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Evaluation of Serum Total Calcium, Mg $^{+2}$, Na^{+} and K^{+} Levels in Sudanese Women with Preeclampsia in Shendi town, River Nile State, North Sudan

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Abstract
Pre-eclampsia is a pregnancy complication that affects both the mother and the fetus. It is a major cause of both maternal and neonatal morbidity and mortality.
The currentstudy was conducted in Shendi town from April to July 2018, to evaluate minerals level (Ca+2,Mg+2,Na+,K+) in women with preeclampsia.
A total number of80pregnant womenwasenrolled in the study. Fiftyof them with precclampsia as case group and 30 were of normal blood pressure as control group.Venous blood samples were collected in lithium heparin anticoagulant containers from each participant for measurement of (Ca^{+2}, Mg^{+2}, Na^{+}, K^{+}.)
There was statistically significant variation between mean potassium level of women with preeclampsia and control group (3.94& 4.11) mg/dl, with *P*.value of (0.00) and that of magnesium in women with preeclampsia and control (1.30&1.90) mg/dl, with*P*.value (0.02).
There was statistically insignificant variation neither between mean level of sodium women with preeclampsia and control (136.80 &136.80) mg/dl with *P.value of (0.95) nor that of calcium in women with preeclampsia and control (8.20&0.90) mg/dl, with P.value (0.89).*

Keywords: Pre-cclampsia, Sudanese pregnant women, Albuminurea, Calcium, Magnesium, Sodium, Potassium.

Introduction
The incidence rate of pre-eclampsia stands at 3-10% globally, butits etiology remains unknown. Factors such as obesity, diabetes, calcium (Ca^{2+}) deficiency, advanced maternal age, oxidative stress; placental ischaemia, genetic factors and immune maladaptation have been implicated. Altered calcium metabolism role in the pathogenesis of this disorder is suggested by epidemiologic evidence linking low dietary level of calcium with increased incidence of pre-eclampsia. Changes in intracellular calcium and magnesium concentrations seem to be involved in the pathogenesis of preeclampsia. On the basis of the vasodilating therapeutic effects of magnesium salts, it is suggested that a deficiency in magnesium contributes to the development of vasoconstriction in pre-eclampsia.
Total body calcium of (1000) g. (99%) is bound in the skeleton and the rest is distributed through the intracellularfluids. Calcium biologic role includebone and teeth formation,Enzyme regulation, Blood clotting (cofactor for factors vii,ix,x),cell growth and division and maintenance of plasma membrane stability.
Potassium is the major intracellular cation in the body, with total amount of (3000) mmol, of which about (98%) is intracellular. had Function of potassium in the body include regulation neuromuscular excitability, concentration of the heart, intracellular fluid volume,and hydrogen ion concentration.
Sodium is one of the body's electrolytes, which are minerals that the body needs in relatively large amounts. Electrolytes carry an electric charge when dissolved in body fluids.
Most of body's sodium is located in blood and in the fluids around cells. Sodium helps the

body keep fluids in a normal balance. Sodium plays a key role in normal nerve and muscle function.

Magnesium is fourth most abundant cation in the body and second most abundant intracellular ion.Magnesium acts as Co factor of more than 300 enzymes, including enzyme involved protein synthesis and glycolysis.It is also important in the maintenance of ribosomes, nucleic acids, some proteins Itplays a pivotal role in the physiological regulation of blood pressure. This may explain thetherapeutic benefit of magnesium in the treatment of preeclampsia.

Hypertension during pregnancyis defined as a systolic blood pressure (SBP) ≥ 140 mmHg and/or a diastolic blood pressure (DBP) ≥ 90 mmHg and is classified into four categories preeclampsia, chronic hypertension, chronic hypertension with superimposed preeclampsia, and gestational hypertension [(1)].

Hypertension is considered to be mild, moderate or severe when SBP is ≥ 140, 150 or 160 mmHg or DBP is ≥ 90,100 or 110 mmHg, respectively [(2)].

Preeclampsia was usually defined as new-onset hypertension (i.e. SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg) and proteinuria (> 0.3 g/day) arising after 20 weeks of gestation in a previously normotensive woman.. Alternatively, a urine protein (mg/dL)/creatinine ratio (mg/dL) ≥ 0.3 has good sensitivity (98.2%) and specificity (98.8%) as a diagnostic tool [(3)]. Conversely, a positive qualitative dipstick test for proteinuria provides too variable results to be considered as a reliable diagnostic tool of proteinuria. It can be used if no other method is readily available. In that case only, a 1+ dipstick result is considered as the cut-off for the diagnosis of proteinuria.

Proteinuria is no longer considered as mandatory for the diagnosis of preeclampsia [(4,5)]. Consequently, in the absence of proteinuria, preeclampsia can be diagnosed as newonset hypertension associated with:

- Thrombocytopenia < 100.000/µL.
- Elevated liver transaminases (> twice the normal values).
- Impaired renal function (with serum creatinine > 1.1 mg/dL or doubling of serum creatinine level in the absence of any other renal disease).
- Pulmonary edema.
- New onset visual or cerebral disturbances.

Severe preeclampsiais defined as preeclampsia associated with any of the following:

- Severe hypertension (i.e. SBP ≥ 160 mmHg and/ or DBP ≥ 110 mmHg).
- Thrombocytopenia < 100.000/µL.
- Impaired liver function with liver transaminases higher than twice the normal values.
- Severe and persistent right upper quadrant (RUQ) or epigastric pain not accounted for by any other diagnosis.
- Renal insufficiency defined as serum creatinine >1.1 mg/dL or a doubling of serum creatinine in the absence of other renal disease.
- Massive proteinuria > 5 g/day.
- Pulmonary edema, – new-onset cerebral or visual disturbances.
- Fetal growth restriction (FGR).

However, recent studies have demonstrated minimal to no influence of the severity of proteinuria on pregnancy outcome in preeclampsia [(4, 6)].

Preeclampsia complicates (5 to 8%) of all pregnancies. This represents (8.5 million) cases a year worldwide. This pathology remains one of the three leading causes of maternal death. [(1,2)]. Renal failure, pulmonary edema, liver failure or rupture, seizures (eclampsia), disseminated intravascular coagulation (DIC), retinal detachment; cortical blindness, abruptio placentae, and hemorrhage represent other complications of preeclampsia. All contribute to preeclampsia-associated maternal morbidity and mortality. Five percent of severe preeclamptic patients are admitted to an ICU. Finally, preeclampsia is known to increase the risk of developing a cardiovascular disease later in life by a factor of two (2).

Regarding the fetus and the neonate, preeclampsia is responsible for (5%) of stillbirths in infants without congenital abnormalities, accounts for 8-10% of the overall preterm birth rate, and for (15-20%) of the overall FGR and very low birth weight [(7)]

As opposed to normal pregnancy, preeclampsia is characterized by an immunologically-initiated impaired trophoblast invasion of the spiral arteries between 8 and 16 gestation weeks. This abnormal invasion of placenta nourishing arteries leads to a failure of their remodeling. Failed remodeling impairs the transformation of small high resistance muscular arteries into large capacitance vessels. Consequently, the utero-placental blood flow progressively fails to meet the needs. Placental ischemia ensues, with oxidative stress, inflammation, apoptosis, and structural damage [(8)].

As a consequence of placental ischemia, secondary mediators are released. During normal pregnancy, placental growth factor (PlGF) and vascular endothelial growth factors (VEGF) are potent proangiogenic substances. They enhance the vasodilating properties of prostaglandins (PG) and nitrous oxide (NO), and promote endothelial health. In preeclampsia, several anti-angiogenic factors are produced. They are responsible for angiogenic imbalance, impaired vasodilation and an endothelial dysfunction. The soluble fms-like tyrosinekinase (sFlt-1) antagonises VEGF and PlG. Soluble endoglin (sEng) antagonises TGF-β, and blocks NO. This imbalance between pro and anti-angiogenic factors produces generalized endothelial dysfunction, microangiopathy, and vasospasm. These rise to the various signs and symptoms of this multisystemic disease, which become clinically evident after 20 gestation weeks [(8, 9)].

Different hemodynamic states have been describedto explain underlying mechanism of hypertension in preeclamptic patients. These range from low cardiac output (CO) with increased systemic vascular resistance (SVR) to a hyperdynamic state with increased CO associated with an increased stroke volume and a moderate increase in SVR [(10,15,)].These different hemodynamic situations might be related to the early or late onset of preeclampsia, as well as to its severity [(16)]. Use of cardiac output, and not only blood pressure, as an endpoint when treating severe preeclampsia might improve the hemodynamic management of these patients [(17, 18,,19,20,21)].

Eclampsia occurs in 0.5% of pre-eclamptic patients without severe features, and in 2-3% of severe preeclampsia. This corresponds up to 10/10000 deliveries in developed

countries, and up to 157/10000 deliveries in developing countries [22]. Eclamptic seizures contribute substantially to maternal morbidity and mortality [23, 24,25, 26].

Several factors are associated with an increased risk of preeclampsia such asantiphospholipid syndrome, past history of preeclampsia, pregestationaldiabetes,multiple gestation. nulliparity, family history of preeclampsia, body mass index (BMI) > 30 before pregnancy, age ≥ 40 years, pre-existing hypertension, pre-existing renal disease, and pregnancy interval > 10 years [27, 28].

Biomarkers of preeclampsia and its severity have also been proposed [8, 29]. Placental expression and serum levels of sFlt-1 inpreeclamptic women are increased during active disease, as compared with normal pregnancy [30].

Preeclamptic patients have higher levels of natriuretic peptide than non preeclamptic patients [31].

Women at high risk of preeclampsia should receive low dose aspirin daily from gestation week 12 to 37. Statins, by stimulating hemoxygenase expression, inhibit sFlt-1 release and promote VEGF [9].

Rationale

Preeclampsia and its complication is considered one of the commonest obstetrical complication in Sudan. It is a major cause of morbidity and mortality worldwide.Overall(10% - 15%) of maternal death are directly associated with preeclampsia and eclampsia.Calcium, magnesium, sodium and potassium contribute significantly in the functioning of the vascular smooth muscles, Hence the present study was designed to evaluate the role of these electrolytes in the genesis of preeclampsia or pregnancy induced hypertension(PIH) in ShendiLocality.

Objectives

The general objective of the current study was to evaluate serum levels of calcium, magnesium, sodium and potassium in Sudanese women with pre-eclampsiaas well as factors such as body mass index as possible etiological factors for pre-eclampsia.

Materials and methods

This was cross sectional, hospital based study**,** conducted at Shendi town in Sudan, from March to July 2018.The study samples comprised 80 pregnant women, 50 were women with pre-clampsia as case groupand 30healthy pregnant women as control group. Both groups werematched for duration of gestation.

All women included in the study were in their third trimester (gestational age of ≥26weeks). They were pregnant women with blood pressure more than 140/90 mmHg during the third trimester of pregnancy, with excretion of more than 300mg of urinary protein per 24hours and have edema.

The control group included pregnant women with normal blood pressure, absence of proteinuria and without any other systemic or endocrine disorder and age-matched with the case group.

Fiveml of venous blood was collected from each participant in plain containers. Serum was separated by centrifugation at 300 rpm for5 minutes.

Serum total calciumwas assayed by Methyl thymol blue method.Serum Mg^{+2} was assayed by standard method of MindrayBs 200.Sodium and potassium ions (Na^{+}&K^{+}) were assayed by ion selective electrode for (Na^{+}&K^{+}) by standard method of Easylyte(Medica) in the clinical chemistry laboratory in El –mekNimir University Hospital in Shendi.

Three levels of control sera were run with every batch of the assays to ensure accuracy and quality assurance.

Data analysis

All collected data was analyzed using statistical package for social sciences (SPSS), for windows, version 16.0. The data was represented as mean ± stander deviation.Mean values were compared using paired student t-test for calculating degree of variation, *P*. value<0.05 was considered as statistically significant. Analysis of variance (ANOVA) was used for continuous data and the statistical results were presented as means ± SEMs.

Ethical considerations

Ethical approval for the study was obtained from the Board of the Faculty of Graduates Studies and Scientific Research in Shendi University. Verbal informed consent for participation in the study was obtained from each participant before recruitment into the study. Procedure of venous blood sampling was explained to the participants. All participants were informed about the research objectives and procedures during the interview period.

Results

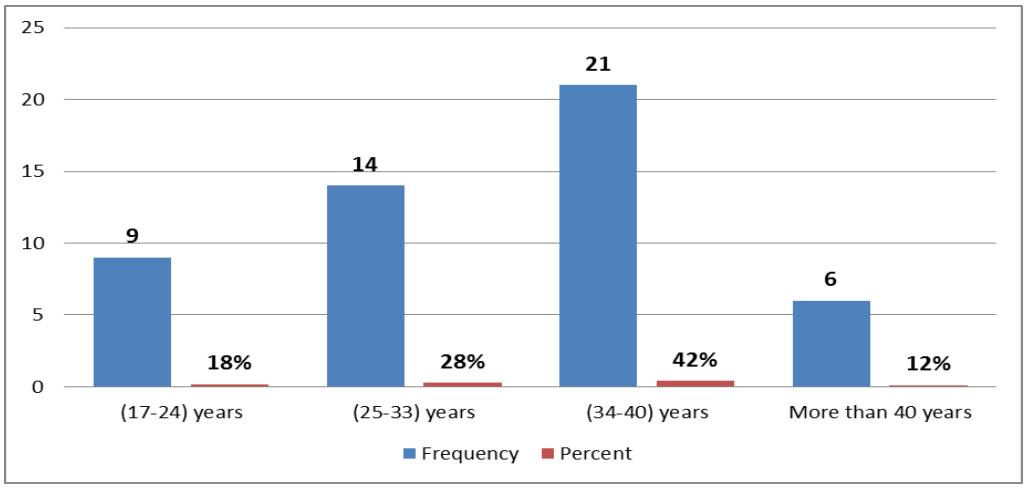

Fig. 1: The distributionof agecategories in the study group

Table 1: BMI, GA, parity and Blood pressure profiles in the study groups

	Study group	Frequency	Mean	*P.* value	Correlation
Body mass index (kg/m^2)	Test	50	26.5	0.02 #	Significant
	Control	30	25.6		
Gestational age(weeks)	Test	50	32.7	0.913	Insignificant
	Control	30	32.0		
Number of pregnancy	Test	50	1.88	0.696	Insignificant
	Control	30	1.86		
Systolic pressure (mmHg)	Test	50	151.2	0.02 #	Significant
	Control	30	106.2		
Diastolic blood pressure (mmHg)	Test	50	102.6	0.40	Insignificant
	Control	30	73.8		

Table 2: Maternal biochemical parameters

	Study group	Frequency	Mean	*P.* value	Correlation
Haemoglbin concentration (g/dl)	Test	50	11.5	0.03 #	Significant
	Control	30	10.2		
Albuminurea (by dipstick test(+)	Test	50	2.8	0.00 #	Significant
	Control	30	.00		

Table 3: Maternal electrolytes concentration (mg/dl)

Electrolytes concentration (mg/dl)	Study group	Frequency	Mean	*P.* value	Correlation
Calcium	Test	50	8.2	0.89	Insignificant
	Control	30	9.0		
Magnesium	Test	50	1.3	0.02 #	Significant
	Control	29	1.9		
Sodium	Test	50	136.8	0.95	Insignificant
	Control	30	136.8		
Potassium	Test	50	3.94	0.00 #	Significant
	control	30	4.11		

Discussion

The result displayed in table (1) showed that the mean of BMI ((kg/m^2) in women with preeclampsia was (26.5) and in the control group was (25.6) withP.value of (0.02).Thus BMI increased in women with pre-eclampsia, in agreement with the findings reported by (Hauger, et al.2008) that the risk of pre-eclampsia was highest among overweight pregnant women [32].

Also the mean of systolic pressure (mmHg) in women with preeclampsia was (151.2) and in the control group was (106.2). The systolic pressure was increased in women with pre-eclampsia with *P*.value of (0.02), and this result supported the findings reported early by (Redman CWG, et al.1976) in the Lancet [33].

The result illustrated in table (2) revealed increasedalbuminurea in pre-eclamptic women with*P*.value of (0.000) as well as Hbconcentration with *P*.value of (0.03).

The mean concentration of serum Mg^{+2}(mg/dl) in women with preeclampsia was (1.3) versus (1.9) in the control group. This findings illustrated decreased serum Mg^{+2}in women with preeclampsia with *P*.value (0.02), which coincided with the findings in Sudanese pregnant women with precclampsia reported by (MohannedAbdala Elhassan Sidahmed, et al. 2017)[34].

The mean concentration of serum$^+$ (mg/dl) in women with preeclampsia was (3.94) compared to (4.11) in the control group.This result proveddecreased serum potassium in women with preeclampsia with the *P*.value of (0.00), also in agreement with the findings reported by (MohannedAbdala Elhassan Sidahmed, et al. 2017) [34].

Also the result appeared in table (3) showed no association between preeclampsia and concentration of serumNa^+, with insignificant *P*.value of (0.95),which was in agreement with the findings reported by(Ebenezer OwusuDarkwa, et al. 2017) in Ghana[35].

The meanconcentration of serum Ca^{+2} level in women with pre-eclampsis was (8.1) compared to (9.2) in the control group with statistically insignificant *P*.value of (0.89).This results questioned the association between preeclampsia and serum concentration of Ca^{+2}in agreement with the findings reported by (Ugwuja El et al. 2016) in Nigerian women with pre-eclampsia [36]...In contrast to this findingsAbdelmageedElmugabil, et al (2016) reporteda low calcium and a higher magnesium level in pre-eclamptic Sudanese women [37].

So far the etiology of preeclampsia still remains ambiguous.Placental defects and oxidative stress early during pregnancy in affected pregnancies were suggested as possible underlying cause [38,39]

Micronutrients and trace elements are integral part of a robust antioxidant body system, there for future researches should include other elements such as iodine selenium, as part of a whole cluster, so as to provide strong evidence-basefindingsthatcould be implemented for prevention of preeclampsia.

Conclusion

On the basis of these results the study it could be concluded thatpre-eclampsia occurs mostly in the age group (34-40) yearsin senior primigravida,in their third trimester.

Recommendation

Pre-eclampsia associated with decreasing serum concentration level of Mg^{+2} and K^+ and no association existed with serum concentration level ofNa^+ and Ca^{+2}

level. Therefore, it is recommended for pregnant women to take nutrients dense food items rich in these trace elements; calcium, magnesiumand potassium such as green leafy, vegetables, nuts, seeds, fish,beans and avocados. It is also recommended to decrease intake of calories dense food items to achieve ideal body weight.

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