Serum sodium and potassium levels in preeclampsia: A case-control study in a large tertiary hospital in Ghana

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Abstract: Background: Preeclampsia remains a poorly understood complication of pregnancy affecting 5–14% pregnancies worldwide. Recent studies indicate that serum electrolytes may play a role in preeclampsia since it is a vascular endothelial disorder. Aim: To compare serum sodium and potassium levels between preeclamptics and normotensive pregnant women in a tertiary hospital in Ghana. Methods and materials: This was a case-control study consisting of 30 preeclamptics and 30 normotensive pregnant women recruited consecutively at their first third trimester pre-natal visit at Korle-Bu Teaching Hospital. Serum sodium and potassium were analysed using Sherwood Flame Photometer (Model 420 Sherwood Scientific Ltd, UK). Analysis was done using Statistical Package for Social Sciences (SPSS®) software version 20.0 and presented as means (standard deviation). A \( p \)-value of ≤0.05 was judged significant. Results: There was a significantly reduced \( p < 0.001 \) serum sodium levels in preeclamptics (mean = 136.13; SD = 4.17 mmol/L) compared to normotensive pregnant women (mean = 142.17; SD = 5.66 mmol/L). There was a significantly reduced \( p < 0.001 \) serum potassium levels in preeclamptics (mean = 3.45; SD = 0.54 mmol/L) compared to normotensive pregnant women (mean = 3.98; SD = 0.36 mmol/L). Conclusion: The reduced levels of serum sodium and potassium in preeclampsia as compared to normotensive pregnant women, suggests that changes in these electrolytes may be associated with preeclampsia.

About the Author

Ebenezer Owusu Darkwa was an MPhil student at the department of Physiology, University of Ghana at the time of carrying out this study. This study is part of the research on the role of some selected serum electrolytes and nitric oxide in the pathophysiology of preeclampsia in Ghanaian women. He is a consultant Anaesthesiologist and a lecturer at the Department of Anaesthesia, University of Ghana, Korle-Bu Teaching Hospital. The research team has a large interest in body fluid and electrolytes physiology in general. His research interest is in electrolyte physiology of pregnant women and how it affects their general health perioperatively.

Public Interest Statement

Preeclampsia is a complication of pregnancy with most deaths occurring in low to middle income countries. The cause of preeclampsia largely remains unknown. Changes in maternal serum mineral ions during pregnancy have been suggested as a possible cause. Research on maternal deficiencies of mineral ions during pregnancy in Ghana is lacking. This study was therefore carried out to examine the role maternal blood levels of sodium and potassium play in the development of preeclampsia. We observed in our study, a marked reduction in maternal sodium and potassium in pregnancies complicated by preeclampsia.
1. Introduction
Preeclampsia is one of the commonest aetiologies of foetal and maternal mortality and morbidity (Sukonpan & Phupong, 2005). It is a multi-system disorder affecting approximately 5–7% of all pregnancies worldwide and it is the commonest, yet least understood disease of pregnancy (Ziaei, Ranjekesh, & Faghihzadeh, 2008). The incidence of preeclampsia in developing nations is estimated to be 4–18% (Villar, Betran, & Gülmezoglu, 2001). Sixteen percent of all maternal mortality in developed countries and 9% of maternal mortalities in Asia and Africa is said to be due to hypertensive disorders in pregnancy (Khan, Wojdyla, Say, Gülmezoglu, & Van Look, 2006). Eighteen percent of 724 total maternal deaths at Korle-Bu Teaching Hospital in Ghana between 1984 and 1994 were due to hypertensive disorders in pregnancy including preeclampsia (Lassey & Wilson, 1998). Whilst earlier studies suggested that preeclamptics after delivery had no increased risk of adverse long term outcomes than non-preeclamptics from the general population (Chesley, Annitto, & Cosgrove, 1976), current studies, however, suggest the reverse (Wilson et al., 2003).

Theories of the pathophysiology of preeclampsia involve both maternal and foetal factors. Though the aetiology of preeclampsia remains unclear, many theories suggest abnormal placentation and abnormal trophoblastic invasion as a possible cause (Smith & Kenny, 2006). It has been postulated that fluctuations in maternal serum ions may be the precipitating cause of elevated blood pressures in preeclampsia (Sidahmed & Abubaker, 2017; Tabassum, Al-Jameil, Ali, Khan, & Al-Rahed, 2015).

In developing countries, dietary deficiency of various mineral ions have been established to have a role in blood pressure regulation in pregnant women with a consequent development of preeclampsia (Aziz & Mahboob, 2014; Ephraim, Osakunor, Denkyira, Eshun, & Anto, 2014; Kanagal et al., 2014).

Studies have reported that serum calcium and magnesium levels have a vasomotor activity on blood vessels in pregnancy, whilst others have reported a varying conclusion on the effects of serum sodium and potassium levels on vasomotor activity during pregnancy (Ephraim et al., 2014; Yussif, Salih, Sami, & Mossa, 2009).

Serum sodium levels has been observed to be reduced in both preeclampsia and pregnancy induced hypertension as compared to normotensive pregnant and non-pregnant women (Indumati, Kodliwadmath, & Sheela, 2011; Pitkin, Kaminetzky, Newton, & Pritchard, 1972; Ravid, Massarwa, Biron-Shental, & Fejgin, 2005; Searcy, 1969; Tarik & Ward, 2011). There is a reduced intrarenal production of cyclic GMP (cGMP), endothelin and prostaglandin E2 (PGE2) with resultant sodium retention, hypertension and thrombosis in preeclampsia (Clark, Cotton, Hankins, & Phelan, 1997). In preeclampsia there is alteration in cell membrane sodium transport leading to extravascular accumulation of sodium with a reduced plasma sodium level (Clark et al., 1997; Searcy, 1969). However, other studies found no significant change in serum sodium levels of preeclampsics compared to normal pregnant women (Adewolu, 2013; Bera et al., 2011; Rizk, 1997; Yussif et al., 2009). Caughey and colleagues also noted increased sodium levels in preeclampsia compared to normotensive pregnant women (Caughey, Stotland, Washington, & Escobar, 2005).

Various studies have reported a statistically non-significant change in the serum potassium levels in preeclampsia and hypertensive pregnant patients compared to normotensive pregnant women.
(Adewolu, 2013; Bera et al., 2011; Clark et al., 1997; Siddiqui & Rana, 1993; Singh, Dighe, Singh, & Othman, 1993). However, Yussif et al. (2009) observed a significantly reduced serum potassium level in hypertensive pregnant women compared with normal pregnant women and proposed a raised serum sodium and a reduced serum potassium level as a pathologic cause of hypertension in pregnancy. Yussif et al. (2009) concluded that a low potassium diet combined with a normal sodium diet can cause sodium retention and therefore development of hypertension. Handwerker, Altura, & Altura (1995) however noted an elevated serum potassium level in preeclampsia compared to normal pregnant women.

Considering the above mentioned literatures, the serum sodium and potassium profile in preeclampsia compared with normal pregnancy is inconclusive. These electrolytes seem to play a role in vasomotor activity during pregnancy and may possibly have a role in the pathophysiology of preeclampsia. Literature, however, is yet to reach an agreement on the role these electrolytes play in the development of preeclampsia. This study sought to compare the serum sodium and potassium levels between preeclamptic and normotensive pregnant women in a tertiary hospital in Ghana.

2. Materials and methods

2.1. Study design
This was a case-control study conducted at the Obstetrics and Gynaecology clinic of Korle-Bu Teaching Hospital, Ghana between March and June, 2016.

2.2. Study site
The survey site was the Korle-Bu Teaching Hospital, the premiere and the largest tertiary hospital in Ghana affiliated to the University of Ghana School of Medicine and Dentistry. The hospital has a 2,000 bed capacity. The obstetrics and gynaecology department of the hospital has a 350 bed capacity with 3 operating theatre suites. The department has 65 doctors, 200 nurses and midwives, with a daily antenatal attendance of 100 patients, and a total annual delivery between 10,000 and 12,000.

2.3. Subjects/Target population
The study population included normotensive pregnant women and preeclamptics aged 18-35 years attending the obstetrics and gynaecology clinic at Korle-Bu Teaching Hospital and who gave their informed consent, except:

(1) Pregnant and preeclamptics on any medical treatment other than iron and folic acid.
(2) Pregnant and preeclamptics with chronic hypertension, history of kidney disease, diabetes mellitus, cardiac diseases and neuromuscular disorders.

The International Society for the Study of Hypertension in Pregnancy criteria (Tranquilli et al., 2014) was used for the diagnosis of preeclampsia.

2.4. Sampling and sample size determination
At their first third trimester (29–40 weeks) pre-natal visit to the hospital, patients fulfilling the inclusion criteria were consecutively recruited into the study after obtaining an informed consent. Considering a total of 10,000 deliveries at Korle-Bu Teaching hospital, with 1.5% difference between normotensive pregnant women and preeclamptics and 5% margin of error. Using the formula \( n = \frac{N \times X}{X + N - 1} \) where \( X = Z_{\alpha/2}^2 \times p \times (1 - p)/E^2 \), 30 preeclamptics and 30 normotensive pregnant women were recruited consecutively into the study at the ratio of 1:1.

2.5. Procedure used
After obtaining an informed consent, participants’ age, parity, height and weight were recorded on a data collection form.
Blood pressure measurements were taken at the first third trimester pre-natal visit using a sphygmomanometer (Accuson, Italy) and a stethoscope. Measurements were done on the right arm with the patients in the sitting position. Two measurements were done per patient at 15 min interval and averaged.

Three millilitres of blood was drawn from the cubital vein using a sterile 19G hypodermic needle fixed on a 5 ml syringe after cleansing the site to be punctured with methylated spirit. Aseptic conditions were adhered to. The blood sample was transferred into a plain test tube, immediately sent to the laboratory and then spun at a speed of 4,000 rpm for 10 mins to separate serum from cells. Serum obtained was stored in a freezer at a temperature of −20°C prior to analysis. Serum sodium and potassium were analysed using Sherwood Flame Photometer (Model 420 by Sherwood Scientific Ltd, UK) and values recorded on data collection forms.

2.6. Statistical analysis
Data collected was entered into Microsoft Access database 2010 (Microsoft® USA) and analysis done using Statistical Package for Social Sciences (SPSS®) software version 20.0. The demographic and anthropometric parameters such as age, weight, height and BMI were reported as means (standard deviations) in a tabular form. The serum sodium and potassium levels were presented in a bar chart. Independent t-test was employed to compare the significant difference in the means of serum sodium and potassium between preeclampsia and normotensive pregnant women. A p-value ≤ 0.05 was considered statistically significant.

3. Results
A total of 60 third trimester pregnant women were recruited into the study. This consisted of 30 preeclamptics and 30 normotensive pregnant women. The characteristics of the recruited women are shown in Table 1. Compared to the normotensive pregnant women, a significant difference was observed in the mean systolic (p < 0.001), diastolic (p < 0.001) and mean arterial pressures (p < 0.001) of the preeclamptics.

There was a significantly reduced (p < 0.001) serum sodium levels in preeclamptics [136.13(4.17) mmol/L] compared to normotensive pregnant women [142.17(5.66) mmol/L] (Figure 1).

There was a significantly reduced (p < 0.001) serum potassium levels in preeclamptics [3.45 (0.54) mmol/L] compared to normotensive pregnant women [3.98(0.36) mmol/L] (Figure 2).

4. Discussion
Our study showed no statistically significant difference between maternal age and preeclampsia (p = 0.358), similar to the findings of other studies (Ganesh, Unnikrishnan, Nagaraj, & Jayaram, 2010; Table 1. Demographic and clinical characteristics of the patients

| Parameter   | Preeclampsics | Normotensive pregnant women | p-value |
|-------------|---------------|-----------------------------|---------|
|             | Mean (SD)     | Mean (SD)                   |         |
| n           | 30            | 30                          |         |
| Age (years) | 30.97 (5.51)  | 29.93 (2.60)                | 0.358   |
| Parity      | 1.70 (1.42)   | 1.13 (1.41)                 | 0.567   |
| BMI (kg/m²) | 32.03 (7.52)  | 30.50 (5.50)                | 0.374   |
| SBP (mmHg)  | 170.13 (23.69)| 116.47 (13.38)              | <0.001* |
| DBP (mmHg)  | 106.30 (18.79)| 67.57 (8.54)                | <0.001* |
| MAP (mmHg)  | 126.20 (20.86)| 83.87 (8.85)                | <0.001* |

*Significant at p < 0.05; n—sample size; SD—standard deviation; BMI—body mass index; SBP—systolic blood pressure; DBP—diastolic blood pressure; MAP—mean arterial pressure.
Shamsi et al., 2010) but contradicts the findings of Macdonald-Wallis et al. (2011). This difference may be accounted for by the differences in population characteristics.

Our study also showed no statistically significant difference between BMI and preeclampsia \((p = 0.374)\) similar to the findings of Onyebule et al. (2014); however, other studies have reported an association of high BMI with preeclampsia (Hauger, Gibbons, Vik, & Belizán, 2008; Munazza et al., 2011; Poorolajal & Jenabi, 2016).

The mean systolic, mean diastolic and mean arterial pressures of the preeclamptics were significantly higher than that of the normotensive pregnant women \((p < 0.001)\). This was however expected in view of the criteria used for diagnosis of preeclampsia. Mean arterial pressure has been observed to be predictive of preeclampsia even though other studies have reported otherwise (Redman, Beilin, Bonnar, & Wilkinson, 1976).

There are two mechanisms by which sodium has been proposed to affect blood pressure. Excess sodium intake causes expansion of intravascular and extravascular fluid volume resulting in increased venous return and cardiac output and therefore increased blood flow to tissues. Persistence of this triggers an autoregulatory mechanism causing increased peripheral resistance (Sullivan & Martin, 1994). The “peripheral arterial vasodilation hypothesis” also postulates an increased endothelial damage with sodium and water retention and hence an increase in sensitivity to angiotensin (Schrier & Briner, 1991).
Though literature is inconclusive on the picture of serum sodium levels in preeclamptics compared to normotensive pregnant women, with some observing no significant difference (Adewolu, 2013; Bera et al., 2011; Rizk, 1997; Yussif et al., 2009) and others observing a significant increase (Caughey et al., 2005), this study, in agreement with findings of other studies (Indumati et al., 2011; Pitkin et al., 1972; Searcy, 1969; Tarik & Ward, 2011), noted a significantly reduced serum sodium levels in preeclamptics in comparison to normotensive pregnant women ($p < 0.001$).

Preeclampsia clinically manifests as hypertension, proteinuria with or without oedema during pregnancy. Even though preeclamptics have an adequate electrolyte and water content, these are mainly situated in the interstitium with a resultant decreased intravascular circulating volume. This decrease in intravascular circulating volume results in activation of baroreceptors and release of antidiuretic hormone (ADH) causing water retention and natriuresis. This sequence of events leads to a reduction in serum sodium and may account for the observed significantly reduced serum sodium levels in preeclamptics. It has also been observed that a defective placenta seen in preeclampsia is unable to produce a vasopressinase, an enzyme which inactivates ADH and therefore a build-up of ADH in preeclamptics (Chung, Kluge, Schrier, & Anderson, 1987). The ADH levels of the subjects in this study were however not measured.

Alteration of natriuretic factors as being responsible for reduced serum sodium levels seen in preeclampsia has also been suggested in literature. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels has been noted to be increased in preeclampsia even though this is not a uniform finding (Graves, 2007; Reis et al., 2003; Tihtonen, Kööbi, Vuolteenaho, Huhtala, & Uotila, 2007). These factors cause natriuresis and hence a fall in serum sodium levels. This study however did not measure the levels of natriuretic factors.

The reduced serum sodium levels in preeclamptics observed in this study could also be dilutional. There are reports of dilutional hyponatraemia in preeclampsia with or without associated nephrotic syndrome in literature (Hayslett, Katz, & Knudson, 1998; Magriples, Laifer, & Hayslett, 2001). Preeclampsia is one of the commonest causes of nephrotic syndrome that occurs during pregnancy (Fisher, Ahuja, Luger, Spargo, & Lindheimer, 1977). There is a difficulty distinguishing between preeclampsia and renal disease as a cause of hyponatraemia. The distinction is usually possible in retrospect, as clinical signs of preeclampsia generally resolve within 12 weeks postpartum, whilst proteinuria due to underlying renal disease does not (Chua & Redman, 1992).

From this study, there was a significant reduction in mean serum potassium levels in preeclamptics compared to normotensive pregnant women ($p < 0.001$) as shown in Figure 2. Manjareeka and Nanda (2012) and Yussif et al. (2009) made a similar observation in an Indian and Iraqi population respectively while other studies (Adewolu, 2013; Bera et al., 2011; Siddiqui & Rana, 1993; Singh et al., 1993) observed no statistically significant difference in the serum potassium level between hypertensive pregnant women and normotensive pregnant women in India. However, Handwerker et al. (1995) have also reported a statistically significant elevation of serum potassium levels in preeclampsia compared to normotensive pregnant women.

Ninety percent of total body potassium is located intracellularly whilst sodium is mainly located extracellularly. The difference in predominant locations is influenced by the Na+/K+-ATPase (Delgado, 2004). In preeclampsia and pregnancy induced hypertension there is an abnormality in the transport of sodium and potassium across the cell membrane of vascular smooth muscles which regulates blood pressure (Arumanayagam & Rogers, 1999). An earlier study (Pikilidou et al., 2007) has established an inverse relationship between serum potassium levels and severity of hypertension. This shows that raised serum potassium may have a beneficial effect on blood pressure regulation. The mechanism explaining the relationship between reduced serum potassium levels and poor blood pressure control is poorly understood. Reduced levels of serum potassium enhance vascular responsiveness to vasopressors such as norepinephrine (Bianchetti, Weidmann, Beretta-Piccoli, & Ferrier, 1987). Decreased release of nitric oxide by the endothelial cells may be the mediating factor
Taddei et al., 1994). This leads to vasoconstriction and increased platelet aggregation which increases blood pressure and therefore poor protection against hypertension caused by induced endothelial injury which has been implicated in the pathogenesis of preeclampsia (Vane, Ånggård, & Botting, 1990).

It has also been observed that reduced serum potassium levels also reduce sodium excretion through probable changes in reabsorption of sodium in the proximal tubule or loop of Henle of the kidney resulting in elevated blood pressure (Gallen et al., 1998). In fact it has been observed that a diet low in potassium coupled with individual’s usual sodium intake can lead to sodium retention and therefore hypertension (Yussif et al., 2009).

There was weak non-significant correlations between mean arterial pressures and serum sodium and potassium levels (Figures 3 and 4). An $R^2$ value of 0.3 and 4% was obtained respectively for sodium and potassium. This implies that serum sodium levels and serum potassium levels may...
account for only 0.3 and 4% in the variability of mean arterial pressure in preeclampsics respectively. Other factors may therefore be involved, hence, it would be difficult predicting mean arterial pressures in preeclampsics using only their serum sodium and potassium levels.

5. Conclusion
We observed a significantly reduced serum sodium and potassium levels in preeclampsics compared to normotensive pregnant Ghanaian women. A non-significant weak positive correlation was found between the two serum ions (sodium levels and potassium levels) and mean arterial pressure in preeclampsics.

The observed reduced levels of serum sodium and potassium in preeclampsia as compared to normotensive pregnant women, suggests that changes in these electrolytes may be associated with preeclampsia.

Authors’ contribution
Ebenezer Owusu Darkwa is a consultant Anaesthetist of the Department of Anaesthesia, Korle-Bu Teaching Hospital. The author designed the study and wrote the manuscript which is part of his MPhil. Physiology thesis. Robert Djagbletey is a consultant Anaesthetist of the Department of Anaesthesia, Korle-Bu Teaching Hospital. He participated in designing the study. Charles Antwi-Boasiako, Head of Physiology Department, School of Allied Health and Biomedical Sciences, University of Ghana helped in preparing the manuscript. Alexander Akowuah and Daniel Sottie of the Department of Anaesthesia, Korle-Bu Teaching assisted in data collection. George Aryee of the Department of Anaesthesia, University of Ghana assisted in data analysis. All authors read and approved the final manuscript.

Ethical approval
Ethical Approval for the study was obtained from the Ethical and Protocol Review Committee of University of Ghana, School of Medicine and Dentistry (Protocol Identification Number: CHS-Em-4-P4.5/2015–2016). Clearance was also received from the Management of the Korle-Bu Teaching Hospital and Heads of Clinical units where the study was conducted.

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