugation was used for analysis. 50ml spot urine sample was collected in a sterile container and used for estimation of calcium-creatinine ratio and microalbuminuria on the same day. If analysis was delayed urine was stored at 2-8^{o}C for 48 hours. It was centrifuged and then used for analysis.

Analysis: Estimation of uric acid by Caraway Method, calcium by modification O-Cresolphthalein Complexone (OCPC) method by Moorehead and Briggs, creatinine by Jaffe's Method and microalbuminuria was estimated by Immunoturbidometry.[6,7] The instrument used was ERBA Semiautoanalyser

Follow-Up: Study subjects were followed up till delivery. At each visit study subjects BP was recorded and dipstick method was used to assess proteinuria.

Pre-eclampsia was defined as hypertension – blood pressure of more than or equal to 140/90 mmHg by using Korotkoff 5th sound for diastolic BP associated with proteinuria. (based on definition of American college of Obstetrics and Gynaecology[8])

Statistical Analysis

The observed data was statistically analyzed by SPSS version 19. The predictive values of uric acid, calcium-creatinine ratio and microalbuminuria was assessed by calculating sensitivity, specificity, positive predictive value and negative predictive value, and also by plotting receiver operating characteristic curves. Area under the curve of 0.9-1 indicating an excellent test, 0.8-0.9 a good test, 0.7-0.8 a fair tests and 0.6-0.7 a poor test.

Results

In our study involving 100 women between 20-24 weeks of gestation, most of them (82%) belonged to the age group of 20 to 30 and the remaining (18%) were below 20 years. Incidence of preeclampsia in this study was 9.27%. Mean gestational age at which preeclampsia developed was 32.44±1.33 weeks. Amongst the 9 who developed preeclampsia, pregnant women aged between 20-30years accounted for 77.8% and pregnant women below 20years accounted for 22,2% of cases. Among the preeclamptic pregnant women 55.6% were primigravida and the rest were multigravida. (Table 1)

From the total pool of 100 pregnant women who participated in the study, 97 women successfully completed the study with 3 loss to follow-up.11 (11.3%) were tested positive (CCR≤0.04) for calcium creatinine ratio. For microalbuminuria, 14(14.4%) were tested positive (30-300mg/L) and 83(85.6%) were tested negative (<30mg/dl). While for serum uric acid, 28(28.9%) were tested positive (>0.45mol/L) and 68(70.1%) were tested negative (<0.45mol/L). (Table 2)

Out of 11 pregnant women who were tested positive for calcium creatinine ratio, 6 developed preeclampsia at a later stage while the rest 5 remained normotensive accounting for false positive cases. Out of 86 women tested negative, 3 developed preeclampsia accounting for false negative and 83 of them remained normotensive. (Table 3)

14 women were tested positive for microalbuminuria, 5 of them eventually developed preeclampsia and 9 remained normotensive accounting for false positive cases. 83 women were tested negative for microalbuminuria and 79 of them were true negatives and remained normotensive. Only 4 women who were tested negative developed preeclampsia at a later stage of pregnancy and were false negative subjects. (Table 4)

More women tested positive for serum uric acid when compared to calcium creatinine ratio and microalbuminuria. However, only 6 women out of 28 tested positive developed preeclampsia showing that 22 women were tested falsely positive. While 3 women of 69 tested negative for serum uric acid developed the disease accounting for false negative cases and 66 remained normotensive accounting for true negative cases. (Table 5)

The results of diagnostic accuracy tests involving sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for calcium-creatinine ratio, microalbuminuria and uric acid are as follows. The sensitivity of calcium creatinine ratio and uric acid was 66%, while that of microalbuminuria was lower at 56%. The specificity of the calcium creatinine ratio was the highest being 94%, followed by that of the microalbuminuria having the specificity of 89% and uric acid had the least specificity of 25%. The positive predictive value of calcium creatinine ratio, microalbuminuria and uric acid was 54%, 36% and 21% respectively. The negative predictive values were comparatively higher for all the three test variables. The negative predictive test for calcium creatinine ratio was 97%, microalbuminuria was 95% and uric acid was 91%. (Table 6)

The predictive ability of calcium-creatinine ratio, microalbuminuria and uric acid was further evaluated using area under of receiver operator characteristic curve analysis. This revealed calcium creatinine to be an excellent predictor with the largest area under curve of 0.908, microalbuminuria was found to be a good test with an area under the curve of 0.873 and serum uric acid had an area under the curve of 0.799, suggesting it to be the least predictor of preeclampsia among the others.

Discussion

Preeclampsia is the most common complication associated with pregnancy and is one of the major cause of maternal and foetal morbidity and mortality. Clinically preeclampsia is diagnosed by new onset gestational hypertension after the 20th week of gestation and proteinuria. However, preeclampsia is a complex multi system syndrome and far more than simply gestational hypertension.[9] Recent progress in understanding the disease process along with the availability of better research tools have led to the development of numerous tests to preeclampsia.

Among our study subjects of 100 asymptomatic women screened for uric acid, calcium creatinine ratio and microalbuminuria between 20-24weeks of gestation, calcium creatinine ratio turned out be an excellent predictor do preeclampsia. Many studies have found decreased excretion of calcium in urine to be

associated with development of preeclampsia. The underlying pathology of this is theoretically attributed to the decreased intestinal absorption, increased calcium uptake by fetus or increased renal tubular reabsorption of calcium.[10] Our observations for calcium creatinine ratio with sensitivity, specificity, PPV and NPV of 69%, 98%, 85.6% and 95.5% respectively are in accordance with that of CN Sheela et al[11] who found calcium to creatinine ratio to be a good predictor of the disease. In another study undertaken by Izumi et al[12] during less than or equal to 12 weeks of gestation revealed measurement of calcium creatinine ratio to be of limited use in predicting preeclampsia, as 12weeks is too early for changes to appear. Dutt V et al[13] studied that pre-eclamptics admitted to the labor room for safe confinement have a significant hypocalciuria, however they found calcium creatinine ratio to have a low sensitivity and positive predictive value. Another study by Amandeep Kaur et al[14] found calcium creatinine ratio in the third trimester of pregnancy to be an effective predictor of the disease. Kazeroomi et all[15] and Kar et al[16] evaluated the calcium creatinine ratio between 20-24 weeks of gestation and 20-34 weeks of gestation suggesting calcium creatinine ratio to be a good test for predicting preeclampsia. Our study observations are in accordance with these two studies. The predictive ability of calcium creatinine ratio was further assessed by plotting receiver operating characteristic curve. We obtained an area under the curve of 0.908 indicating calcium creatinine ratio to be an excellent predictor of preeclampsia. Thus calcium creatinine ratio could be used as one of the screening tests for asymptomatic pregnant women between 20-24 weeks for preeclampsia.

Microalbuminuria in a spot urine sample turned out to be a good predictor of preeclampsia with sensitivity, specificity, PPV and NPV of 56%, 89%, 36% and 95%. It has been studied that 9 weeks prior to manifestation of PIH there is an increasing trend in the albumin excreted in urine starting from 28th week of gestation. The early increase in urinary albumin excretion suggests that in PIH morphological and/ or functional changes of glomerular capillary wall takes place before the clinical signs of the disease manifest.[17] Proteinuria being one of the major manifestations of preeclampsia, estimation of microalbuminuria detects minute quantities of microalbumin. Our study observations are in accordance with that of Salako et al[18] who have concluded microalbuminuria to be a good predictor of preeclampsia with high sensitivity of 88.9% but having low positive predictive value of 22%. The study by CN Sheela et al[11] has stated microalbuminuria to be a fair test in predicting preeclampsia with a lower sensitivity and specificity of 53.8% and 86% respectively. We further evaluated the predictive ability of our test parameter by subjecting it to receiver operating characteristic curve analysis, which revealed an area under the curve of 0.87, indicating microalnuminuria to be a good test in predicting preeclampsia. This is similar to results by Mabel Kankam[19], who found microalbuminuria to be a good predictor with area under curve of 0.84. Estimation of microalbuminuria in a spot urine sample is a simple testand has been found to have excellent predictive value. Hence, it can be recommended as a screening test for preeclampsia and could be offered to all asymptomatic pregnant women between 20-24 weeks of gestation during their routine antenatal visit.

In contrast to calcium creatinine ratio and microalbuminuria, we found estimation of uric acid to be a satisfactory test in predicting preeclampsia with sensitivity, specificity, positive predictive value and negative predictive value of 66%, 25%, 21% and 91% respectively. Reduced uric acid clearance secondary to reduced glomerular filtration rate, increased reabsorption and decreased secretion accounts for increased serum uric acid levels in women with preeclampsia.[20,21] Our results are accordance with that of Jacobson et al,[22] where women with risk factors for hypertensive disorders of pregnancy were studied, and it was seen that a rise in uric acid levels at 24 weeks gestation was a poor predictor for both transient hypertension and preeclampsia. Similarly Mabel Kankem,[19] studied pregnant women more than or equal to 20 weeks of gestation and found uric acid to be a poor predictor with low sensitivity, specificity and area under receiver operating characteristic curve. Augustin[23] have concluded that there is no evidence that determination of serum uric acid levels can be used to predict disorders related to hypertension induced in pregnancy. A systematic review conducted by Thangaratinan et al[9] concluded uric acid to be good predictor of maternal and fetal outcomes across various studies, setting and population. Receiver operating characteristic curve analysis of uric acid revealed an area under the curve of 0.799, suggesting uric acid to be a satisfactory predictor of preeclampsia. Over many decades, estimation of uric acid among pregnant women has been used to evaluate prediction of preeclampsia and has also been used to assess severity of the disease. However, our study findings suggest that serum uric acid estimation could not be used to screen pregnant women for prediction of preeclampsia during routine antenatal check up.

Limitations

We could not include study subjects as per sample size calculation as we had to enroll only those pregnant women between 20-24 weeks of gestation attending one OBG OPD in the month of May(as this study was conducted towards ICMR project). As we had designed a prospective study, we had to enroll study subjects only during month of May and subsequent months were used for follow up.

Conclusions

Within our limitations, we concluded that calcium creatinine ratio and microalbuminuria could be used as screening tests to predict development of preeclampsia among asymptomatic pregnant women between 20-24 weeks of gestation.

Future scope

This study could be extended by serial measurement of calcium creatinine ratio, microalbuminuria and serum uric acid during each ANC starting from 20th week of gestation and compare their efficacy as predictor of preeclampsia.

Acknowledgements

We extend our sincere gratitude to the staff of Biochemistry Department and OBG Department for providing the necessary support towards smooth conduction of this study. This study was conducted as a part of ICMR project and we extend our humble gratitude to ICMR.

Table 1: Baseline characteristics

1.	Age group of study subjects	<20 years	18
		20-30 years	82
2.	Mean gestational age at which preeclampsia developed	32.44±1.33	
3.	Age of patients who developed PIH	24±3.54	
4.	Parity	Primigravida	5
		Multigravida	4

Table 2: Number of test positive pregnant women

Test parameter	Test Positive (n%)	Test Negative (n%)	Total
Calcium-creatinine ratio	11	86	97
Microalbuminuria	14	83	97
Serum Uric acid	28	69	97

Table 3: Association of Calcium-creatinine with pre-eclampsia

Calcium-creatinine ratio	Preeclampsia (n%)	Normotensive (n%)	Total
Test Positive ≤ 0.04	True Positive (6)	False Positive (5)	11
Test Negative > 0.04	False Negative(3)	True Negative (83)	86

Table 4: Association of Microalbuminuria ratio with pre-eclampsia

Microalbuminuria	Preeclampsia (n%)	Normotensive (n%)	Total
Test Positive 30-300mg/L	True Positive (5)	False Positive (9)	14
Test Negative < 30 mg/L	False Negative(4)	True Negative (79)	83

Table 5: Association of Serum Uric acid with pre-eclampsia

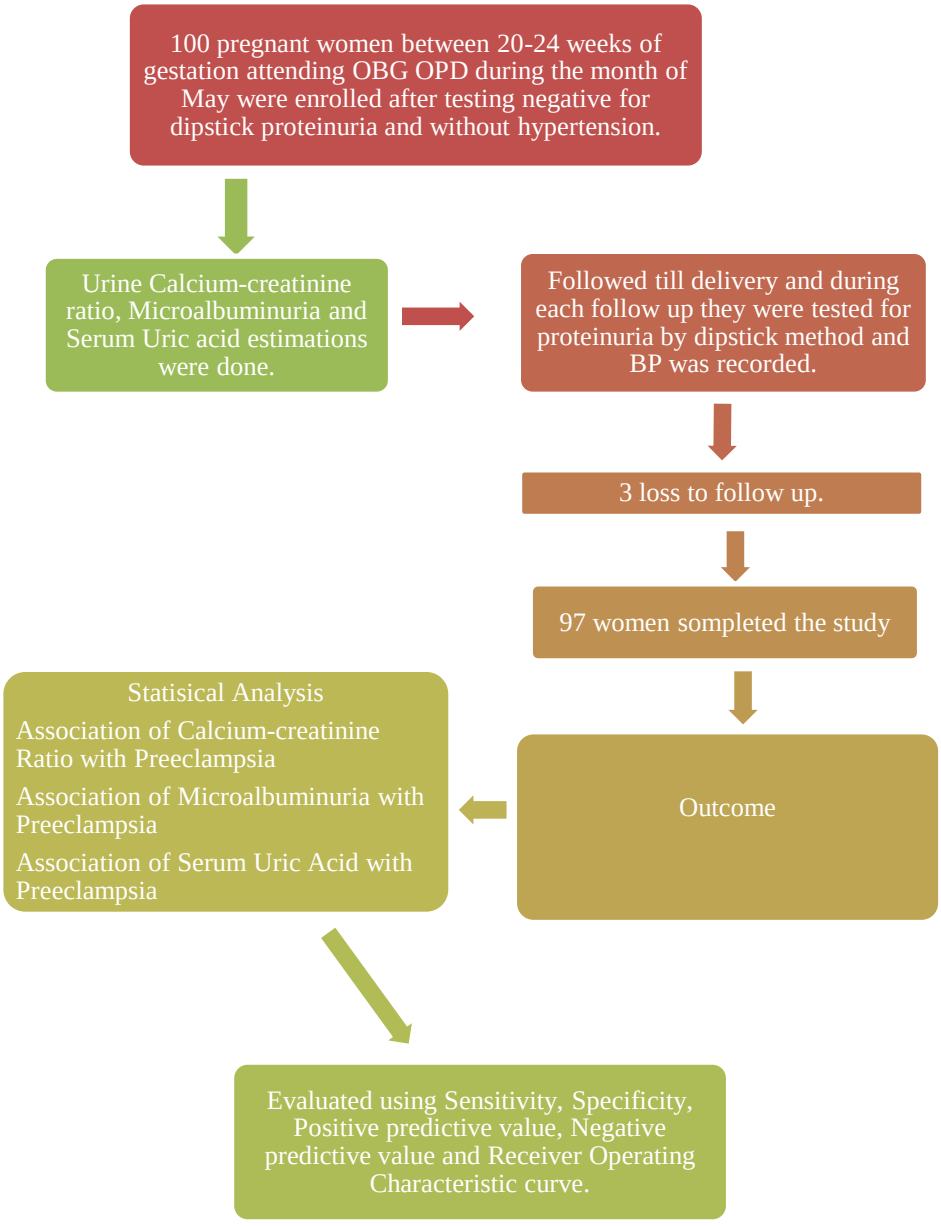
Serum Uric acid	Preeclampsia (n%)	Normotensive (n%)	Total
Test Positive > 0.45mol/L	True Positive (6)	False Positive (22)	28
Test Negative < 0.45mol/L	False Negative(3)	True Negative (63)	69

Table 6: Results of statistical analysis

Test variable	Sensitivity	Specificity	PPV	NPV
Calcium creatinine ratio	66%	94%	54%	97%
Microalbuminuria	56%	89%	36%	95%
Uric acid	66%	25%	21%	91%

Table 7: Predictive values of calcium creatinine ratio, microalbuminuria and serum uric acid using Receiver operating characteristic Curve analysis

Test result variable	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Microalbuminuria	0.873	0.033	0.000	0.735	1.000
Calcium creatinine ratio	0.908	0.033	0.000	0.844	0.973
Uric acid	0.799	0.069	0.003	0.665	0.934



References

1. HMSO. Report on confidential Enquiries into Maternal Deaths in the United Kingdom. London, UK: RCOG, 1997-99.2001
2. Farah Saleh, Shazia Shukar-ud-din, Nargis Soomro. Serum uric acid as predictor model for pre-eclampsia. Pakistan journal of surgery : 2010; 26(3):246-51.
3. DC Dutta. Hypertensive disorders in pregnancy. In : Hiralal Konar. Ed.Text book of Obstetrics, 7th edition.Kolkata : New central Book agency (P) Ltd;2011 : 220-4.
4. Redman CW, Beilin LJ, Bonnar J. Renal function in pre-eclampsia. J Clin Pathol Suppl. 1976; 10:91-94.
5. Taufeild PA, Ales KL, Resnik LM, Druzin ML, Gertner JM, Laragh JH. Hypocalciuria in pre-eclampsia. N Engl J Med 1987; 316:715-8.
6. Burtis CA and Ashwood ER eds. Tietz textbook of clinical chemistry and molecular diagnostics, 4th edn. Philadelphia: W R Saunders Cp; 2006; 798-800, 807-808, 1896-902.
7. Pesce AJ, Fring CS, Gauldine J. Spectral techniques. In: Kaplan LA, Pesce AJ, Kazmlerczak SC edts, Clinical Chemistry. 4th edn. Mosby; 2008;100-03.
8. American College of Obstetrics and Gynaecologists. Management of preeclampsia. Technical Bulletin No.1 Washington, DC; American College of Obstetrics and Gynaecology,1986.
9. S Thangaratinam, KMK Ismail, S Sharp, A Cooper, KS Khan. Accuracy of serum uric acid in predicting complication of preeclampsia a systemic review. BJOG 2006; 113: 369-78.
10. Bilgin T, Kuttu O, Kimya Y et al. Urine calcium excretion in preeclampsia. T kin J Obstet Gynecol 200; 10:29-32.
11. Sheela C N,Beena S R, Mhaskar Arun. Calcium creatinine ratio and microalbuminuria. The journal of obstetrics and gynecology of India January/ February : 2011;72-6.
12. Izumi A, Minakami H, Kuwata T et al. Calcium to creatinine ratio in spot urine samples in early pregnancy and its relation to the development of preeclampsia. Metabolism 1997; 46:107-8.
13. Dutt V, Dev NM. Evaluation of urinary calcium-creatinine ratio as a diagnostic tool in the management of preeclampsia. Int J Med Sci Public Health 2016;5:1635-8.
14. Amandeep Kaur, Mridula Mahajan. Serum and Urinary Calcium and Creatinine Levels in the 3rd Trimester of Normal Pregnant and preeclamptic females. Int J of Recent Scientific July 2015; Vol. 6. Issue 7:4908-13.
15. Kazeroomi T, Hamze-Nejadi S. Calcium to creatinine ratio in a spot sample of urine for early prediction of preeclampsia. Int J Gynaecol Obstet 2003;80:279-83.
16. J Kar, K Srivatsava, RK Mishra et al. Role of Urinary Calcium creatinine ratio in pregnancy induced hypertension. Journal of Obstetrics and Gynaecology of India: 2002;52: 39-42.
17. Misiani R, Marchesi D, Tirboschi G et al. Urinary albumin excretion in normal pregnancy and pregnancy induced hypertension. Nephron 1991;59:416-422.
18. Salako BL, Olayemi O, Odukogbe At et al. Microalbuminuria in pregnancy as a predictor of preeclampsia and eclampsia. West Afr J Med 2003;22:295-300.
19. Mabel Kankam Agyiri. Accuracy of Urine Microalbumin and Serum Uric Acid in the diagnosis of Preeclampsia[Dissertation on the internet]. International repository for Knust. Kwame Nkrumah University of Science and technology. 2015 (cited 2016 Oct) Available form: http://hdl.handle.net/123456789/9176
20. Fadel HE, Northrop G, Misenhimer HR. Hyperuricemia in preeclampsia A reappraisal. Am J Obstet Gynecol 1976;125:640-7.
21. Chesley LC, Williams LO. Renal glomerular and tubular function in relation to the hyperuricemia of preeclampsia and eclampsia. Am J Obstet Gynecol 1945;50:367-75.
22. Jacobson S, Imhof Regine, Manning N et al. The value of Doppler assessment of the uteroplacental circulation in predicting preeclampsia or intrauterine groeth retardation. Am J Obstet Gynecol 1990; 162:110
23. Augustin P, Helseth G, Cook EF, Sison C. A prediction model for superimposed preeclampsia in women with chronic hypertension during pregnancy. Am J Obstet Gynecol. 2004;191:1666-72.