DOI: 10.7860/NJLM/2018/37232:2310

Original Article

Biochemistry Section

# Serum Calcium and Magnesium levels in Pre-eclampsia

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## ABSTRACT

**Introduction:** Pre-eclampsia (PE) is a disorder of pregnancy characterised by hypertension with proteinuria after 20 weeks of pregnancy in previously normotensive and non-proteinuric patients which may progress to seizures (eclampsia) and maternal and foetal death if emergency delivery is not performed. Environmental and nutritional factors may play a role in the aetiology of pre-eclampsia. Pregnant women in the developing countries consume diets with lesser amounts of essential minerals and vitamins. Among all, there exists an alteration in Calcium (Ca) and magnesium (Mg) metabolism during pregnancy which could be a potential factor causing pre-eclampsia.

**Aim:** The present study was conducted to assess, compare and correlate serum total Ca, Mg and uric acid level in pre-eclampsia and normotensive pregnancy.

**Materials and Methods:** This is a hospital based comparative cross-sectional study which was conducted from March 2016 to February 2017. Serum Ca, Mg and uric acid as estimated by Cobas c311 Auto analyser. Data were analysed using SPSS version 21.0.

**Results:** Mean Serum Ca and Mg was significantly lower in PE compared to normotensive pregnant women (8.69±1.59 mg/dL and 1.91±0.36 mg/dL versus 10.13±0.66 mg/dL and 2.08±0.12 mg/dL).Serum Uric acid and creatinine was raised in PE compared to the control women respectively.

**Conclusion:** The findings of the present study demonstrates lower levels of serum total Ca and Mg in pre-eclampsia compared to normal pregnancy. Serum total Ca level was found decreasing with the severity of pre-eclampsia, though the finding was statistically insignificant.

**Keywords:** Electrolytes, Gestational Hypertension, Pregnancy, Uric acid

## INTRODUCTION

Pregnancy is commonly complicated with hypertensive disorders accounting for approximately 2-10% of the total gestations [1,2]. Pre-eclampsia is a disorder of pregnancy characterised by high maternal systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg measured on two occasions separated by at least 6 hours with associated proteinuria more than 300 mg or persistent >30 mg/dL (>1+ dipstick) in random urine sample [3]. The disorder usually progresses in the third trimester of pregnancy and worsens over time [4,5]. Patients with gestational hypertension and pre-eclampsia, both are characterised by similar risks like increased maternal age, obesity, low levels of serum Ca, Mg and increased concentration of uric acid [5]. Environmental and nutritional factors may play a role in the aetiology of pre-eclampsia. Pregnant women in the developing countries generally consume diets with lesser amounts of essential minerals and vitamins. An inadequate intake might be harmful not only for the mother but also for the growing foetus. Although the aetiology of this disease is not fully elucidated and placental ischemia is considered to have a major role in the pathogenesis [6]. Pre-eclampsia develops in 4-5% pregnancies worldwide and it is a leading cause of maternal and foetal death in developing countries like Nepal. A WHO Survey on Maternal and Perinatal Health, in 2014 showed 2.18% preeclamptic deliveries out of 8265 deliveries. Among all preeclamptic outcome, 38.12% and 24.43% were reported with low birth weight and preterm deliveries respectively. In this survey the perinatal death were reported as 10.75% compared to 1.08% maternal mortality [7,8]. Pregnancy may induce hypertension in women who are apparently normotensive before pregnancy [9]. Risk stratification and prediction of severity at an early stage in pre-eclampsia helps in appropriate management and timing of foetal delivery in order to avoid serious sequelae like eclampsia [10]. Studies have reported that changes in levels of trace elements in blood such as Ca and Mg observed in preeclamptic patients may contribute to the pathogenesis of pre-eclampsia. Decreased serum Ca level has been reported to cause increased blood pressure by stimulation of parathyroid hormone and renin release. Ca might have an indirect effect on smooth muscle function by increasing Mg levels which in turn causes peripheral vasodilatation [11,12]. Various studies have evaluated several biochemical parameters, including serum Ca, Mg and uric acid, during the first or second trimester of pregnancy, as potential

predictors of pre-eclampsia [13,14]. Women belonging to the low socio-economic backgrounds consume Mg even below the recommended levels and studies have shown that Mg supplementation reduces foetal growth retardation, low birth weight and pre-eclampsia. Successful management of eclamptic seizures with Mg therapy strongly suggest that women with Mg deficiency might develop pre-eclampsia [15-19]. Moreover, the results from most of the studies are inconsistent and does not state the importance of these trace elements in the prediction of severity of pre-eclampsia.

Thus, the present study was undertaken to assess serum total Ca, Mg and uric acid level in pre-eclampsia and normotensive pregnancy. The study also highlights the association of serum Ca, Mg and uric acid level with severity of pre-eclampsia.

## MATERIAL AND METHODS

It was a hospital based comparative cross-sectional study conducted from March 2016 to February 2017 for duration of one year after the ethical approval from Institutional Review Committee (IRC). This study was done in Department of Biochemistry in collaboration with Department of Obstetrics and Gynaecology, BPKIHS, Dharan, Nepal. Convenient sampling was done to enroll the study participants and informed consent was obtained from all the study participants.

### Sample Size Calculation

Based on the literature of Abdellah A et al., [15], the Ca and Mg level reported in the preeclamptic group was (7.56±0.82 mg/dL) and (1.75±0.11 mg/dL) and in the control group was (8.69±0.34 mg/dL) and (1.87±0.11 mg/dL) respectively.

Sample size was calculated based on Mg level because the lower minimum difference of mean was observed in the Mg as compared to Ca i.e. 0.12mg/dL. Based on this, assuming Mg as normally distributed in each groups with S.D. 0.11 and the true differences between the mean is 0.12 mg/dL. We need to enroll 19 cases in each arm to be able to reject null hypothesis. The mean in between the two groups are equal with probability of power 90% and 5% level of significance (using power and sample size program, PS version 3.0.32) [http://ps-power-and-sample-size-calculation.software.informer.com]

Adding 10% more in the study sample, the final sample size was made 21 in each group.

Sample Size Calculation:

$$n = \frac{(Z\alpha/2 + Z\beta)^2 \, 2\alpha^2}{\delta^2}$$

Though, the sample size was calculated as 21, but during the enrollment total of 37 cases and control was included in the present study.

### The inclusion criteria for the case and control

**For case (n=37):** American College of Obstetricians and Gynaecologists (ACOG), 2002 guidelines were applied for recruitment of cases which are maternal systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg measured on two occasions separated by at least 6 hour, with associated proteinuria >300 mg /day or persistent >30 mg/dL (>1+ dipstick) in random urine sample or qualitative, >1+, after 20 weeks of gestation [20].

**For control (n=37):** Age and trimester matched normotensive and non-proteinuric pregnant women.

The exclusion criteria included presence of any self-reported acute illness, diagnosed cardiac, renal or hepatic disease, any current treatment of cardiac or blood pressure related morbidities, history of any surgeries and heavy alcohol or recreational drug use and those who are not willing to take part in the study.

The common inclusion criteria for both groups were: normal foetal morphology and the absence of concomitant disease and gestation between 24 and 36 gestational weeks.

Convenient sampling technique was applied for recruitment of cases and control and an informed consent was taken from each participants before enrolling them in the study.

### Categorisation of Pre-eclampsia

PE was further categorized into 3 groups namely mild, moderate and severe PE on the basis of National Institute for Health and Care Excellence (NICE) guidelines, 2011. The categorisation are as follows; Mild PE: SBP140-149 mmHg and DBP- 90-99 mm Hg; Moderate PE; SBP- 150-159 mm Hg and DBP 100-109 mmHg; Severe PE; SBP- 160 mm Hg and DBP- 110 mm Hg [21].

### Anthropometric and Clinical characteristics

Gestational age, parity, Body Mass Index (BMI), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and mean arterial pressure (MAP) were recorded in both the study groups. The results of PE group were compared with that of the healthy age and gestational week matched control group.

### Biochemical Analysis

Estimation of serum Ca was done by 5-nitro-5'-methyl-BAPTA (NM-BAPTA) method and Mg via decrease in the xylidyl blue absorbance photometrically. Serum uric acid and creatinine levels were measured by Uricase, peroxidase method and kinetic Jaffe' method respectively. All the parameters were assessed in cobas c311 autoanalyser.

## STATISTICAL ANALYSIS

Data was collected, entered using Microsoft Excel™ and analysed using Statistical Package of Social science (SPSS) version 11.5 Normality of the data was tested by Kolmogorov and Smirnov test. All data were expressed in terms of figure, percentage, mean and standard deviation. Descriptive statistics was used to express the demographic data. For parametric variables, independent t-test and Pearson

correlation coefficient was used to assess the relation between quantitative variables. Linear regression was used for association of the variables with SBP and DBP. Logistic regression analysis was done to determine the association of serum Ca, Mg and uric acid levels in mild versus moderate and mild versus severe pre-eclampsia respectively. p<0.05 is considered as statistically significant.

## RESULTS

This is a hospital based comparative cross-sectional study conducted from March 2016 to February 2017. Thirty seven diagnosed cases of pre-eclampsia and 37 healthy pregnant women as controls were enrolled in the study. The demographic characteristics and mean blood arterial pressure is depicted in [Table/Fig-1]. It was noted that POG, BMI, SBP, DBP and MAP was significantly higher in preeclampsia as compare to control group (p<0.001). [Table/Fig-2] depicts the comparison of biochemical parameters between the groups. We observed a significant difference in serum Ca, Mg, creatinine and uric acid levels between PE and healthy control group. Biochemical parameters of the study population showed that mean serum total Ca and Mg levels were significantly reduced in pre-eclampsia as compared to the healthy control group. Multi-linear regression analysis of serum Ca, Mg and uric acid showed that serum Ca (regression coefficient= -6.91, p-value=0.001), Mg (regression co-efficient= -16.76, p-value= 0.76) and uric acid (regression coefficient= 4.34, p-value= 0.001) predict the outcome of SBP depicted in [Table/Fig-3]. Similarly, multi-linear regression analysis of serum Ca (regression coefficient= -4.88, p-value= 0.001), Mg (regression co-efficient= -5.66, p-value= 0.68) and uric acid (regression coefficient= 3.75, p-value= 0.001) showed that serum Ca, Mg and uric acid predict the outcome of DBP as depicted in [Table/Fig-4]. Multinomial regression analysis of the study variables in Pre-eclampsia depicts that the level of serum Ca, Mg and uric acid is not associated significantly with the severity of pre-eclampsia i.e. from mild to moderate or mild to severe pre-eclampsia. Our findings suggest that decrease in serum Ca level is associated with increase in severity of pre-eclampsia, though the association was statistically insignificant as depicted in [Table/Fig-5].

| General Characteristics | PE (n=37) | Control (n=37) | p-value |
|---|---|---|---|
| Age (years) | 26.72±5.39 | 25.97±4.97 | 0.542 a |
| POG (weeks) | 36.00±2.90 | 31.17±4.30 | 0.001 a* |
| BMI (kg/m$^2$) | 29.26±5.40 | 24.08±3.66 | 0.001 a* |
| SBP (mmHg) | 143.61±17.26 | 108.61±8.33 | 0.001 a* |
| DBP (mmHg) | 97.22±9.44 | 67.78±6.80 | 0.001 a* |
| MAP (mmHg) | 208.42±21.75 | 153.79±11.30 | 0.001 a* |

**[Table/Fig-1]:** Demographic and clinical characteristics of the study participants.
POG: Period of Gestation; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure; a: Independent sample t-test;
*p value <0.05 considered to be statistically significant

| Biochemical Parameters | Pre-eclampsia (n=37) | Control (n=37) | p-value |
|---|---|---|---|
| Calcium (mg/dL) | 8.69±1.59 | 10.13±0.66 | 0.001a* |
| Magnesium (mg/dL) | 1.91±0.36 | 2.08±0.12 | 0.001 a* |
| Creatinine (mg/dL) | 0.49±0.24 | 0.30±0.07 | 0.001 a* |
| Uric Acid (mg/dL) | 4.40±2.14 | 2.70±0.80 | 0.013 a* |

**[Table/Fig-2]:** Biochemical parameters of the study participants.
a: Independent sample t-test;
*p-value <0.05 is considered to be statistically significant

| Variables | Coefficient | SE | t-value | p-value |
|---|---|---|---|---|
| Intercept | 189.56 | 19.84 | - | - |
| Calcium (mg/dL) | -6.91 | 1.50 | -4.5 | 0.001* |
| Magnesium (mg/dL) | -16.76 | 17.83 | -0.94 | 0.35 |
| Uric Acid (mg/dL) | 4.34 | 1.15 | 3.7 | 0.001* |

**[Table/Fig-3]:** Multiple linear regression analysis of SBP with the ANOVA table for the model
Coefficient: Regression coefficient; SE: Standard error;
*p-value <0.05 is considered to be statistically significant

| Variables | Coefficient | SE | t-value | p-value |
|---|---|---|---|---|
| Intercept | 119.80 | 15.29 | - | - |
| Calcium (mg/dL) | -4.88 | 1.15 | -4.21 | 0.001* |
| Magnesium (mg/dL) | -5.66 | 13.74 | -0.41 | 0.68 |
| Uric Acid (mg/dL) | 3.75 | 0.88 | 4.22 | 0.001* |

**[Table/Fig-4]:** Multiple linear regression analysis of DBP with the ANOVA table for the model.
Coefficient: Regression coefficient; SE: Standard error;
*p-value <0.05 is considered to be statistically significant

| Variables | β (Regression Coefficient) | Standard Error | Level of Significance |
|---|---|---|---|
| **Mild v/s Moderate Pre-eclampsia** | | | |
| Calcium (mg/dL) | -0.314 | 0.643 | 0.69 |
| Magnesium (mg/dL) | 1.214 | 1.268 | 0.33 |
| Uric Acid (mg/dL) | 0.188 | 0.792 | 0.81 |
| **Mild v/s Severe Pre-eclampsia** | | | |
| Calcium (mg/dL) | -0.194 | 0.95 | 0.83 |
| Magnesium (mg/dL) | 1.378 | 1.371 | 0.31 |
| Uric Acid (mg/dL) | 0.138 | 0.958 | 0.88 |

**[Table/Fig-5]:** Multinomial regression analysis for severity of pre-eclampsia.
*p-value <0.05 is considered to be statistically significant

## DISCUSSION

Pre-eclampsia has been considered as a disease of unknown pathophysiology. Numerous aetiologies has been put forward in light of this serious condition of pregnancy [22-24]. Altered concentration of various trace elements has

been reported during pregnancy [25,26]. Serum Ca and Mg are two intracellular ions that are very important for cellular metabolism such as muscles contractibility, secretion, neuronal activity as well as cellular death [22]. Changes in the levels of Ca, Mg and copper in all the trimesters of pregnancy and zinc during mid and late pregnancy and postpartum period have been reported. Moreover, reduction in serum Ca, Mg and zinc during pregnancy has been attributed as a possible contributor among the various aetiologies of PE, therefore supplementation of these elements in diet may be of high value to prevent this devastating condition [25].

The present study depicts lower serum Ca and Mg in preeclapmsia compared to normal pregnant women, i.e. serum Ca (8.69±1.59 mg/dL versus 10.13±0.66 mg/dL) and serum Mg(1. 91±0.36 mg/dL versus 2.08±0.12 mg/dL) respectively. This is in accordance with the study reported from other parts of the world [11-17]. Maternal hypocalcemia during pregnancy has been known for more than 40 years. Total serum Ca tends to decrease over the course of pregnancy in normal women and decreased significantly during pre-eclampsia. The effect of serum Ca on changes in blood pressure could be explained by the level of intracellular concentration of Ca. Lower total serum Ca eventually causes increased intracellular Ca concentration leading to constriction of smooth muscles in blood vessels and increased vascular resistance [26-29].

Similarly, reduced Mg is most often seen during pregnancy. Hypomagnesaemia in most pregnant women is associated with haemo-dilution, renal clearance during pregnancy and increased demand by the growing foetus. Mg levels may have significant effects on cardiac excitability, vascular tone, contractility and reactivity. Low Mg levels thus, can lead to a reduced cerebral blood flow, cerebral vasospasm and increase in neuronal burst [30].

Furthermore, previous reports suggest that altered Ca homoeostasis, as exhibited by increased Ca excretion, is associated with higher blood pressure levels [31]. Low serum Ca levels may also increase blood pressure by stimulating parathyroid hormone and renin release, which in turn increases intracellular Ca in smooth muscle, leading to vasoconstriction. The observation is further supported by the 2011 WHO recommendation, which found a higher risk of pre-eclampsia in pregnant women with low dietary intake of Ca and recommended supplementation for such women [32]. This implies that Ca levels may play a role in hypertensive disorders in pregnancy.

Serum Uric acid has been employed as a pathogenic factor in pre-eclampsia [33]. The results from the present study depicts significantly increased serum uric acid in Pre-eclampsia compared to normal pregnant women in accordance to study done by Niraula A et al., Powers RW et al., Pramanik T et al., and Patel T et al., [10,34-37]. Literature reports numerous predictive biochemical indicator for the prediction of severity in Pre-eclampsia with none of them showing desirable sensitivity and specificity. Retrospective studies have shown a significant association between serum uric acid and severity of Pre-eclampsia [38-39]. This finding is supported by the present study as well which demonstrates an increased mean serum uric acid (4.40±2.14 mg/dL) in pre-eclampsia compared to that of normal pregnant women (2.70±0.80 mg/dL) with the difference between the two groups being statistically significant. Hyperuricemia in PE is mainly the result of decreased GFR and increased tubular reabsorption, but it may also occur due to amplified placental production of uric acid caused by increased metabolism of purines in the placenta, acidosis, or an increase in the activity of xanthine oxidase/dehydrogenase, thus being not only a marker of pathological state and renal dysfunction but also playing a role in pathogenesis of the disease [20, 39-41]. Multi-logistic regression have shown that pregnancy in advanced maternal age (≥ 40 years) was associated with a two-five fold increase in the odds of developing PE as reported by various studies [12-13]. Low serum Ca has been attributed as one of the aetiology for the development of hypertension in pregnancy which eventually leads to Pre-eclampsia [12,14-16]. The present study has shown that preeclamptic patients have significantly lower serum Ca and Mg levels. Association of serum Ca, Mg and uric acid level in mild, moderate and severe pre-eclampsia depicts that Ca was negatively correlated in these patients but the difference in between mild v/s moderate and mild v/s severe pre-eclampsia was statistically insignificant.

## LIMITATIONS

We did not find any definite trend in level of total serum Ca, Mg, uric acid and age of gestation with the severity of pre-eclampsia probably due to disparity in number of study population between mild, moderate and severe case. The present study is a cross-sectional study so we recommend a prospective study with equal number of mild, moderate and severe cases of pre-eclampsia to establish the definite mechanism of Ca and Mg metabolism in severity of pre-eclampsia.

## CONCLUSION

The present study reveals that low serum Ca and Mg levels are associated with pre-eclampsia, which might be attributed to the development and progression of the disease. Also, the present study highlights a decrease of serum Ca with severity of pre-eclampsia. Thus, these trace elements along with other serum biomarkers would definitely be helpful in effective management of pre-eclampsia.

## ACKNOWLEDGEMENT

The author acknowledges B.P. Koirala Institute of Health Sciences, Dharan, Nepal for funding and providing the opportunity to conduct the study and all the patients without whom the study would not have been possible.

## REFERENCES


[1] DC Dutta, H Konar, In: DC Dutta's Textbook of Obstetrics, edited by H Konar, 8Th Edition , (JAYPEE The Health Service Publisher, New Delhi, 2013), pp. 219-240.

[2] The World Health Report 2005. Make Every Mother and Child Count, Geneva.2005.

[3] Eiland E, Nzerue C, Faulkner M."Preeclampsia 2012," Journal of Pregnancy, vol. 2012, Article ID 586578, 7 pages, 2012.

[4] Dekker GA, Sibai BM. Aetiology and pathogenesis of preeclampsia: current concepts. Am J Obstet Gynecol. 1998;179(5):1359-75.

[5] Roberts JM, August PA, Bakris G, Barton JR, Bernstein IM, Druzin M, et al. Hypertension in pregnancy. Report of the American College of Obstetrician and Gynecologists' task force on hypertension in pregnancy. Obstet Gynecol. 2013;122(5):1122-31.

[6] Al-Jameil N, Aziz Khan F, Fareed Khan M, Tabassum H. A brief overview of preeclampsia. J Clin Med Res. 2014;6(1):01-07.

[7] Kumru S, Godekmerdan A, Kutlu S, Ozcan Z. Correlation of maternal serum high-sensitive C-reactive protein levels with biochemical and clinical parameters in preeclampsia. Eur J Obstet Gynecol Reprod Biol. 2006;124(2):164-67.

[8] Bilano VL, Ota E, Ganchimeg T, Mori R, Souza JP . Risk Factors of Preeclampsia/ Eclampsia and Its Adverse Outcomes in Low- and Middle- Income Countries: A WHO Secondary Analysis. PLoS One. 2014;9(3):e91198.

[9] Conde-Agudelo A, Belizan J.M. Risk factors for preeclampsia in a large cohort of Latin American and Caribbean women. BJOG. 2000;107(1):75-83.

[10] Patel T and Dudhat A. Relationship of serum uric acid level to maternal and perinatal outcome in patients with hypertensive disorders of pregnancy. Gujarat Med J. 2014; 69(2):45-47.

[11] Kanagal DV, Rajesh A, Rao K, Harshini DU, Shetty H, Kumari S et al. Levels of Serum Calcium and Magnesium in Pre-eclamptic and Normal Pregnancy: A Study from Coastal India. J Clin Diagn Res. 2014; 8(7):OC01-OC04.

[12] Ephraim RK, Osakunor DN, Denkyira SW, Eshun H, Amoah S, Anto EO. Serum calcium and magnesium levels in women presenting with pre-eclampsia and pregnancy-induced hypertension: a case-control study in the Cape Coast metropolis, Ghana. BMC Pregnancy Childbirth. 2014;14:390.

[13] Vafaei H, Dalili M, Hashemi SA. Serum concentration of calcium, magnesium and zinc in normotensive versus preeclampsia pregnant women: A descriptive study in women of Kerman province of Iran. Iran J Reprod Med, 2015;13(1):23-26.

[14] Pairu J, Triveni GS, Manohar A. The study of serum calcium and serum magnesium in pregnancy induced hypertension and normal pregnancy. Int J Reprod Contracept Obstet Gynecol. 2015;4(1):30-34.

[15] Abdellah A, Abdrabo AA. Assessment of serum calcium, magnesium, copper and zinc levels in Sudanese pregnant women with pre- eclampsia. Glo Adv Res J Med Med Sci. 2014;3(2):033-036.

[16] Ibraheem NJ, Obiade DS. Serum calcium level and some physiological markers during Pre-eclampsia and normal pregnancy in Babylon province women. Al-Kufa Journal for Biology. 2013;5(2):01-11.

[17] Akhtar S, Begum S, Ferdousi S. Calcium and Zinc Deficiency in Preeclamptic Women. J Bangldesh Soc Physiol. 2011;6(2):94-99.

[18] Khadem N, Ayatollahi H, Vahid Roodsari F, Ayati S, Dalili E, Shahabian Met al.Comparison of serum levels of Tri-iodothyronine (T3), Thyroxine (T4), and Thyroid-Stimulating Hormone (TSH) in preeclampsia and normal pregnancy. Iranian Journal of Reproductive Medicine. 2012;10(1):47-52.

[19] Sendhav S, Khubchandani A, Gandhi P, Sanghani GH, Vadhel A. Comparative Study of Serum Uric Acid, Calcium and Magnesium in Preeclampsia and Normal Pregnancy. Journal of Advance Researches in Biological Sciences. 2013; 5(1):55-58.

[20] ACOG Committee on Obstetric Practice. Diagnosis and Management of Preeclampsia and Eclampsia. ACOG Practice Bulletin No. 33. American College of Obstetrics and Gynceologists. Int J Gynaecol Obstet. 2002;77(1):67-75.

[21] Hypertension in pregnancy the management of hypertensive disorders during pregnancy Hypertension in pregnancy: full guideline final DRAFT (February 2010):01-244.

[22] Atamer Y, Kocyigit Y, Yokus B, Atamer A, Erden AC. Lipid peroxidation, antioxidant defense, status of trace metals and leptin levels in preeclampsia. Eur J Obstet Gynecol Reprod Biol. 2005;119: 60-66.

[23] Serdar Z, Gur E, Develioglu O, Colakogullari M, Dirican M. Placental and decidual lipid peroxidation and antioxidant defenses in preeclampsia lipid peroxidation in preeclampsia. Pathophysiology. 2002; 9:21-25.

[24] Liu J, Yang H, Shi H, Shen C, Zhou W, Dai Q, Jiang Y. Blood copper, zinc, calcium, and magnesium levels during different duration of pregnancy in Chinese. Biol Trace Elem Res. 2010;135(1-3):31-37.

[25] Jain S, Sharma P, Kulshreshtha S, Mohan G, Singh S. The role of calcium, magnesium, and zinc in preeclampsia. Biol Trace Elem Res. 2010;133:162-70.

[26] Ingec M, Nazik H, Kadanali S. Urinary calcium excretion in severe preeclampsia and eclampsia. Clin Chem Lab Med. 2006;44(1):51-53.

[27] Lopez-Jaramillo P. Calcium, nitric oxide, and preeclampsia. Semin Perinatol. 2000; 24(1):33-36.

[28] Szmidt-Adjide V, Vendittelli F, David S, Bredent-Bangou J, Janky E. Calciuria and preeclampsia: a case–control study. Eur J Obstet Gynecol Reprod Biol. 2006; 125(2):193-98.

[29] Kesteloot H, Tzoulaki I, Brown IJ, Chan Q, Wijeyesekera A, Ueshima H et al. Relation of urinary calcium and magnesium excretion to blood pressure: the international study of macro- and micro-nutrients and blood pressure and the international cooperative study on salt, other factors, and blood pressure. Am J Epidemiol. 2011; 174(1):44-51.

[30] Odom MJ, Zuckerman SL, Mocco J. The role of magnesium in the management of cerebral vasospasm. Neurology Research International. vol. 2013, Article ID 943914, 8 pages, 2013.

[31] Selina A, Shelina B, Sultana F. Calcium and Zinc deficiency in preeclamptic women. J Bangladesh Soc Physiol. 2011; 6(2):94-99.

[32] WHO Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia 2011. Geneva: World Health Organization. 2011.

[33] Bainbridge SA, Roberts JM. Uric acid as a pathogenic factor in preeclampsia. Placenta. 2008;29 (suppl A):S67-S72.

[34] Niraula A, Lamsal M, Majhi S, Khan SA, Basnet P. Significance of Serum Uric Acid in Pregnancy Induced Hypertension. J Natl Med Assoc. 2017;109(3):198-202.

[35] Niraula A, Lamsal M, Baral N et al. Cystatin-C as a Marker for Renal Impairment in Preeclampsia. J Biomark. 2017;2017:7406959

[36] Powers RW, Bodnar LM, Ness RB, Cooper KM, Gallaher MJ, Frank MP et al.Uric acid concentrations in early pregnancy among preeclamptic women with gestational hyperuricemia at delivery. Am J Obstet Gynecol. 2006; 194(1):160.

[37] Pramanik T, Khatiwada B, Pradhan P. Serum uric acid level in normal pregnant and preeclamptic ladies: a comparative study.

Nepal Med Coll J. 2014;16(1):30-32.
[38] Stone JL, Lockwood CJ, Berkowitz GS, Alvarez M, Lapinski R, Berkowitz RL. Risk factors for severe preeclampsia. Obstet Gynecol. 1993;83(3):357-61.
[39] Parrish M, Griffin M, Morris R, Darby M, Owens MY, Martin JN Jr. Hyperuricemia Facilitates the Prediction of Maternal and Perinatal Adverse Outcome in Patients with Severe/Superimposed Preeclampsia. J Matern Foetal Neonatal Med. 2010;23(12):1451-55.
[40] Koopmans C. M., van Pampus M. G., Groen H., Aarnoudse J. G., van den Berg P. P., Mol, B. W. 2009. Accuracy of serum uric acid as a predictive test for maternal complications in preeclampsia: bivariate meta-analysis and decision analysis. Eur J Obstet Gynecol Reprod Biol. 2009;146(1):08-14.

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**FINANCIAL OR OTHER COMPETING INTERESTS:** None.

Date of Publishing: **Oct 01, 2018**