EPH - International Journal of Medical and Health Science
ISSN (Online): 2456-6063
Volume 03 Issue 02 June 2017

DOI: https://doi.org/10.53555/eijmhs.v4i2.32

SERUM LEVELS OF SELECT MICRONUTRIENTS IN PRIMIGRAVIDA WITH PREECLAMPSIA VERSUS THEIR NORMOTENSIVE COUNTERPARTS: A CASE CONTROL STUDY AT A TERTIARY TEACHING HOSPITAL IN KENYA.

Pulei AN[1*], Kinuthia J[2], Omondi Ogutu[3]
*[*1]Lecturer, Department of Human Anatomy, University of Nairobi, Consultant Obstetrician Gynecologist*
[2]Head of Research and Programs, Kenyatta National Hospital, Consultant Obstetrician Gynecologist
[3]Chairman and Associate professor, Department of Obstetrics and Gynecology, University of Nairobi

Corresponding Author: -

Abstract:-

Background: *Preeclampsia (PE) is a one of the leading causes of maternal mortality as well as morbidity and long-term disability to mothers and newborns in sub-Saharan Africa. Various micronutrients have been implicated in its pathophysiology. Supplementation of some of these micronutrients, like calcium being recommended as part of the preventive strategies of PE in resource-poor countries. The status of these micronutrients and their relationship with PE vary from population to population.*

Objective: *To investigate the serum levels of select micronutrients (Vitamin D, calcium, zinc, and selenium) in preeclamptic and normotensive primigravid women in a tertiary teaching hospital in Kenya.*

Methods: *This was a case-control study. Primigravid controls matched for age and gestation with those with preeclampsia were included in the study. Data on their demographic and obstetric, nutritional were obtained. They were interviewed on frequency of consumption of specific nutrient rich foods. Blood samples were obtained for serum analysis of Vitamin D, Calcium, Selenium and Zinc levels.*

Results: *108 participants were included. There were no significant differences in age, educational level and income level between the two study groups. Mean serum calcium and Vitamin D levels were significantly lower among the participants with preeclampsia. The mean serum vitamin D level amongst cases and controls was 20.8±10.2 ng/ml and 28.6±7.9 ng/ml respectively ($p<0.001$) while the serum calcium levels were 2.2±0.3mmol/l for the cases and 2.3±0.09mmol/l for the controls ($p=0.024$). There was no statistically significant association between serum levels of Selenium and Zinc with preeclampsia. Most of the controls consumed diets rich in calcium in comparison to the cases. The controls were more likely to consume fish, one of the dietary sources of Vitamin D, compared to the cases. There were no differences in consumption of foods rich in zinc and selenium.*

Conclusion: *Pregnant women with preeclampsia have lower serum levels of calcium and vitamin D compared to their normotensive counterparts.*

Keywords*: Preeclampsia, Micronutrients, Vitamin D, Calcium, Selenium, Zinc*

INTRODUCTION

Preeclampsia (PE) is an unpredictable pregnancy specific condition characterized by new onset hypertension and either proteinuria or end organ dysfunction after 20 weeks gestation in a previously normotensive woman (ACOG 2013). PE and related hypertensive disorders of pregnancy continue to be a global problem. They constitute the top 5 causes of maternal mortality in the world (WHO 2014). Worldwide, 76,000 pregnant women and 500,000 babies die each year from PE and related hypertensive disorders (Duley 2009). In developing countries, 15-20% of maternal mortality is attributable to PE (Sibai et al., 2005). The incidence of preeclampsia alone in the world ranges from 2-8% (Walker 2000). In Kenya, the incidence varies from 1.5-9% (Kibaru 1992, Wangwe 2002, Njogu 2007). WHO estimates that the number of new cases of PE, one of the major causes of maternal mortality, to be seven times higher in low resource countries? Maternal mortality continues to burden Sub- Saharan African countries. Kenya has a high maternal mortality ratio (MMR), which has ranged from 500 to 600 per 100,000 live births, in the past decade (WHO 2015). Some counties in Kenya have even higher MMR of up to 1000 per 100,000 live births (Red Cross 2011). There has been minimal change in the MMR for Kenya from 2003 to 2014. Kenya therefore did not achieve the millennium development goal (MDG) goal 5 and is unlikely to achieve the sustainable development goals (SDGs) if the same trend continues. Preeclampsia and related hypertensive disorders are leading causes of maternal mortality and morbidity in Sub-Saharan Africa accounting for 19% of maternal deaths (WHO 2010). In a study done in the central province of Kenya, which has one of the lowest MMR (124 per 100,000) eclampsia was the second cause of death accounting for 7% of maternal deaths (Muchemi and Gichogo 2014). Reducing these hypertensive disorders of pregnancy largely depends on identification of modifiable risk factors and preventing them such as micronutrient deficiencies. Multiplemicronutrient (MMN) deficiencies often coexist among women of reproductive age. They are exacerbated in pregnancy due to the increased demands, leading to potentially adverse effects on the mother and developing fetus. Malnutrition has been thought to contribute largely to high rates of preeclampsia in developing countries due to the resultant deficits in certain trace elements (Caughey et al., 2005). While studying Isfahanian pregnant women, Paknahad et al., (2008) established a link between low dietary intake of foods containing calcium, zinc among others and subsequent development of pregnancy induced hypertension. Women in the developing countries are thought to consume diets that are low in minerals and vitamins. Poor quality diet is not unusual among Kenyans in both urban and rural environments; for example, the documented deficiency of vitamin D is as high as 79.4% in women attending antenatal care at an urban hospital (Dodia 2013). Though supplementation with MMNs has been recommended, this should be informed by deficiencies existing in the specific population. There is evidence that indicating a role for micronutrients supplementation in preventing some pregnancy disorders such as preeclampsia, particularly where there are deficiencies (Hofmeyr 2007). Little information is available in our region on the contribution of vitamin D, calcium, selenium and zinc in development of PE.

METHODS

Study design: Case control study.

Study setting: Kenyatta National Hospital is a regional Teaching and Referral hospital with 1800 bed capacity. It has a busy reproductive health department that conducts 20-50 deliveries per day. The prevalence of preeclampsia in this institution is 5%.

Study population: 108 primigravid women with preeclampsia ≥ 20 weeks gestation seen at the Kenyatta National Hospital matched for healthy pregnant women at the same gestation. These comprised 54 cases (those with preeclampsia) and 54 controls (normotensive women) matched for age (±2years) and gestational age (± 2 weeks).

Study procedure: After approval from the Kenyatta National Hospital/University of NairobiEthics/Review Committee (KNH-ERC) and seeking permission from the hospital administration, patients with preeclampsia were consented. They were then interviewed and had their demographic, obstetric parameters and dietary habits recorded in data collection sheets and blood samples obtained from them for determination of serum calcium, selenium, and zinc and Vitamin D levels. The blood taken was put in specimen bottles with a serum separator gel and taken to a diagnostic laboratory in Nairobi for analysis. The same was done for normotensive pregnant women in the same gestation and age. Dietary intake, for some foods rich in the micronutrients of concern, was assessed by means of a semi-quantitative food frequency questionnaire (FFQ) and 24-hour dietary recall, which was filled by a trained research assistant. Participants were asked to report their frequency of consumption of each food item during the previous year on a daily, weekly or monthly basis. Routine daily or weekly intake was classified as frequent, while monthly, occasional or once in a while was classified as infrequent. The specific foods rich in vitamin D asked about in this study included mushroom, fish and eggs while for calcium it was milk, cheese, yoghurt and green vegetables.

RESULTS

A hundred and eight primigravid women were included in this study (54 cases and 54 controls). Of these, 72% were between ages 20-30 years. Most, 90% had attained at least secondary. Sixty one percent had an average income of less that Ksh 10,000 (Table 1). The average gestational age was 35.2 ±4.4 weeks for the preeclamptic women and 35.4±4.4 weeks for the normotensive ones. For the cases, 38.9% had preeclampsia without features of severity (formerly mild preeclampsia) while 61.1% had severe preeclampsia. The average systolic and diastolic blood pressure among the cases was 155.7±17.4 and 105 ±10.2 respectively.

Table 1: Demographic characteristics of the study population

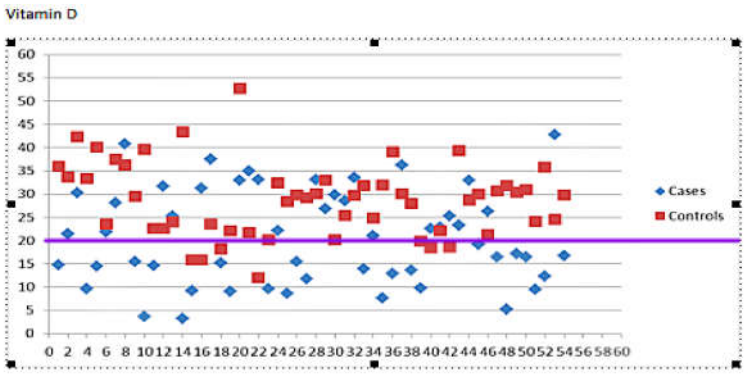
Characteristic		Total	Cases (n=54)	Control (n=54)	P-Value
Age distribution: (n=108)	<=20years	17(15.7)	9(16)	8(15)	
	21-30 years	78(72.2)	37(69)	41(76)	
	31-40 years	13(12.1)	8(15)	5(9)	0.62
Religion: (n=103)	Christian	102(99)	50(100)	52(98)	-
	Muslim	1(1)	0(0)	1 (2)	
Education level: (n=108)	Primary	10(9)	4(8)	6 (11)	
	Secondary	86(80)	45(83)	41(76)	
	Tertiary	12(11)	5(9)	7(13)	0.631
Average monthly income (n=106)	<10,000	65 (61)	36 69)	29 (54)	
	>=10,000	41(39)	16(31)	25 (46)	0.101
Marital status: (n=105)	Not married	28(27)	13(25)	15(29)	
	Married	77(73)	40(75)	37(71)	>0.999

There was no statistically significant association between serum levels of Selenium and Zinc with preeclampsia. The mean serum vitamin D level amongst cases and controls was 20.8±10.2 ng/ml and 28.6±7.9 ng/ml respectively (p<0.001). Serum calcium levels were 2.2±0.3mmol/l for the cases and 2.3±0.09mmol/l for the controls (p=0.024) as is shown in (Table 2). Vitamin D deficiency was more likely to be present among women with preeclampsia compared to the normotensive controls: 50% versus 13% respectively (p=<0.001) (Fig. 1). More controls consumed diet rich in calcium compared to controls. Vitamin D levels correlated negatively with systolic (Pearson's correlation-0.255, P-0.008) and diastolic blood pressure (Pearson's correlation -0.326, P-0.001). The relationship between serum calcium and serum vitamin D for the women with preeclampsia revealed a weak positive correlation between them, such that those with low calcium are more likely to also have low vitamin D serum levels. This correlation was not statistically significant (Pearson Correlation= 0.121, P-value=0.214). Fig 2

Table 2: Distribution of the mean serum levels of the micronutrients among the preeclamptic and normotensive primigravida

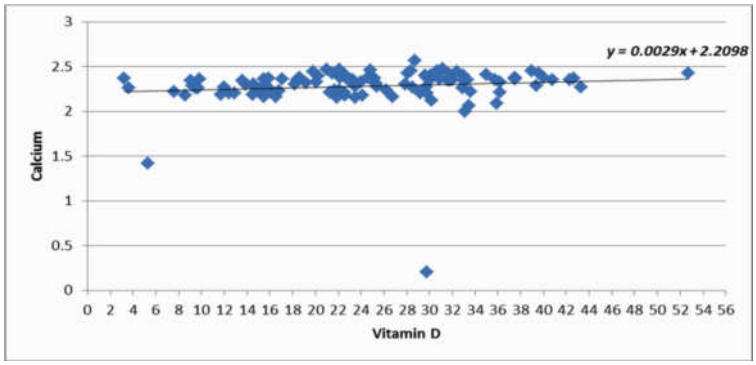
Micronutrient	Study group ± SD		P-Value
	Cases (n=54)	Controls (n=54)	
Vitamin D	20.8±10.2	28.6±7.9	<0.001
Selenium	103.5±33.3	99.7±24.7	0.498
Zinc	9.9±3.7	10.7±3.5	0.28
Calcium	2.2±0.3	2.3±0.09	0.024

Fig 1: Illustration of vitamin D levels among the study subjects. Deficient levels of Vitamin D (25-OH) is < 20ng/ml asrepresented by the purple line. Blue triangles are the cases while the red squares are controls. Note that most of the casesare below this line (The y axis is Vitamin D in ng/ml while the X-axis are the study participants: 54 cases and 54 controls)



Study Participants

Figure 2: Correlation between serum levels of vitamin D and calcium among the study population



Pearson Correlation= 0.121
P-value=0.214

Regarding consumption of specific micronutrient rich food, it was noted that the normotensive women consumed more fish (good dietary source of Vitamin D) as well the calcium rich foods such as milk, yoghurt, and cheese calcium compared to those with preeclampsia (Table 3).

Table 3: Proportion participants who consume specific foods rich in Vitamin D, calcium, selenium and zinc among the preeclamptics and the controls.

Consumption of specific vitamin D rich foods					
Food	Consumption	Total (%)	Cases (%)	Controls (%)	P-Value
Fish (n=106)	Frequent	65(61)	27(51)	38(72)	0.028
	Occasional/Never	41(39)	26(49)	15(28)	
Eggs (n=106)	Frequent	79(75)	39(74)	40(75)	0.823
	Occasional/Never	27(25)	14(26)	13(25)	
Mushroom (n=108)	Consumed in the past month	22(20)	10(19)	12(22)	0.632
	Never	86(80)	44(81)	42(78)	
Consumption of specific foods rich in calcium					
Cheese (n=107)	Frequent	9 (8)	2(4)	7(13)	0.093
	Occasional/Never	98(92)	52(96)	46(87)	
Yoghurt (n=107)	Frequent	45(42)	16(30)	29(54)	0.014
	Occasional/Never	62(58)	37(70)	25(46)	
Milk (n=108)	Frequent	74(69)	33(61)	41(76)	0.097
	Occasional/Never	34(31)	21(39)	13(24)	
Green vegetables (n=102)	Frequent	95(93)	49(96)	46(90)	0.436
	Occasional/Never	7(7)	2(4)	5(10)	
	Occasional/Never	76(71)	41(77)	35(65)	

DISCUSSION

Similar to the findings of other studies, Vitamin D deficiency was more likely to be present among women with preeclampsia than those who were normotensive ones with incidences of 50% and 13% respectively. Ringrose et al., (2011), also found that 29% of the women with preeclampsia were deficient of vitamin D compared to 13% of the normotensive women. These women with preeclampsia were are also more likely to have low mean serum Vitamin D levels in comparison to normotensive ones. These findings are in agreement with other authors in other LMIC (Singla et al., 2015 and Mohaghegh et al., 2015, Gupta et al., 2016). Even though black race is an independent risk factor for vitamin D deficiency, with reported incidences of between 66-100% in black populations, countries with traditions of whole body covering due to religious reasons, such as India, Turkey and Iran, had lower means of Vitamin D than ours for both the preeclamptics and normotensive women. Further, in Northwest Iran a study by Sadin et al., (2015), found that none of the women in their study had sufficient levels of Vitamin D. These authors established that the percentage of deficiency and insufficiency of vitamin D was 60% and 40% respectively for women with preeclampsia compared to 10% and 90% for those who were normotensive controls. Several mechanisms have been postulated on how low vitamin D status would result in preeclampsia. First Vitamin D is thought to play a role in the synthesis and regulation of genes that are responsible for early placental development (Novacovic et al., 2009). Second, Vitamin D has been thought to be a potent endocrine suppressor role in renin biosynthesis for the regulation of the renin-angiotensin system (RAS), an important regulator of fluid metabolism (Bukacak et al., 2015). Thirdly, it plays a role in placental immunomodulation, and is thought to have antiinflammatory properties (Diaz et al., 2009). The relationship between vitamin D and preeclampsia is complex, some authors have pointed out that low levels of this micronutrient in the second trimester may be an indicator of preeclampsia (Bodnar et al., 2007). Whether to supplement vitamin D in pregnancy is still a puzzle. A recent met analysis of 15 trials by DeRegil et al., (2016); showed that supplementation of Vitamin D by a single or continued dose, may increase serum

levels with resultant benefits of risk reduction for preeclampsia, low birth weight and preterm birth. Whether this can be implemented, as part of routine antenatal care requires policy changes for specific regions. RCOG (2014) recommends routine supplementation of Vitamin D in pregnancy particularly for those at risk, such as those with dark skin, hidden from the sun, obese or socially excluded. Patients with preeclampsia had lower levels of serum calcium in this study. Other studies done in LMIC have presented similar findings (Sukonpan and Phupong 2005, Mohieldein et al., 2007, Farzin and Sajadi 2012, Abdella and Adrabo 2013, Kanagal et al., 2014, Al Jameil et al., 2015). Notably, countries in Africa and India presented much lower levels of serum calcium in both cases and controls. The World Health Organization (WHO) proposed supplementing calcium for women in regions that are calcium deficient (Palacios and Pena-Rosas 2010). Encouraging dietary intake of foods rich in calcium maybe an easier alternative so as to reduce pill load. This study established nutritional habits relate to the status of serum calcium in our setup. Even though other studies have found that low serum selenium and zinc occur in women with preeclampsia, this was not the case in our study. Ghaemi et al., 2013 and Farzin and Sajadi 2012 in Iranian population presented significantly lower levels of Se in PE group. Among Nigerian patients, Akinloye 2010 also presented lower levels in the PE groups. Serum Zinc levels has also been established to be lower among women with preeclampsia in various studies (Akinloye et al., 2010, Akhtar et al., 2011, Farzin and Sajadi 2012, Al Jameil et al., 2015).

CONCLUSION

Patients with preeclampsia exhibited low levels of calcium and Vitamin D in comparison to their normotensive counterparts. Certainly, the incidence of vitamin D deficiency is high among patients with preeclampsia. Contrary to what has been presented in other populations, serum levels of zinc and selenium did not show any association with preeclampsia

RECOMMENDATIONS

Calcium and vitamin D supplementation for pregnant women thought to be deficient in these micronutrients or who are at risk of preeclampsia is recommended. Pregnant women should receive nutritional advice to encourage deliberate consumption of locally available foods known to be rich in these micronutrients such as milk, natural yoghurt, green vegetables, fish and eggs.

ACKNOWLEDGEMENT

We would like to thank the health workers at the Department of Reproductive health of the Kenyatta National Hospital and the University of Nairobi for their support when conducting this study. We are also grateful to the Lancet Laboratories for their help in biochemical analysis. **Funding:** The first author funded this study. It was part of her requirements for completion of Master of Medicine in Obstetrics and Gynaecology.

Conflict of interest: None

REFERENCES

[1]. American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 2013; 122:1122.

[2]. WHO. *World Health Statistics 2014.* Geneva, World Health Organization; 2014.

[3]. Duley L. The Global Impact of Preeclampsia and eclampsia. *Serum Perinatol.* 2009; 33 (3): 130-137.

[4]. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *Lancet.* 2005; 365(9461): 785-799

[5]. Walker JJ. Pre-clampsia. *Lancet.* 2000; 356: 1260-1265

[6]. Kibaru J. Outcome of pregnancy in patients with hypertensive disease. Postgraduate dissertation. University of Nairobi. 1992

[7]. Wangwe J. Reviewing pregnancy outcome in patients with hypertensive disease at Pumwani maternity hospital. Postgraduate dissertation. University of Nairobi. 2002

[8]. Njogu NK. Preclampsia; prevalence, maternal and neonatal outcome at the Aga khan University Hospital (unpublished master's dissertation). 2007. University of Nairobi.

[9]. Caughey AB, Stotland NE Washington AE, Escobar GJ. Maternal ethnicity, paternal ethnicity, and parental ethnic discordance: predictors of preeclampsia. Obstet Gynecol.2005 l; 106(1):156-61.

[10].Paknahad Z, Talebi N, Azadbakht L. Dietary determinants of pregnancy induced hypertension in Isfahan. *JRM.* 2008; 13(1): 17-21.

[11].Dodia RH. Prevalence of Vitamin D deficiency in anethnic African Urban obstetric population in an equatorial city hospital (unpublished master's dissertation). 2013. Aga Khan University, East Africa.

[12].Hofmeyr GJ, Duley L, Atallah A. Dietary calcium supplementation for prevention of preeclampsia and related problems: a systematic review and commentary. *BJOG*. 2007; 114: 933–943.

[13].Ringrose JS, PausJenssen AM, Wilson M, Blanco L, Ward H, and Wilson TW**.** Vitamin D and hypertension in pregnancy. *Clin Invest Med.* 2011; 34 (3): E147-54.

[14].Singla R, Gurung P, Aggarwal N, Dutta U, Kochhar R. Relationship between preeclampsia and vitamin D deficiency: a case control study Arch Gynecol Obstet. 2015 ;291(6):1247-51.

[15].Mohaghegh Z, Abedi P, Dilgouni T, Namvar F, Ruzafza S The relation of preeclampsia and serum level of 25-hydroxyvitamin D in mothers and their neonates: a case control study in Iran. *Horm Metab Res.* 2015; 47(4): 284-288

[16].Gupta S, Aziz N, Sekhon L, Agarwal R, Mansour G, Li J, Agarwal A. Lipid peroxidation and antioxidant status in preeclampsia: a systematic review. *Obstet Gynecol Surv*. 2009; 64(11): 750-759.
[17].Sadin B, Gargari BP, Tabrizi FPF. Vitamin D Status in Preeclamptic and Non-preeclamptic Pregnant Women: A Case-Control Study in the North West of Iran. Health Promot Perspect. 2015; 5 (3): 183–190.
[18].Novakovic B, Sibson M, Ng HK, Manuelpillai U, Rakyan V, Down T, Beck S, Fournier T, Evain-Brion D, Dimitriadis E, Craig JM, Morley R, Saffery R. Placenta-specific methylation of the vitamin D 24-hydroxylase gene: implications for feedback autoregulation of active vitamin D levels at the fetomaternal interface. J Biol Chem. 2009; 284:14838–48.
[19].Bakacak M, Serin S, Ercan O, Köstü B, Avci F, Kılınç M, Kıran H, Kiran G. Comparison of Vitamin D levels in cases with preeclampsia, eclampsia and healthy pregnant women. *Int J Clin Exp Med*. 2015 Sep 15;8(9): 16280-6. eCollection 2015.
[20].Diaz L, Noyola-Martinez N, Barrera D, Hernández G, Avila E, Halhali A, Larrea F. Calcitriol inhibits TNF-alpha-induced inflammatory cytokines in human trophoblasts. *J Reprod Immunol.* 2009; 81:17–24.
[21].Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM. Maternal vitamin D deficiency increases the risk of preeclampsia. *J. Clin. Endocrinol Metab*. 2007; 92(9): 3517-3522.
[22].De-Regil LM, Palacios C, Lombardo LK, Peña-Rosas J. Vitamin D supplementation for women during pregnancy. Cochrane Database Syst Rev. 2016 ;(1): CD008873. doi: 10.1002/14651858.CD008873.pub3
[23].RCOG. Vitamin D in Pregnancy. Scientific Impact Paper No. 43. 2014.
(https://www.rcog.org.uk/en/guidelines-research-services/guidelines/sip43/)
[24].Sukonpan K, Phupong V. Serum calcium and serum magnesium in normal and preeclamptic pregnancy. Arch Gynecol Obstet. 2005; 273(1): 12-16.
[25].Mohieldein AH, Dokem AA, Osman YHM, Idris HMA. Serum calcium level as a marker of pregnancy-induced hypertension. *Sudan JMS*. 2007; 2(4): 245-248.
[26].Farzin L, Sajadi F. Comparison of serum trace element levels in patients with or without preeclampsia. *J Res Med Sci.* 2012; 17(10): 938–941.
[27].Abdellah A, Abdrabo A Assessment of serum calcium, magnesium, copper and zinc levels in Sudanese pregnant women with pre-eclampsia GARJMMS: 2014 Vol. 3(2): 033-036.
[28].Kanagal DV, Rajesh A, Rao K, Devi UH, Shetty H, Kumari S, Shetty PK. Levels of Serum Calcium and Magnesium in Pre-eclamptic and Normal Pregnancy: A Study from Coastal India. *J Clin Diagn Res.* 2014;8(7):OC01-4.
[29].Al-Jameil N, Tabassum H, Ali MN, Qadeer MA, Khan FA, Al-Rashed M. Correlation between serum trace elements and risk of preeclampsia: A case controlled study in Rihadh Saudi Arabia. *Int J Clin Exp Pathol*. 2014; 7(5): 1900-1910
[30].Palacios C, De-Regil LM, Lombardo LK, Peña-Rosas JP. Vitamin D supplementation during pregnancy: Updated meta-analysis on maternal outcomes.J Steroid Biochem Mol Biol. 2016 pii: S0960-0760(16)30025-5. doi: 10.1016/j.jsbmb.2016.02.008. [Epub ahead of print] Review.
[31].Ghaemi SZ, Forouhari S, Dabbaghmanesh MH, Sayadi M, Bakhshayeshkaram M, Vaziri F, Tavana Z A prospective study of selenium concentration and risk of preeclampsia in pregnant Iranian women: a nested case-control study. *Biol Trace Elem Res.* 2013; 152 (2): 174-179
[32].Akinloye O, Oyewale J, Oguntibeju O Evaluation of trace elements in pregnant women with pre-eclampsia. A. J Biotech. 2010; 9(32): 5196-5202
[33].Akhtar S, Begum S, Ferdousi S. Calcium And Zinc Deficiency In Preeclamptic women. *J. Bangladesh Soc Physiol.* 2011; 6(2): 94-99.