International Research Journal of Medical Sciences _____ISSN 2320 – 7353
Vol. **11(2),** 1-9, August **(2023)** *Int. Res. J. Medical Sci.*

Assessment of aldosterone and sodium levels in patients with hypertensive pregnancy disorders attending antenatal care in Central Hospital, Benin City, Nigeria

Atoe K.[1,2,3*], Idogun E.S.[4], Ande A.B.A.[5], Onovughakpo-Sakpa O.E.[4], Ayinboumwan E.[4] and Omozuwa E.S.[6]
[1]Department of Chemical Pathology, Edo State University Uzairue, Edo State, Nigeria
[2]Phytomedicine and Drug Discovery Research Group, Department of Plant Biology and Biotechnology, University of Benin, Benin City, Nigeria
[3]Applied Environmental Biosciences and Public Health Research Group, Department of Microbiology, University of Benin, Benin City, Nigeria
[4]Department of Chemical Pathology, University of Benin, Benin City, Nigeria
[5]Department of Obstetric/Gynecology, University of Benin, Benin City, Nigeria
[6]Department of Obstetric/Gynecology, Edo State University Uzairue, Edo State, Nigeria
atoe.kenneth@edouniversity.edu.ng

Available online at: www.isca.in
Received 25th June 2023, revised 30th July 2023, accepted 25th August 2023

Abstract

Preeclampsia is a hypertensive state that affects 2% to 8% of pregnant adult females globally. Together, decreased advancement of the placenta and aldosterone restriction characterize preeclampsia. In individuals, aldosterone is thought to significantly influence placental and birth weight, why elevated sodium is thought to have a negative impact on this association. The study's goal was to see if this significant correlation suggested that aldosterone and sodium levels could be used as bioindicators for preeclampsia. A prospective case-control study of 248 women was conducted in a secondary healthcare facility in Benin City, Nigeria. Participants in the study were split into two groups: those who had preeclampsia (n=138) and those who did not (n=110). Antecubital venipuncture with a sterile disposable syringe was used to collect 5ml of venous blood from both the subjects and control groups. The study participants also provided spot urine. ELISA® was used to assess plasma aldosterone concentrations, while urine and plasma sodium were determined using an ion selective electrolyte analyzer. Preeclamptic pregnant women had a mean plasma sodium level of 131.24mmol/l, whereas normotensive pregnant women had a little increase to 135.42mmol/l (p>0.05). Although preeclampsia had no influence on urine salt levels regardless of pregnancy stage, it did have an effect on aldosterone levels in the second and third trimesters (211.05-248.30pg/ml). Because preeclamptic individual's aldosterone, plasma, along with urinal sodium concentrations remained unafected by disease occurrence or severity, they cannot be used to predict illness severity in preeclamptic pregnancies.

Keywords: Preeclampsia, aldosterone, hypertension, pregnancy disorder, sodium.

Introduction

Public health concerns with maternal and neonatal mortality exist, especially in the developing nations. Sadly Sub-Saharan African nations are among the hardest hit, and preeclampsia appears to be among the primary contributing factors there[1,2]. Conditions associated with hypertension in pregnancy impact as many as eight percent of pregnancies and constitute among the foremost significant factors to motherly as well as newborn morbidity and mortality globally, particularly in developing countries[1]. In low-income countries with poor medical infrastructure and diagnostic capabilities, preeclampsia is frequently misdiagnosed as pregnancy-induced hypertension. The latter typically occurs anytime blood pressure measurements are exceed 140/90 millimeters of mercury in a normotensive pregnant woman whose blood circulatory rate hasn't been increased before 140 days and who does not have an excess of urinary protein, often known as proteinuria. Preeclampsia as a hypertensive disorder in pregnancy is associated with high blood pressure, kidney dysfunction with proteinuria, and/or evidence of organ damage after 20 weeks of gestation[2]. Other possible organs liable for damage due to the incidence of the disease include the brain, lungs, kidney and liver[2,3].

Preeclampsia could be brought on by a lack of placental implantation during the initial stage of gestation, while the exact aetiology is uncertain. It is also believed to be a complex condition. As a result, early detection may play a crucial role in mitigating the threat to health that it poses in any human ecology. Determination of biomarking capabilities would rely on a number of metabolites shown previously to be associated with the health condition. It is possible that these analytes might be triggered by the early onset of the disease or may raise their inherent concentration levels due to the disease. One of such may just be aldosterone which has been reportedly indirectly associated with the aetiology of preeclampsia[3,4].

The circulatory system undergoes considerable changes during pregnancy, including a reactivation of what is referred to as the

Renin-Angiotensin-Aldosterone System, allowing increases in volume which is necessitated by the concentration of aldosterone. Remarkably, in order to prevent a blood pressure rise which would normally follow RAAS stimulation, an associated pushback to the pressure response of Angiotensin II builds up at the same time. Aldosterone is the primary mineral ocorticoid hormone, produced and secreted by the adrenal cortex's zona glomerulosa in reaction to angiotensin II and potassium. Its role in the pathogenesis of preeclampsia has also been proposed, as several studies have found low aldosterone levels to be an identifiable characteristic of preeclampsia[1,3,4].

Preeclamptic women have decreased RAAS function as well as a strong antiangiogenic state, which consists of elevated amounts of soluble Fms-like tyrosine kinase (sFlt)-1 as well as decreased levels of placental growth factor[4]. This renin-aldosterone system is a major determinant of sodium balance in pregnancy, acting as an antagonist to the natriuretic effects of progesterone, arginine vasopressin, atrial natriuretic factor, and prostaglandins. These values tend to fall into a normal, non-pregnant range in preeclampsia. However, when compared to a normal pregnancy, a two fold increase is seen in aldosterone renin ratio. Furthermore, it has recently been discovered that the plasma aldosterone renin ratio may play a crucial function in aorta systolic pressure, with a corresponding rise in aldosterone quantity increase cardiovascular complications, eventually leading to complete organ failure[5]. The purpose of the research is to compare the amounts of aldosterone hormone, plasma, and urinal sodium in preeclamptic and normal pregnant women. The goal is to demonstrate that considerable concurrent increases in aldosterone levels may be linked to preeclampsia.

Materials and Methods

A prospective case-control study on 248 women was undertaken in the Department of Obstetrics and Gynecology, Central Hospital Benin. The study participants were divided into two sets: those with preeclampsia (n=138) as well as those without (i.e. normotensive, normal pregnancy (n=110). Preeclampsia is characterised by an increase in systolic blood pressure to values higher than 140mmHg as well as a diastolic blood pressure increase beyond 90mmHg, usually following twenty weeks of pregnancy, with significant proteinuria. Usually, there is no history of hypertension or renal disease prior to the 20 weeks; and blood pressure going back to a normal level 12 weeks postpartum.

Exclusion criteria adopted for this study included medical conditions in the mother, such as a history of heart conditions, nephropathy, or diabetic mellitus, thyroid disease, hepatic disease, and any associated disorders like urinary tract infections. A mercurial sphygmomanometer was used to monitor blood pressure of individuals at an inclined posture on a minimum of two consecutive instances. Antecubital venipuncture with a sterile disposable syringe was used to collect 5ml of venous blood from both the subjects and control groups. Spot urine was also collected from the study participants. The whole blood obtained were collected into an Heparinazed bottle, and then immediately separated and the plasma collected into a 5mls plain bottle by a Pasteur pipette. The sample was stored at minus 4 degree until ready for aldosterone and sodium analysis. The Spot urine was collected into a universal container and also stored at minus 4 degree prior to Urinary sodium analysis. Plasma aldosterone concentration estimation was by enzyme linked immunosorbent assay (ELISA)[6] while sodium assay was carried out with the ion selective electrolyte analyser[7].

Ethical approval: All study participants gave their informed consent. They were fully informed about the nature and purpose of this work, and they had the option to resign from the study without affecting the medical care they received. The Hospitals Management Board of Edo State also provided ethical committee approval (Ref. No. A.723/56).

Method of data management and analyses: The results obtained were presented as the average and standard deviation, and the significance of separated means was assessed. Similarities of specific variables were also measured against the average Plasma Sodium level, Urinary sodium level, and Aldosterone concentrations in order to demonstrate the amount of bivariate correlation. When significant connections were found, a regression model comparing aldosterone (dependent var.) against specified factors was given. To demonstrate the performance of a classification model at all classification levels, a Receiver Operating characteristic curve (or ROC) was shown. This demonstrated the sensitivity and specificity of aldosterone as a diagnostic marker for preeclampsia during the trimesters and post-partum. Data obtained were subjected to statistical analyses using the Statistical Package for Social Sciences.

Results and discussion

The Marital status and educational status of respondents have been presented (Table-1). There were a total of 248 study participants, among which 138 were preeclamptic. Among the preeclamptic women, 17.3% were single whereas 56.6% were remarried.

In general, the average concentration of plasma sodium level in pregnant women with preeclampsia was 131.24 millimoles per litres (mmol/l), compared to 135.42mmol/l in normotensive pregnant women ($p<0.05$). The presence of preeclampsia, contrarily, showed no effect on plasma sodium levels. During post delivery, despite considerable increases seen in both the second and third trimesters. Regardless of pregnancy stage, preeclampsia had no effect on Urinary sodium levels. Whereas the occurrence of preeclampsia showed no impact on aldosterone levels throughout the second and third trimesters, a decline in aldosterone levels was noted. Aldosterone levels in preeclamptic women fell from 211.05pg/ml to 248.30pg/ml in normotensive women.

Table-1: Marital status and educational status of respondents.

Respondents		Preeclampsia n (%) (n=138)	Normotensive n (%) (n=110)	Incidence factor (%)	P value
Marital status	Single	12 (17.3)	12 (21.8)	25.00	0.003
	First Marriage	39 (56.5)	32 (58.2)	43.83	
	Remarried	18 (20.1)	11 (20.0)	92.31	
Educational status	None	12 (17.4)	9 (13.1)	100.00	0.433
	Primary	22 (31.8)	11 (15.9)	66.67	
	Secondary	28 (40.6)	13 (18.8)	48.57	
	Post-secondary	19 (27.5)	22 (31.8)	45.24	

Table-2: The mean concentration of plasma and urinary sodium, as well as aldosterone measurements of the pregnant women with preeclampsia comparative to those pregnant women with normal conditions, taken during the 2nd and 3rd trimesters and postpartum.

Period	Analytes	Units	Preeclampsia	Normotensive	Sig.
General Mean	Plasma sodium conc.	mMol/L	131.24 ± 5.4*	136.42 ± 5.82	0.001
	Urinary sodium conc.	mMol/L	70.8 ± 3.4	79.17 ± 13.69	0.22
	Aldosterone levels	pg/mL	254.06 ± 16.27	301.58 ± 6.22	0.095
Second	Plasma sodium conc.	mMol/L	132.90 ± 4.70	135.75 ± 5.78	0.005
	Urinary sodium conc.	mMol/L	75.00 ± 7.00	78.80 ± 9.38	0.728
	Aldosterone levels	pg/mL	244.42 ± 70.10	264.79 ± 13.83	0.559
Third	Plasma sodium conc.	mMol/L	131.20 ± 5.14	136.65 ± 5.14	0.005
	Urinary sodium conc.	mMol/L	66.75 ± 23.55	79.70 ± 14.40	0.236
	Aldosterone levels	pg/mL	285.53 ± 13.85	363.89 ± 14.66	0.113
Postpartum	Plasma sodium conc.	mMol/L	132.00 ± 5.00	136.90 ± 2.30	0.221
	Urinary sodium conc.	mMol/L	60.25 ± 5.00	72.20 ± 13.74	0.089
	Aldosterone levels	pg/mL	211.05 ± 13.35	248.30 ± 7.99	0.002

*Results show Mean ± SD.

Results showed Aldosterone readings in pregnant women with preeclampsia and those of the control group taken between weeks 14-27 and weeks 28-40, likewise at the postnatal period, including the mean concentration of plasma and urinary sodium (Table-3). Clearly, the findings indicated a Test for the Implication of Disconnected Sources of the Study Analytes, including Aldosterone Concentrations and those of Plasma Sodium in the Study Participants, who Initially Presented with Preeclampsia, and Represented by the Use of Trimesters.

There were no statistically significant variations in aldosterone levels between the second and third trimesters (p=0.111). Similarly, there was no difference in plasma sodium levels between the second and third trimesters (p=0.806).

Table-4 illustrates the mean sodium level of the plasma, urea sodium level, and aldosterone levels of patients with preeclampsia classified by disease severity. There were no significant variations in aldosterone levels between mild and severe preeclamptic subjects. Similarly, there were no significant changes in plasma sodium and Urinary sodium levels in severe and mild preeclampsia.

In another dimension, preeclamptic participants' Mean Urinary sodium concentration, Plasma sodium concentration, and levels of Aldosterone were differentiated by BMI (Table-5). In pregnant preeclamptic patients, BMI had no effect on aldosterone, plasma sodium, or Urinary sodium levels.

During the second trimester, similarities of selected variables against the average Plasma Sodium rate, Concentration Urinary sodium and levels of Aldosterone at the second half of pregnancy has been presented (Table-6). Although no significant relationship was found between the test analytes and height, weight, mid-arm circumference, or booking blood pressure measurements, there was an insignificant positive relationship between Urinary sodium and Systolic booking BP. Similarly, there was a lesser (negative) relationship between Urinary sodium and diastolic index BP. However, in the third trimester, there was a significant correlation between aldosterone levels and mid-arm circumference (R=0.552; p<0.01). This relationship, on the other hand, was weak. However, in the third trimester, there was a significant correlation between aldosterone levels and mid-arm circumference (R=0.552; p<0.01). This relationship, on the other hand, was weak.

Table-3: Test for the implication of detached sources of the study analytes including Aldosterone concentrations of plasma sodium in the study participants which presented with preeclampsia, and initially represented by the use of trimesters.

Period 1	Period 2	Aldosterone P value	Plasma Sodium P value
Second	Third	0.111	0.280
	Postpartum	0.576	0.806
Third	Second	0.111	0.280
	Postpartum	0.215	0.827
Postpartum	Second	0.576	0.806
	Third	0.215	0.827

Table-4: Estimated concentration of sodium in plasma and urine along with the level of aldosterone in preeclamptic subjects divided on the brutality level of disease. Results show Mean ± SD; Mild preeclampsia, n=30; Severe preeclampsia, n=60.

Severity	Units	Mild preeclampsia	Severe preeclampsia	Sig.
Aldosterone levels	(pg/ml)	241.68 ± 8.62	237.42 ± 6.63	0.541
Plasma sodium conc.	(mMol/l)+	131.14 ± 9.11	129.17 ± 7.12	0.433
Urinary sodium conc.	(mMol/l)+	68.52 ± 8. 63	73.63 ± 5.28	0.421

Table-5: Mean levels of sodium in plasma and urinary along with the level of aldosterone in preeclamptic subjects based on body mass and weight. Results show Mean ± SD; Normal or control, n=18; overweight, n=14; and obese n=58.

Parameters	Normal BMI	Overweight BMI	Obese BMI	Sig.
Aldosterone (mmol/l)	253.61 ± 12.98	261.76 ± 14.39	217.59 ± 38.75	0.057
Plasma sodium (mmol/l)	133.78 ± 2.17	131.86 ± 3.57	130.59 ± 6.21	0.295
Urine sodium (mmol/l)	60.24 ± 2.93	78.16 ± 4.12	72.01 ± 3.83	0.560

Table-6: Relationships between several factors as well as the 2nd-trimester rates of the average plasma sodium, urinary sodium, and aldosterone. * The association is significant at 0.05.

Factors	Aldosterone	Plasma Sodium	Urinary Sodium
Body Height	-0.328	0.3173	0.1965
Body Weight	-0.173	-0.022	0.182
Mid-arm circumference	-0.19	0.1201	0.0396
Aldosterone	1	-0.2289	0.1703
Plasma sodium levels	-0.289	1	-0.216
Urinary sodium concentrations	0.1603	-0.2216	1
Systolic booking blood pressure	-0.387	0.2088	0.3912*
Diastolic booking blood pressure	-0.351	0.241	0.3399
Systolic index blood pressure	-0.089	0.0982	-0.295
Diastolic index blood pressure	0.0294	0.1315	-0.467*

Table-7: Relationship between several factors in 3rd rimester. The association is significant at ** = 0.01, * = 0.05.

Factors	Body Height	Body Weight	Mid-arm circumference	Systolic Booking	Diastolic booking	Systolic	Diastolic
				Blood pressure		Index blood pressure	
Aldusterone conc.	0.416*	0.581**	0.550**	0.253	0.423*	0.162	0.421*
Plasma sodium levels	0.296	-0.529	-0.547**	0.044	0.003	-0.205	0.088
Urinary sodium conc.	0.049	0.078	-0.075	0.139	0.043	0.135	-0.019

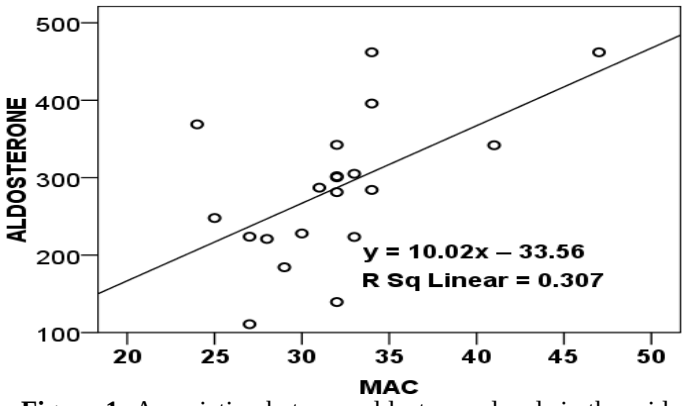

Figure-1: Association between aldosterone levels in the mid-arm conference during the third trimester.

In some circumstances, it is difficult to determine whether a factor analysis was required to better explicate a data set. The Kaiser-Meyer-Olkin (or KMO) metric is commonly used to facilitate this. This is typically used to assess the sampling appropriateness of a data set (Table-8).

In the current investigation, the sig. value of the KMO was determined to be 0.548, indicating that the data set employed in this analysis was adequate. A null hypothesis that the variables in the population correlation matrix are uncorrelated was evaluated with the Bartlett's test, with the null hypothesis rejected if the p-value was less than 0.05.

A brief overview of the non-parametric proposed theory test for comparing normotensive and preeclamptic effects throughout the first trimester and post-partum using aldosterone is shown in Table-9.

The study found that the spread of aldosterone is consistent throughout preeclampsia types. (p>0.05) in both the first and second trimesters (Figure-2). Similar outcomes have been presented for plasma sodium (Figure-3, 4, 5, and Table-10).

Table-8: Kaiser-Meyer-Olkin (KMO) and Bartlett's Test of Sphericity, determined to measure of sampling adequacy during the third trimester of pregnancy in the study group

Test parameter	Values
KMO value	0.54823
Bartlett's Test (Approx. Chi-Square)	102.939
Degree of freedom	66
p-value	0.00245

Table-9: Non-parametric test of hypothesis overview for contrasting normotensive outcome with preeclampsia within the start of a pregnancy and after childbirth using aldosterone.

Duration	Undefined theory	Evaluation	Significance level	Conclusion
First trimester	The flow of aldosterone is uniform among the different groups of preeclampsia	Unrelated samples using the Mann-Whitney U Test	0.100[a]	Retain the null hypothesis
Postnatal period	The circulation of aldosterone is equivalent in all types of preeclampsia	Unrelated samples by Mann-Whitney U Test	0.333[a]	Retain the null hypothesis
The asymptotic importance is demonstrated. The significance level is 0.05. Exact significance is shown for this experiment				

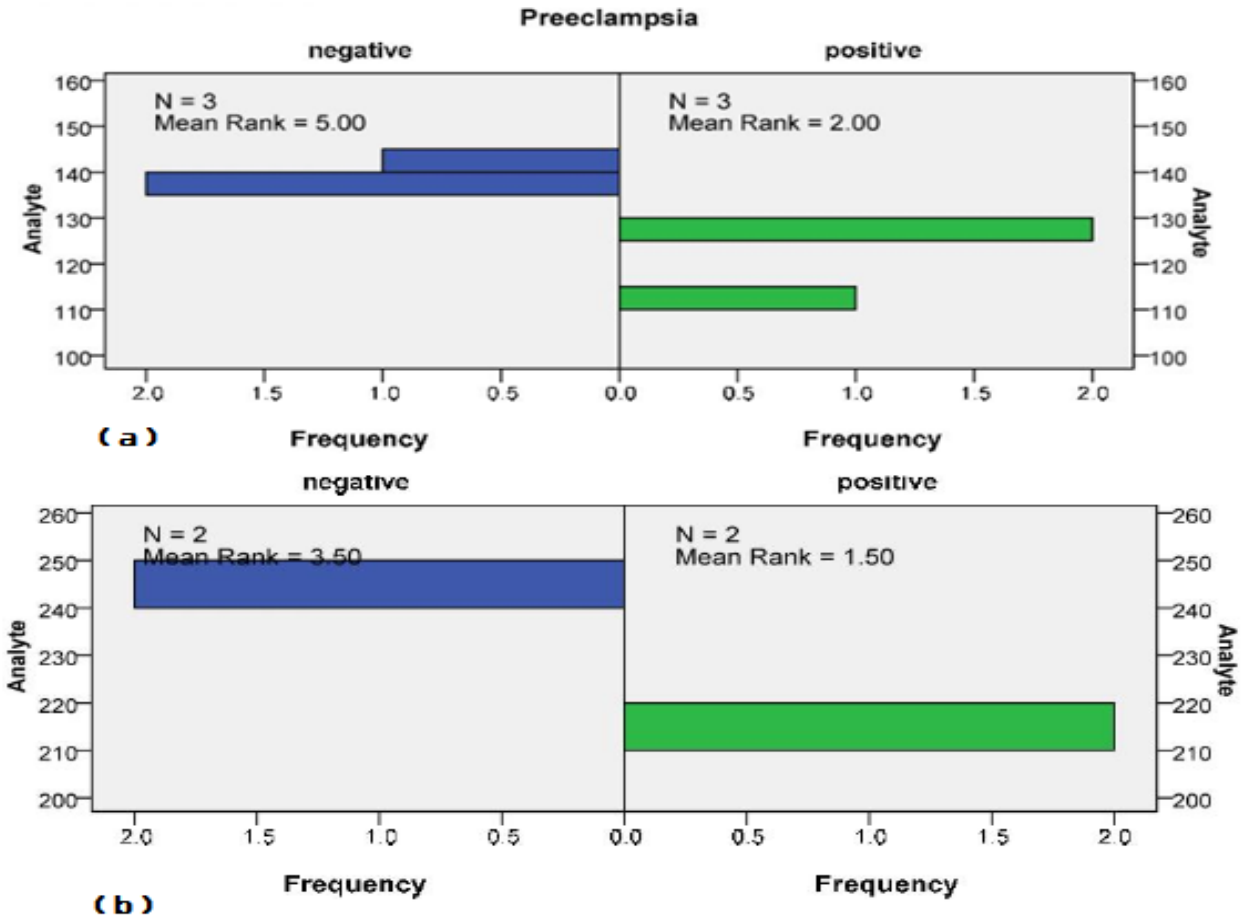

Figure-2: Independent-samples Mann-Whitney U Test for aldosterone detection in preeclampsia Result: a) Within the early phase of pregnancy (b) after childbirth.

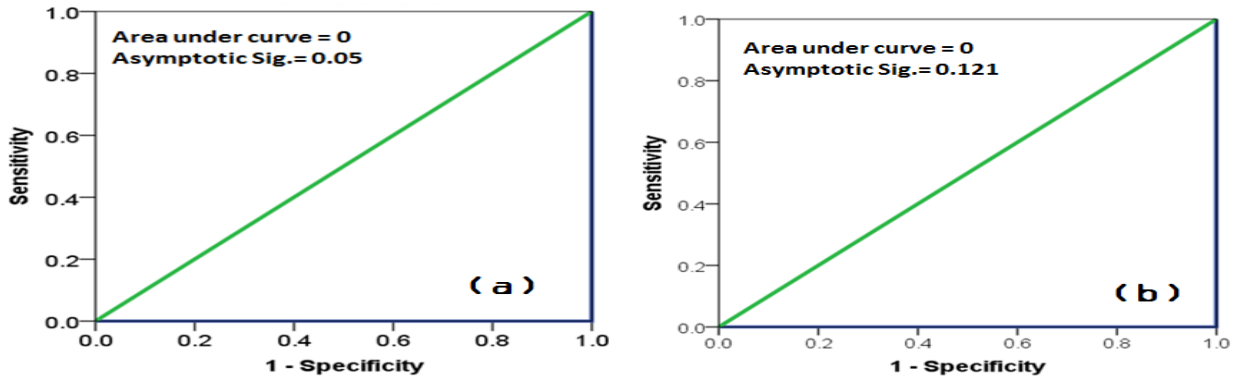

Figure-3: Relative Operating Curve showing level of sensitivity and specificity of aldosterone as a diagnostic marker for determining preeclampsia during the first trimester and postpartum term.

Table-10: Overview of the not- parametric testing procedure in comparing the hypertensive achievement of First trimester and post-partum for plasma sodium.

Period	Null Hypothesis	Test	Sig.	Decision
All trimesters including post-partum observation	The distribution of plasma sodium is the same across categories of preeclampsia	Independent-samples Mann-Whitney U Test	0.000[a]	Reject the null hypothesis
Demonstrated, is a asymptotic relevance. The degree of significance is 0.05				

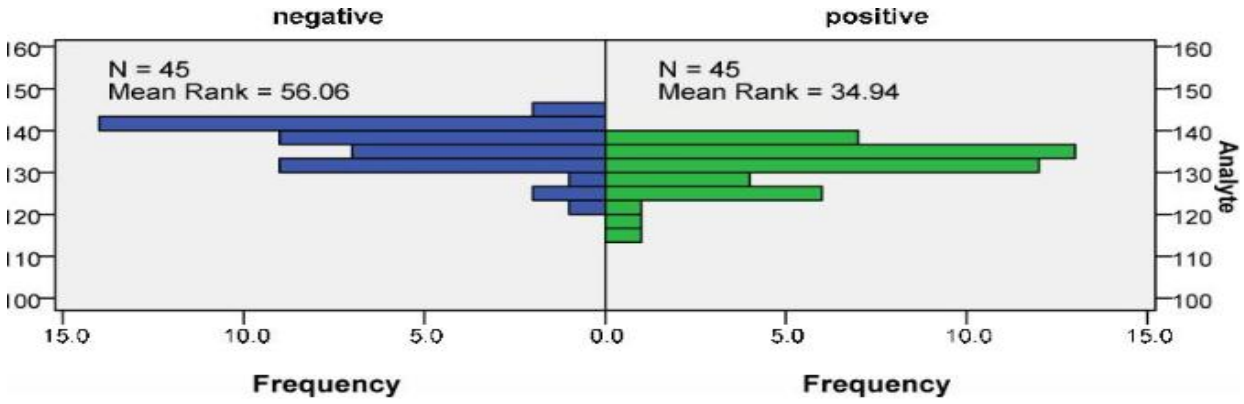

Figure-4: Regardless of the stage of pregnancy, the self-sufficient specimen Mann-Whiskey U test is used to determine the plasma sodium level in preeclampsia.

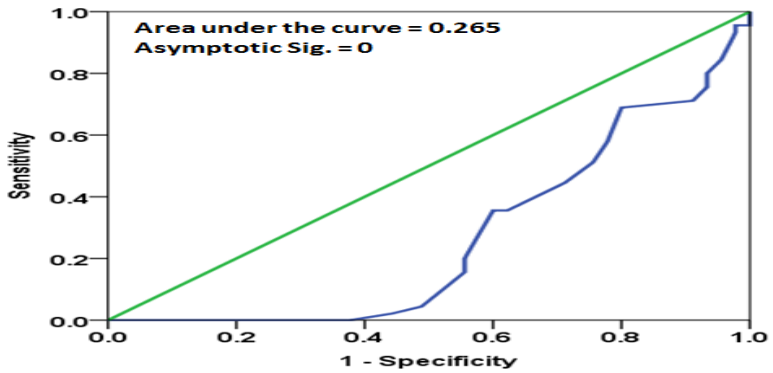

Figure-5: Relative Operating Curve showing level of sensitivity and specificity of plasma sodium as a diagnostic marker for determining preeclampsia irrespective of periodicity of trimester.

Discussion: Preeclampsia is a potentially fatal pregnancy condition. It is the first occurrence of high blood pressure (hypertension) and proteinuria after the twentieth week of pregnancy. It greatly contributes to maternal and neonatal morbidity and mortality globally[8,9]. Several research have been conducted to study the involvement of aldosterone and salt in preeclampsia, however inconsistent results have been reported. In situations of preeclampsia, they may rise, decrease, or even remain unchanged across the trimesters of pregnancy[10].

This study found no statistically significant difference in aldosterone (p=0.111) or sodium (p=0.806) levels between the second and third trimesters in preeclamptic and normotensive pregnant women. Similarly, this study found that disease severity, i.e. moderate and severe preeclampsia, as well as the study participant's body mass index, have no significant effect on aldosterone, urine, and plasma sodium levels. This was in contrast to a study conducted in Caro, Egypt, where Escher & Mohaupt [11] discovered a statistically significant difference between the control, mild preeclampsia, and severe preeclampsia groups (P=0.11). This variance could be attributed to research location and study participant age groups. The majority of our study participants have completed school and higher education.

The current study found that BMI had no influence on aldosterone, plasma sodium, or Urinary sodium levels in pregnant preeclamptic individuals. However, these findings contradicted previous findings that found a statistically significant difference in BMI between the control, mild preeclampsia, and severe preeclampsia groups (P=0.12). Overtime, research has established obesity as a clear risk factor for preeclampsia. Both pre-pregnancy BMI and gestational weight gain, they noted, may increase oxidative stress levels, promote a systemic inflammatory response, and hasten damage to vascular endothelial cells, culminating in preeclampsia[12,13].

The current study found that height, weight, and mid-arm circumference had strong positive correlations with the mean levels of plasma sodium, sodium in the urine, and aldosterone in the 2nd trimester, whereas correlations between systolic booking blood pressure, Diastolic booking blood pressure, systolic index blood pressure, and Diastolic index BP were weak. Cooley et al.[14] found a positive correlation of 0.836 between BMI and MUAC (p=0.01) with increased levels of aldosterone and plasma sodium across the trimesters in women with pre-eclampsia when height and weight were used as a surrogate for BMI in a study on pregnant women in London and Ireland. Fakier et al[15] discovered a similar substantial association between BMI and MUAC.

Aldosterone levels in pregnant women with preeclampsia were lower in all three trimesters compared to normotensive counterparts[16]. Birukov et al.[17] discovered that the levels of aldosterone, plasma sodium as well as Urinary sodium were not linked to preeclampsia incidence.

Nevertheless, the results of non-parametric and diagnostic statistics revealed that relying solely on aldosterone as a diagnostic marker is insufficient. The distribution of aldosterone levels was found to be the same in preeclamptic and normotensive subjects in this investigation.in both the first and second trimesters (P=0.05). The same is true for plasma sodium and sodium in the urine. The consequence is that the levels of aldosterone cannot be utilized in the prediction of changes whatsoever in these analytes.

Conclusion

The levels or concentrations of aldosterone, plasma, and Urinary sodium in patients diagnosed with preeclampsia were not influenced by the trimesters of pregnancy or disease severity. Body Mass Index, on the other hand, has no effect on the levels of aldosterone and salt in preeclampsia. As a result, they cannot be employed as indicators for illness severity in preeclamptic pregnancies.

References

1. Rashid, R. A., Shahid, A., & Liaqat, M. (2018). Frequency of dyslipidimia in pregnant women with pre eclampsia in services hospital lahore. *Indo American Journal of Pharmaceutical Sciences*, 5(5), 4458-4468.

2. Brown, M., Magee, L., Kenny, L., Karumanchi, S. A., Mccarthy, F., Saito, S., ... & Ishaku, S. (2018). The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertension*, 13, S6-S7.

3. Verdonk, K., Visser, W., Van Den Meiracker, A. H., & Danser, A. J. (2014). The renin–angiotensin–aldosterone system in pre-eclampsia: the delicate balance between good and bad. *Clinical Science*, 126(8), 537-544.

4. Verdonk, K., Saleh, L., Lankhorst, S., Smilde, J. I., Van Ingen, M. M., Garrelds, I. M., ... & Danser, A. J. (2015). Association studies suggest a key role for endothelin-1 in the pathogenesis of preeclampsia and the accompanying renin–angiotensin–aldosterone system suppression. *Hypertension*, 65(6), 1316-1323.

5. Brown, M. A., Zammit, V. C., Mitar, D. A., & Whitworth, J. A. (1992). Renin-Aldosterone Relationships in Pregnancy-Induced Hypertension: An Alternative Viewpoint. *American journal of hypertension*, 5(6_Pt_1), 366-371.

6. Lequin, R. M. (2005). Enzyme immunoassay (EIA)/ enzyme-linked immunosorbent assay (ELISA). *Clinical chemistry*, 51(12), 2415-2418.

7. Khalil, S. A., Moody, G. J., & Thomas, J. D. R. (1986). Ion-selective electrode determination of sodium and potassium in blood and urine. *Analytical Letters*, 19(17-18), 1809-1830.

8. Noris, M., Perico, N., & Remuzzi, G. (2005). Mechanisms of disease: pre-eclampsia. *Nature clinical practice Nephrology*, 1(2), 98-114.

9. Yang, X., Yang, Y., Yuan, Y., Liu, L., & Meng, T. (2020). The roles of uterine natural killer (NK) cells and KIR/HLA-C combination in the development of preeclampsia: a systematic review. *BioMed research international*, 2020.

10. He, A., Zhou, Y., Wei, Y., & Li, R. (2020). Potential protein biomarkers for preeclampsia. *Cureus*, 12(6).

11. Escher, G., & Mohaupt, M. (2007). Role of aldosterone availability in preeclampsia. *Molecular aspects of medicine*, 28(2), 245-254.

12. Ornaghi, S., Tyurmorezova, A., Algeri, P., Giardini, V., Ceruti, P., Vertemati, E., & Vergani, P. (2013). Influencing factors for late-onset preeclampsia. *The Journal of Maternal-Fetal & Neonatal Medicine*, 26(13), 1299-1302.

13. Kartikadewi, R., Theresia, E. M., & Meilani, N. (2019). Age, parity and birth spacing to the incidence of preeclampsia. *Int J Public Health Sci*, 8(1), 45-50.

14. Cooley, S. M., Donnelly, J. C., Walsh, T., Durnea, U., Collins, C., Rodeck, C. H., ... & Geary, M. P. (2011). The relationship between body mass index and mid-arm circumference in a pregnant population. *Journal of Obstetrics and Gynaecology*, 31(7), 594-596.

15. Fakier, A., Petro, G., & Fawcus, S. (2017). Mid-upper arm circumference: A surrogate for body mass index in pregnant women. *South African Medical Journal*, 107(7), 606-610.

16. Delles, C., & Freel, E. M. (2013). Aldosterone, vascular endothelial growth factor, and preeclampsia: a mystery solved?. *Hypertension*, 61(5), 958-960.

17. Birukov, A., Andersen, L. B., Herse, F., Rakova, N., Kitlen, G., Kyhl, H. B., ... & Jensen, B. L. (2019). Aldosterone, salt, and potassium intakes as predictors of pregnancy outcome, including preeclampsia. *Hypertension*, 74(2), 391-398.