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Trace Elements, Antioxidants, Uric Acid, C-Reactive Proteins and Estrogen Levels of Preeclamptic Pregnant Women in Owerri, Nigeria

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Authors' contributions

All the Authors collaborated and produced this work. Authors CNN and ASE designed the study. Authors CIN and MTA carried out the study and collected the results. Authors AAE, OCA and CO carried out the statistical analysis of the results. The interpretation of results, preparation and approval of the final manuscript were done by all the Authors.

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ABSTRACT

Aims: The present study investigated levels of trace elements, antioxidants, uric acid, C-reactive proteins and estrogen in preeclamptic pregnant women in Owerri, Imo State, Nigeria using patients from Federal Medical Centre (FMC) and specialists Hospital in Owerri, Nigeria.
Study Design: A total of 350 pregnant women between the ages of 20-40 years from two known hospitals in Owerri were examined for the study. The examined pregnant women were group into 160 normotensive pregnant women as control and 190 preeclamptic pregnant women.
Results and Discussion: Results obtained for serum trace elements revealed significant decrease ($p<0.05$) in preeclamptic pregnant women against normotensive pregnant women. Antioxidant

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vitamins C and E; and estrogen significantly decreased ($p<0.05$) in preeclamptic pregnant women against normotensive pregnant women. Uric acid and C-reactive protein levels increased in preeclamptic pregnant women against normotensive pregnant women. The decrease in trace elements could be linked to development of preeclampsia since some of these trace elements perform antioxidant function. Increased antioxidant activity and lipid peroxidation could be behind the reduced levels of vitamins C and E, and estrogen in preeclamptic pregnant women against normotensive pregnant women.

Conclusion: This study has revealed the trace elements, antioxidants, uric acid, C-reactive proteins, and estrogen levels of preeclamptic pregnant women in Owerri, Nigeria.

Keywords: Antioxidants; estrogen; preeclampsia; hospitals; trace elements.

1. INTRODUCTION

Preeclampsia has been described as a condition marked by high blood pressure in women with no previous history or experience of high blood pressure during pregnancy [1-3]. Al-Jameil et al. [4] noted that preeclampsia is a common medical complication of pregnancy standing next to hemorrhage and embolism among pregnancy related cause of death. It has been reported that in preeclampsia, the systolic BP is 140 mmHg and diastolic BP 90 mmHg in a woman with previously normal blood pressure and with proteinuria 0.3 gm in a 24-hour urine collection or equal to 1+ or 100 mg/dl by dipstick response [4]. The condition normally appears at the late stage of pregnancy in women, though some few earlier occurrences have been reported [5-6]. It has been noted that if preeclampsia condition is not treated, it could lead to eclampsia. Eclampsia is a condition associated with seizures and could seriously place the mother and her unborn child at risk [7]. In severe preeclampsia, the fetus or newborn may have neurological damage induced by hypoxia [8]. Poor nutrition, high body fat, insufficient blood flow to the uterus, genetics as well as malfunctioning placenta that is not known, are among the suspected causes of preeclampsia conditions in pregnant women [9-11]. Generally, first-time pregnancies, pregnant teens, and pregnant women over 40 are at risk of preeclampsia condition [12-13].

Both macro and micro nutrients have important influence on the health of pregnant women and growing fetus [14]. Vitamins, some mineral elements, proteins and fatty acids are always in high demand during pregnancy [4]. Naeye [15] noted that pregnancy is associated with increased demand of all micronutrients such as iron, copper, zinc, vitamin B12, folic acid and ascorbic acid. According to Al-Jameil et al. [4], the deficiency of nutrients could affect pregnancy, delivery and out-come of pregnancy. The roles of copper, zinc and manganese during pregnancy have been reported by Balck [14], WHO [16], Giles and Doyle [17], Ziael et al. [18], Jaiser and Winston [19]. Lipid peroxidation which leads to generation of reactive oxygen species (ROS) has been associated with preeclampsia. ROS has been linked to placental oxidative stress and has been noted to be a key feature in the pathogenesis of preeclampsia [20]. Vitamins C and E are amongst the natural non-enzymatic antioxidants, which are known to generate molecules that fight these reactive oxygen species [21-24]. C-reactive protein is a sensitive marker and has been reported to elicit response characteristics of preeclampsia as noted by Mirzaie et al., [25]. In pregnancy affected by hypertension, increased uric acid has been reported as part of metabolic syndrome at ten weeks [26]. Uric acid has also been reported to have a relationship with estrogen, blood volume, and glomerular filtrates in pregnancy [27].

The present study investigated levels of trace elements, antioxidants, uric acid, C-reactive proteins and estrogen in preeclamptic pregnant women in Owerri, Imo State, Nigeria using patients from Federal Medical Centre (FMC) and specialists Hospital in Owerri, Nigeria.

2. MATERIALS AND METHODS

2.1 Study Area

The present study was carried out in Owerri, the capital of Imo State, southeast geopolitical zone of Nigeria. Owerri covers about 100 square kilometers (40 square meter) and falls within tropical rain forest zone. It lies within the latitude 5°25´-5°29´N and longitude 6°59´-6°30´E. Owerri houses majorly the Igbo speaking tribe of Nigeria, though few people from other tribes found in Nigeria also reside within. The inhabitants of Owerri are predominantly Christians with very few pagans and Muslims.

2.2 Study Population

The Federal Medical Centre and Imo Specialist Hospital were used for this study. A cohort of pregnant women who were attending prenatal care at the antenatal clinic and wards of both hospitals were selected from July 2017 to July 2018. Each participant signed an informed consent form after the procedure and implications were explained using a language the subject would understand. Research and Ethics Committee of both hospitals used granted ethical approval for this study. A total of 350 pregnant women between the ages of 20-40 years were examined for this present study. The examined pregnant women were of two groups of 160 normal pregnant women (normotensive pregnant women) as control; and 190 preeclamptic pregnant women as test group. Each of the hospitals used provided half of the participants that make up each group. Absence of labour and premature ruputure of membrane, febrile illness in pregnancy, metabolic illness such as diabetes mellitus, liver disease, kidney disease, dyslipidemia, HIV, sickle cell disease and history of any other chronic disease were among the exclusion criteria used for the selection of participants. With the help of a standard mercury sphygmomanometer, maternal blood pressure was taken following the methods as described by Ikaraoha et al. [28].

2.3 Blood Sample Collection

Five milliliters of venous blood were collected from each of the participants at delivery and dispensed into the plain container. The collected blood sample was allowed to clot and the serum was separated. The separated serum was stored appropriately under refrigeration and then used for further analysis.

2.4 Analysis of Serum Samples

Serum copper, zinc, and iron trace elements were analyzed following the instructions as contained in their kits. The uricase method using Human diagnostic kit was used for estimation of uric acid [29]. C-reactive protein was estimated by latex agglutination slide test using C-reactive protein reagent kit. Vitamins C and E were determined by 2,4-dinitrophenyl hydrazine spectrophotometric methods and Alpha-Alpha dipyridly method respectively. Estrogen was estimated using Abcam`s estradiol *in vitro* competitive kit.

2.5 Statistical Analysis

The mean and standard deviations of all the results generated were computed. Results were presented as mean ± standard deviation. Students t-distribution at 5% ($p<0.05$) level was used to compute significance. Asterisk (*) was used to depict significant values between corresponding bars of Figs. 2 to 4.

3. RESULTS AND DISCUSSION

Fig. 1 shows the blood pressure of participants. From the Figure, systolic blood pressure of preeclamptic pregnant women was 148±3.07 mmHg against 119.13±2.10 mmHg of normotensive pregnant women. Diastolic blood pressure of preeclamptic was 95.07±1.75 mmHg against 78.20±1.08 mmHg of normotensive pregnant women. Al-Jameil et al. [4] noted that preeclampsia is characterized by development of high blood pressure (hypertension). According to World Health Organization, hypertension is defined as blood pressure persistently equal to or higher than 140 (systolic) /90 (diastolic) mmHg at rest [30]. Both systolic and diastolic blood pressure of preeclamptic pregnant women in this study were significantly higher ($p<0.05$) against those of normotensive pregnant women. The observed systolic and diastolic pressure of preeclamapsia subjects in the present study could be compared with the observation of Al-Jameil et al. [4] who note that in preeclampsia, the systolic BP is 140 mmHg and diastolic BP 90 mmHg in a woman with previously normal blood pressure.

A number of studies conducted to know the relationship between maternal plasma trace elements level and preeclampsia have been reported inconsistently [31]. Fig. 2 shows the levels of serum trace elements in participants. From the Figure, zinc ranged from 7.83-9.15 µg/dl; iron ranged from 6.14-8.05 µg/dl; and copper ranged from 6.43-9.13 µg/dl. The importance of trace elements in preeclampsia relates to the fact that they are found in metalloproteins, ceruloplasmin, superoxide dismutase, and glutathione peroxidase [32]. Essential trace elements such as zinc, iron, copper amongst others are required for maintenance of normal health in human populations [14-16, 33]. Their possible individual roles in preeclampsia have also been reported by different authors [34]. According to Apgar [35], previous studies have suggested that alterations in maternal serum or plasma zinc levels are

found in preeclampsia. Zinc decreased significantly ($p<0.05$) in preeclamptic pregnant women when compared to normotensive pregnant women in this study. Decreased zinc levels in preeclampsia has been reported by Chsolm et al. [36], Adeniyi [37] and Diaz et al. [38]. Al-Jameil et al. [4] attributed low serum zinc in preeclampsia to reduced concentrations of transport proteins. Zinc deficiency has been linked to increase in lipid peroxidation [39] while Tamura et al. [40] attributed such decrease to reduce in zinc binding proteins and increase in transfer of zinc from the mother to fetus. Malek-mellouli et al. [41] reported iron status in pregnant women and its changes during preeclampsia. Significant increase in compounds associated with iron such as hemoglobin, haematocrit, serum ferritin and transferrin saturation during pregnancy, which later develops preeclampsia has been reported by Tasneem and Zafar [42]. Iron has been linked to oxidative stress and in radical form has been linked to pathogenesis of preeclampsia [42]. Iron in preeclampsia pregnant women in the present study reduced significantly ($p<0.05$) against normotensive pregnant women (Control). This is inconsistent with the increase reported by Kandi et al. [43], who noted that the raised serum iron levels in turn alters the iron related parameters like total iron binding capacity(TIBC), serum ferritin, transferrin, and percent saturation; and the work of Rayman et al. [44]. Raffeeinia et al. [45] noted that copper is an important trace element which takes part in structure of many enzymes like lysyl oxidase, cytochrome coxidase, tyrosinase, dopamine-β-hydroxylase, peptidylgly-cine alpha-amidating monooxygenase, monoamine oxidase, ceruloplasmin, and copper–zinc superoxide dismutase. It has been reported that copper can produce the highly reactive hydroxyl radical. According to Fang et al. [46], the generation of highly reactive hydroxyl radical can begin lipid peroxidation process which may cause endothelial cell damage. According to Raffeeinia et al. [45] and Ilhan et al. [47], many studies have shown that copper concentration increased in preeclampsia patients. However, copper decreased significantly ($p<0.05$) in preeclamptic pregnant women against the normotensive pregnant women (Control) in the present study. This observation is line with earlier work of Kanagal et al. [48] on copper levels in preeclampsia: a study from coastal South India, Akinloye et al. [49] and Ugwu et al. [50]. The decrease in levels of zinc and copper in this study agree with the earlier observation of Akinloye et al. [49], Kanagal et al. [48] and Ikaraoha et al. [28]; but inconsistent with the study of Ohad et al. [51], who reported higher levels of copper and zinc in preeclampsia cases. The observed decrease in trace elements in the present study could be linked to development of preeclampsia since some of these trace elements perform antioxidant function as well.

Pregnancy generally imposes physiological stress on expectant mothers which results in the utilization of antioxidants. According to Kashinakunti et al. [52] and Mehmet et al. [53], free radicals and other damaging reactive

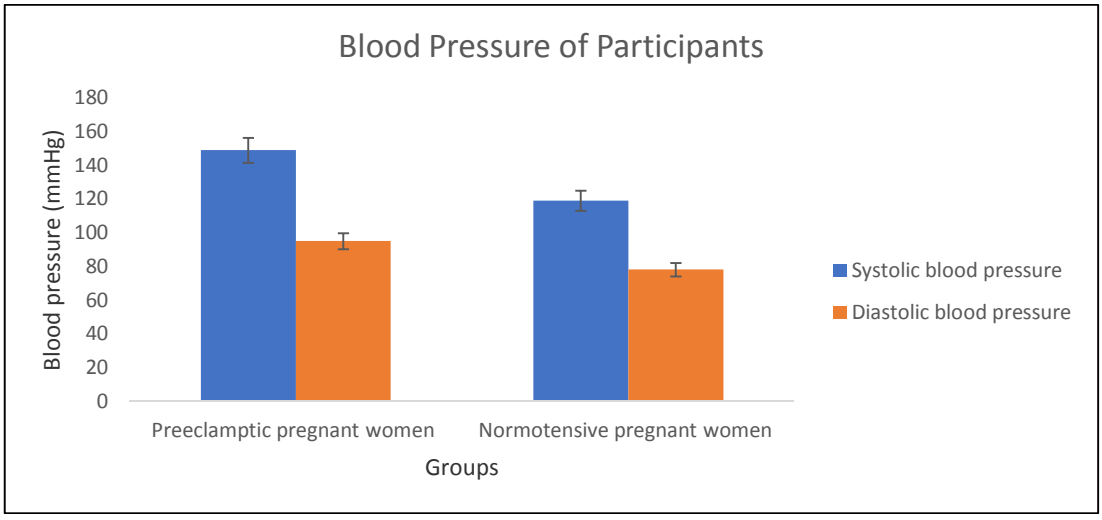

Fig. 1. Blood pressure of participants

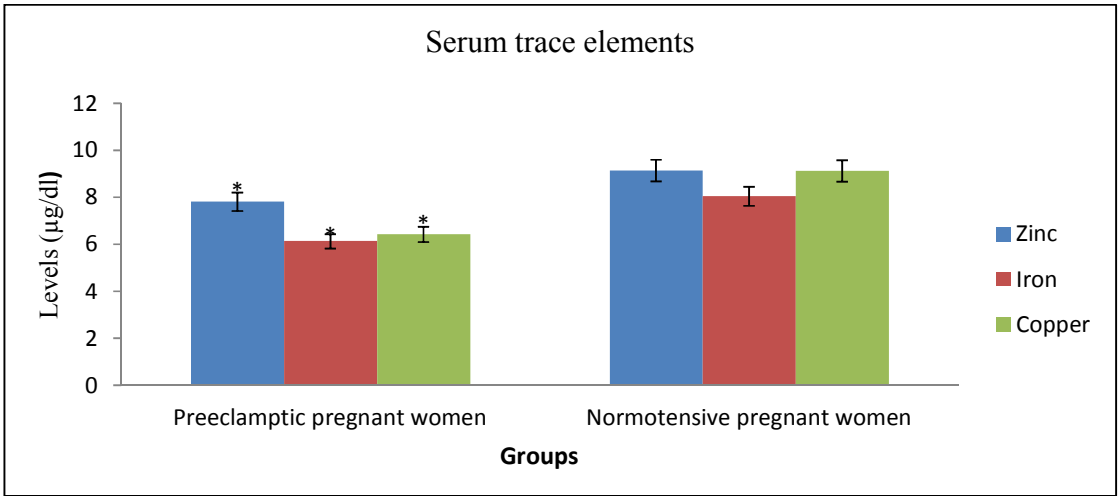

Fig. 2. Levels of serum trace elements in participants

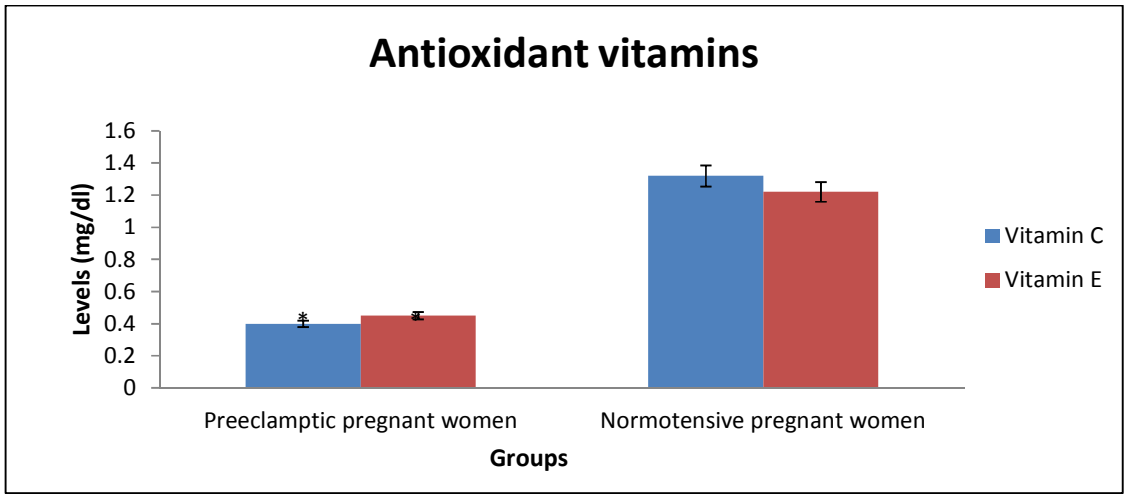

Fig. 3. Vitamin levels of participants

oxygen species, such as the superoxide anions are in oxidative metabolic processes, their activation is thought to increase during preeclampsia. Fig. 3 shows vitamin levels of participants in the present study. From the Figure, vitamin C ranged from 0.40-1.32 mg/dl; and vitamin E from 0.45-1.22 mg/dl. This study revealed that vitamins C and E levels of preeclamptic pregnant women reduced significantly ($p<0.05$) when compared to normotensive pregnant women. The studies of Kashinakunti et al. [52], Kiondo et al. [54], Chappell et al. [55] and Wang and Walsh [56] have reported decreased levels of vitamin C level in preeclampsia patients. Rokeya [57] observed the reduction of plasma vitamin E in preeclampsia. The scavenging or antioxidant roles of vitamins C and E are increased in preeclampsia cases because of increased lipid peroxidation. This may have resulted in excessive utilization of these vitamins causing their reduction in the body preeclampsia pregnant women.

Levels of uric acid, C-reactive proteins and estrogen are presented in Fig. 4. From the Figure uric acid ranged from 5.56-7.59 mg/dl; C-reactive protein was between 0.96-4.16 mg/dl; while estrogen ranged from 166.32-236.38 pg/ml. Elevated uric acid is another component of the preeclampsia syndrome that was recognized many years ago, though it has been found to be

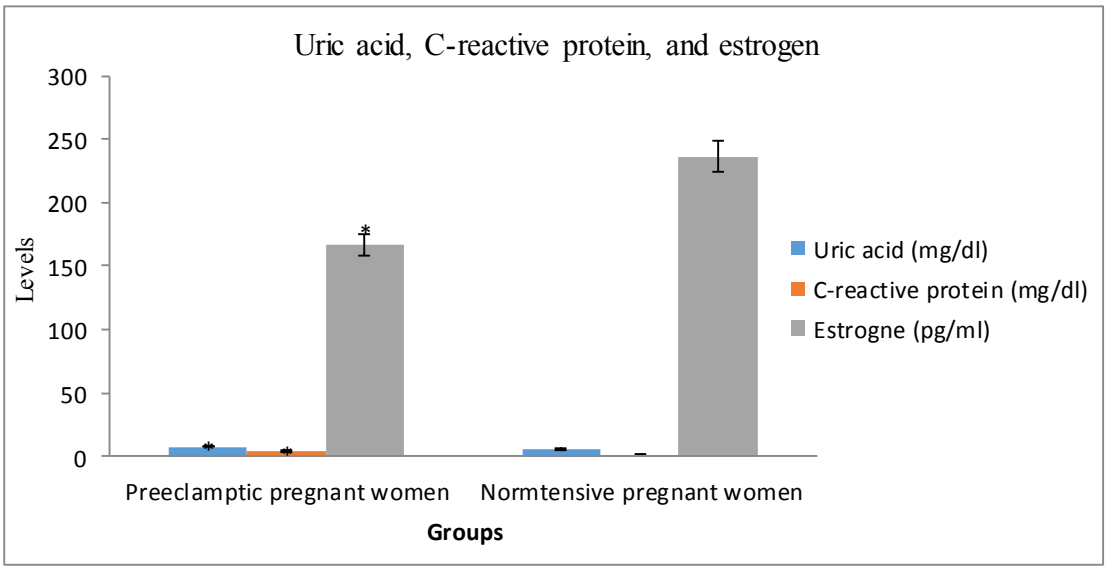

Fig. 4. Levels of uric acid, C-reactive protein and estrogen levels of participants

a poor predicator of the disorder [58-60]. Lam et al. [61] reported that increased uric acid level is a key clinical feature of preeclampsia; higher levels correlate with significant maternal and fetal morbidity and mortality. Uric acid increased significantly ($p<0.05$) in preeclampic pregnant women than normotensive pregnant women in the present study. This is in line with the work of Bainbridge and Robert [62] who noted that hyperuricemia is a characteristic feature preeclampsia. Increased level of uric acid in preeclampsia subjects can be attributed to hyervolemia, increased xanthine oxidase activity; and increased foetal and maternal tissue damage. Markus [63] noted that preeclampsia is a disease characterized by increased antiangiogenesis and inflammation. C-reactive protein *(*CRP*)* is a substance produced by the liver in response to inflammation. A high level of C-reactive protein in the blood is a marker of inflammation. For a long time, a role of CRP in preeclampsia has been conceived. Parchim et al. [64] unravel a mechanism which might account for placental and also for kidney injury and arterial hypertension in preeclamptic disease. C-reactive protein reduced significantly ($p<0.05$) in preeclampsia pregnant women than normotensive pregnant women in the present study. Parchim et al. [64] demonstrated the placenta as production site for CRP in addition to the liver in nonpregnant conditions. Barkane et al. [65] reported that during pregnancy, estrogen is produced primarily in the placenta by conversion of androgen precursors originating from maternal and fetal adrenal glands. Estrogen significantly decreased ($p<0.05$) in preeclampsia pregnant women against normotensive pregnant women in the present study. The observation is not in line with the study of Barkane et al. [65] who noted that aberrant production of estrogens could play a key role in preeclampsia symptoms because they are exclusively produced by the placenta and they promote angiogenesis and vasodilation.

4. CONCLUSION

In conclusion, reduced serum levels of trace elements, antioxidant vitamins and estrogen were observed in pregnant women with preeclampsia condition against normotensive pregnant women. Uric acid and C-reactive proteins levels followed increased trend in preeclampic pregnant women when compared to those of normotensive pregnant women. The decrease in trace elements could be linked to development of preeclampsia since some of these trace elements perform antioxidant function. Increased antioxidant activity and lipid peroxidation could be behind the reduced levels of vitamins C and E, and estrogen in preeclamptic pregnant women against normotensive pregnant women. The study has revealed the trace elements, antioxidants, uric acid, C-reactive proteins, and estrogen levels of preeclamptic pregnant women in Owerri, Imo State, Nigeria.

CONSENT

Each participant signed an informed consent form after the procedure and implications were explained using a language the subject would understand.

ETHICAL APPROVAL

Research and Ethics Committee of both hospitals used granted ethical approval for this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Penny J, Shennan A, Halligan A, Taylor D, De Swiet M, Anthony J. Blood pressure me asurement in severe pre-eclampsia. The Lancet. 1997;349(9064):1518.
2. Gaym A, Bailey P, Pearson L, Admasu K, Gebrehiwot Y, Team ENEA. Disease burden due to pre-eclampsia/eclampsia and the Ethiopian health system's response. International Journal of Gynecology & Obstetrics. 2011;115(1):112-116.
3. Aoki S, Toma R, Kurasawa K, Okuda M, Takahashi T, Hirahara F. Expectant management of severe preeclampsia with severe fetal growth restriction in the second trimester. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health. 2014;4 (1):81-86.
   Available:http://dx.doi. org/10.1016 /j.preghy. 2013.11.006
4. Al-Jameil N, Tabassum, H, Al-Mayouf H, Aljohar, HI, Alenzi ND, Hijazy SM, Khan FZ. Analysis of serum trace elements-copper, manganese and zinc in preeclamptic pregnant women by inductively coupled plasma optical emission spectrometry: A prospective case controlled study in Riyadh, Saudi Arabia. Int J Clin Exp Pathol. 2014;7(5):1900-1910.
5. Asif N, Nagia A, Khaula K, Shahdia S. Incidence of Gestational High Blood Pressure. PJMHS. 2013;7(2):397-399.
6. Cunningham FG, Roberts JM, Taylor RN. Chapter 2 - The clinical spectrum of preeclampsia. In R. N. T. M. R. G. C. D. Lindheimer (Ed.), Chesley's Hypertensive Disorders in Pregnancy (Fourth Edition) San Diego: Academic Press. 2015;25-36.
7. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: Systematic review of controlled studies. BMJ. 2005;330(7491):565.
8. Hernandez-Diaz S, Toh S, Cnattingius S. Risk of pre-eclampsia in first and subsequent pregnancies: prospective cohort study. BMJ. 2009;18:338:b2255.
   DOI: 10.1136/bmj.b2255.
9. Haelterman E, Qvist R, Barlow P, Alexander S. Social deprivation and poor access to care as risk factors for severe pre-eclampsia. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2003;111(1):25-32.
10. Haddad B, Kayem G, Deis S, Sibai BM. Are perinatal and maternal outcomes different during expectant management of severe preeclampsia in the presence of intrauterine growth restriction? Am J Obstet Gynecol. 2007;196(237):e1–5.
11. Belghiti J, Kayem G, Tsatsaris V, Goffinet F, Sibai BM, Haddad B. Benefits and risks of expectant management of severe preeclampsia at less than 26 weeks gestation: The impact of gestational age and severe fetal growth restriction. Am J Obstet Gynecol. 2011;205(465): e1–6.
12. Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). Am J Obstet Gynecol. 1993;169(4):1000–6.
13. Hall DR, Odendaal HJ, Steyn DW. Expectant management of severe pre-eclampsia in the mid-trimester. Eur J Obstet Gynecol Reprod Biol. 2001;96:168–72.
14. Black RE. Micronutrients in pregnancy. Br.J Nutr. 2001;85-197.
15. Naeye R, Blane W, Paul C. Effects of maternal nutrition on human fetus. Pediatr. 1973;52:494-503.
16. WHO trace elements in human nutrition and health. Geneva: WHO Press. 1996;72-104.

17. Giles E, Doyle LW. Copper in extremely low-birth weight or very preterm infants. Am Acad Pediatr. 2007;8: 159-64.
18. Ziael S, Ranjkesh F, Faghihzadeh S. Evaluation of 24-hourcopper in pre-eclamptic vs normotensive pregnant and nonpregnant women. Int J Fertil Steril 2008;2:9-12.
19. Jaiser SR, Winston GP. Copper deficiency myelopathy: Review. J Neurol. 2010;257:869-81.
20. Rumiris D, Purwosunu Y, Wibowo N, Farina A, Sekizawa A. Lower rate of preeclampsia after antioxidant supplementation in pregnant women with low antioxidant status. Hypertens Pregnancy. 2006;25:241-53.
21. Nino HV, Shah, W. Vitamins In: Fundamentals of Clinical Chemistry. Tietz, N.W. (ed.) 2nd edition. WB Saunders, Philadelphia. 1986;547-550.
22. Naidu AK. Vitamin C in human health and disease is still a mystery; an overview. Nutrition Journal. 2003;2(7):1-10.
23. Niki E. Free radical. Biological and Medicine. 2014;66:3-12.
24. Nimse BS, Pal D. Free radical, natural antioxidants and their reaction mechanism. Royal Society of Chemistry. 2015;5:27986-28006.
25. Mirzale F, Rahimi-Shorbaf F, Kazeroine A. Association of maternal serum C-reactive protein levels in severity of preeclampsia. Acta Medica Iranica. 2008; 4(4):293-296.
26. Robert JM, Bodnar LM, Lain KY, Hubel CA, Markovic N, Ness RB, Pwers RN. Uric acid is as important as proteinuria in identifying foetal risk in women with gestational hypertension. Hypeetension. 2005;46:1263-1269.
27. Bainbridge S, Robert JM. Uric acid as a pathogenic factor in preeclampsia. Placenta. 2008;29: 67-72.
28. Ikaraoha IC, Mbadiwe NC, Anetor JI, Ojareva IA. Serum trace metals in pre-eclamptic Nigerians. Asian Journal of Medical Sciences. 2015;7(3):78-83.
29. Fossati LP, Berti G. Use of 3, 5-dichloro-2-hydroxybenzenesulfonic acid/4-aminophenazone chromogenic system in direct enzymic assay of uric acid in serum and urine. Clin Chem. 1980; 26(2):227-231.
30. World Health Organization. A global brief on hypertension. Silent killer, global public health crisis, 2013. World Health Organization Web site.

    Avaiable:http://www.who.int/cardiovascular_diseases/publications/global_brief_hypertension/ en/

    (Accessed April 2013)
31. Harma M, Harma M, Kocyigit A. Correlation between maternal plasma homocysteine and zinc levels in preeclamptic women. Biol Trace Elem Res. 2005;104:97-105.
32. Lao TT, Chin RKH, Mark YT, Swaminath R, Iam YM. Plasma and erythrocytes zinc and birth weight in pre-eclampsia pregnancies. Archives Gynoecology and Obsterics. 2010;247:167-171.
33. Chan S, Gerson B, Subramaniam S. The role of copper, molybdenum, selenium and zinc in nutrition and health. Clinical & Laboratory Medicine. 1998;18(4):673-685.
34. Acikgoz S, Harma M, Mungan G, Can M, Demirtas S. Comparison of angiotensin-converting enzyme, malonaldehyde, zinc, and copper levels in preeclampsia. Biological Trace Elements Research. 2006;113(1):1-8.
35. Apgar J. Zinc and reproduction. Ann Rev Nutr. 1985;5:43-68.
36. Chisolm JC, Handorf CR. Zinc, cadmium, metallothionein, and progesterone: do they participate in the etiology of pregnancy induced hypertension? Med Hypotheses. 1985;17:231-242.
37. Adeniyi AFF. The implication of hypozincemia in pregnancy. Acta Obstet Gynecol Scand. 1987;66:579-581.
38. Diaz E, Halhali A, Luna C, Diaz L, Avila E, Larrea F. Newborn birth weight correlates with placental zinc, umbilical insulin-like growth factor I and leptin levels in preeclampsia. Arch Med Res. 2002;33:40-47.
39. Yousef MI, El Hendy HA, El-Demerdash FM, Elagamy EI. Dietary zinc deficiency induced-changes in the activity of enzymes and the levels of free radicals, lipids and protein electrophoretic behavior in growing rats. Toxicology. 2002;175:223-234.

40. Tamura T, Goldenberg RL, Johnston KE, Dubard M. Material plasma and zinc concertation and pregnancy outcome. American Journal of clinical Nutritional. 2000;71:109-113.
41. Malek-mellouli M, Amara FB, Loussaief W, Reziga H. Iron status in pregnant women and its changes during preeclampsia. La tunisie Medicale. 2013;91(10):577-582.
42. Tasneem Z, Zafar I. Iron stataus in preeclampsia. Professional Med J. 2008;15(1):74-80.
43. Kandi S, Sudhakar T, Ramadevi C, Venugopal B, Rajkumar Rafi M, Ramana KV. Pre-eclampsia and iron status: A review. American Journal of Medical and Biological Research. 2014;2(6):121-123.
44. Rayman MP, Barlis J, Evans RW, Redman CW, King LJ. Abnormal iron parameters in the pregnancy syndrome preeclampsia. Am J.Obstet Gynecol. 2002;187(2):412-418.
45. Rafeeinia A, Tabandeh A, Khajeniazi S, Marjani AJ. Serum Copper, Zinc and Lipid Peroxidation in Pregnant Women with Preeclampsia in Gorgan. The Open Biochemistry Journal. 2014;8:83-88.
46. Fang YZ, Yang S, Wu G. Free radicals, antioxidants and nutrition. Nutrition. 2002;18:872-879.
47. Ilhan N, Ilhan N, Simsek M. The changes of trace elements, malondialdehyde levels and superoxide dismutase activities in pregnancy with or without preeclampsia. Clin. Biochem. 2002;35:393-397.
48. Kanagal DV, Aparna R, Kavyar R, Harish S, Prasanna KS, Harshinid U. Zinc and copper levels in preeclampsia: a study from coastal South India. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2014;3(2):370-373.
49. Akinloye O, Oyewale OJ, Oguntibejum OO. Evaluation of trace elements in pregnant women with pre-eclampsia. African Journal of Biotechnology. 2010;9(32):5196-5202.
50. Ugwu EI, Ejikeme BN, Ugwu NC, Obeka NC, Emmanuel IA, Onyechi O. Comparison of plasma copper, iron and zinc levels in hypertensive and non-hypertensive pregnant women in Abakaliki, South Eastern, Nigeria. Pakistan Journal of Nutrition. 2010;9(12):1136-1140.
51. Ohad K, Tal OP, Lazer T, Tamir BA, Mazor M, Witnitzer A, Sheiner E. Severe preeclampsia is associated with abnormal trace elements concentrations in maternal and foetal blood. Am J Obstet Gynecol. 2009;201:280-281.
52. Kashinakunti SV, Sunitha H, Gurupadappa K, Shankarprasad DS, Suryaprakash G, Ingin J.B. Lipid peroxidation and antioxidant status in preeclampsia. Al Ameen J Med Sci. 2010;3(1):38-41.
53. Mehmet H, Muge H, Ozcan E. Measurement of total antioxidant response in pre-eclampsia with a novel automated method. Eur J Obstet Gynecol & Reprod Biol. 2005;118(1):47-51.
54. Kiondo P, Welishe G, Wandabwa J, Wamuyu-Maina G, Bimenya GS, Okong P. African Health Sciences. 2011;11(4):566-572.
55. Chappell LC, Seed PT, Briley A, Kelly SRN, Frank J, Hunt BJ, et al. A longitudinal study of biochemical variables in women at risk of preeclampsia. Am J Obstet Gynecol. 2002; 187(1):127-136.
56. Wang Y, Walsh SW. Antioxidant activities and mRNA expression of superoxide dismutase, catalase and glutathione peroxidase in normal and pre-eclamptic placenta. J Soc Gynecol Investig. 1996;3:179-184.
57. Rokeya B. Lipid peroxidation and antioxidant status in preeclampsia. Journal of Enam medical College. 2011;1(20):56-59.
58. Redman CW, Beilin LJ, Bonnar J, Wilkinson RH. Plasma-urate measurements in predicting fetal death in hypertensive pregnancy. Lancet. 1976;1:1370–1373.
59. Chesley LC. Diagnosis of preeclampsia. Obstet Gynecol. 1985;65:423–425.
60. James MR, Lisa MB, Kristine YL, Carl AH, Nina M, Roberta BN, Robert WP. Uric acid is as important as proteinuria in identifying fetal risk in women with gestational hypertension. Hypertension. 2005;46:1263-1269.
61. Lam C, Lim KH, Kang DH, Karumanchi SA. Uric acid and preeclampsia. Semin Nephrol. 2005; 25(1):56-60.
62. Bainbridge SA, Robert JM. Uric acid as a pathogenic factor in preeclampsia. Placenta. 2008; Suppl A:S67-72.

63. Markus GM. C-reactive protein and its role in preeclampsia. Hypertension. 2015;65:285-286.

64. Parchim NF, Wang W, Iriyama T, Ashimi OA, Siddiqui AH, Blackwell S, Sibai B, Kellems RE, Xia Y. Neurokinin 3 receptor and phosphocholine transferase: missing factors for pathogenesis of C-reactive protein in preeclampsia. Hypertension. 2015;65:430–439.

65. Berkane N, Liere P, Oudinet JP, Hertig A, Lefèvre G, Pluchino N, Schumacher M' Chabbert-Buffet N. From pregnancy to preeclampsia: Akey role for estrogens. Endocr Rev. 2017;38(2):123-144.

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