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Comparative Study Of Stress Marker (CORTISOL) Levels in Preeclamptic Pregnant Women in the Third Trimester Of Pregnancy

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Abstract. *At present, little is known in Nigeria and globally about the association between stress and cortisol secretion in normotensive and preeclamptic pregnant women. Preeclampsia is a pregnancy complication that involves high blood pressure and organ damage, and it has been associated with various physiological alterations. This study aims to determine the comparative levels of cortisol, a stress marker, in preeclamptic pregnant women in the third trimester of pregnancy. Cortisol levels are known to fluctuate in response to stress, and altered levels may indicate an underlying pathophysiological process. Forty (40) consenting pregnant women were recruited from St. Philomina Catholic Hospital, Edo State, Nigeria. Blood samples were collected and spun in a bucket centrifuge at 2500 RPM (rounds per minute) for 10 minutes. The plasma was stored frozen in plain sample bottles and analyzed for cortisol levels using the enzyme-linked immunosorbent assay (ELISA) method. The data obtained were analyzed using GraphPad Prism 9 software. Results were expressed as mean ± SEM, and a P-value of ≤ 0.05 was considered statistically significant. The study found that cortisol levels significantly increased from 226.4 ± 36.53 nmol/L in normotensive women to 370.7 ± 36.47 nmol/L in preeclamptic women ($p<0.05$, <0.0081). This increase was statistically significant, suggesting that elevated cortisol levels in preeclamptic women may be linked to stress and potentially to oxidative stress cascade activation. These findings contribute to the understanding of stress-related physiological changes in preeclampsia and may offer insights for future diagnostic or therapeutic approaches.*

Keywords: *Cortisol, Normotensive, Preeclampsia, Pregnant women*

1. INTRODUCTION

Cortisol is a primary stress hormone produced by the adrenal glands, and it plays a significant role in the body's response to stress. It regulates several physiological processes, including metabolism, immune response, and stress adaptation. In the context of preeclampsia, a condition characterized by high blood pressure and organ dysfunction during pregnancy, cortisol levels have been of particular interest. Previous studies have suggested that cortisol secretion may

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be altered in preeclamptic women, potentially contributing to the pathophysiology of the disease [1]. However, the exact relationship between cortisol and preeclampsia remains underexplored, especially in terms of comparative studies between normotensive and preeclamptic pregnant women.

Stress has been identified as a contributing factor in the development and progression of preeclampsia. Elevated levels of stress markers, including cortisol, have been observed in women with preeclampsia, suggesting that stress may play a role in triggering or exacerbating the condition. Stress-related physiological changes, such as increased sympathetic nervous system activity and alterations in vascular function, are thought to contribute to the high blood pressure and organ damage associated with preeclampsia [2]. Understanding the role of stress and cortisol in preeclampsia could provide valuable insights into potential mechanisms of the disease and aid in the development of early detection strategies.

Preeclampsia is a complex and multifactorial pregnancy complication that poses significant risks to both maternal and fetal health. It is characterized by high blood pressure, proteinuria, and organ damage, particularly to the kidneys, liver, and brain [3]. The condition can lead to severe complications, such as organ failure, eclampsia, and maternal death, as well as preterm birth and fetal growth restriction. Globally, preeclampsia affects approximately 2-8% of pregnancies and remains one of the leading causes of maternal and fetal morbidity and mortality [4]. Despite its prevalence, the exact causes and mechanisms underlying preeclampsia are not fully understood, making early detection and prediction of the condition critical for preventing severe outcomes.

Early detection of preeclampsia is crucial for effective management and to reduce the risk of complications. Timely interventions, such as the administration of antihypertensive medications and the careful monitoring of both maternal and fetal well-being, can help mitigate the severity of the condition. However, the current methods of diagnosing and predicting preeclampsia are limited and often only effective once the disease has already manifested. Therefore, there is a need for novel biomarkers and diagnostic tools that can predict the onset of preeclampsia in its early stages.

This study aims to compare cortisol levels in preeclamptic and normotensive pregnant women in the third trimester of pregnancy. By analyzing cortisol levels, the research seeks to identify potential early indicators of preeclampsia, which could lead to better prediction models for the disease. The findings of this study may contribute to improving maternal and fetal outcomes

by facilitating earlier interventions and personalized management strategies for women at risk of preeclampsia.

2. LITERATURE REVIEW

Cortisol is a glucocorticoid hormone secreted by the adrenal cortex in response to stress and low blood glucose levels. It plays a critical role in various physiological processes, including metabolism, immune regulation, and maintaining cardiovascular homeostasis. Cortisol secretion follows a circadian rhythm, with peak levels in the early morning and a gradual decline throughout the day. During pregnancy, cortisol levels naturally increase due to the activity of the hypothalamic-pituitary-adrenal (HPA) axis and placental secretion of corticotropin-releasing hormone (CRH), contributing to fetal development and maternal adaptation (9). Preeclampsia is characterized by systemic endothelial dysfunction, heightened inflammatory responses, and increased oxidative stress. These pathological changes may be influenced by dysregulated cortisol levels. Studies have reported significantly elevated maternal cortisol levels in preeclamptic pregnancies compared to normotensive pregnancies. This hypercortisolism may result from overactivation of the maternal HPA axis and placental CRH production in response to stress (10). Increased cortisol levels can exacerbate hypertension by enhancing vascular sensitivity to angiotensin II and impairing endothelial nitric oxide production. Additionally, cortisol contributes to insulin resistance and metabolic disturbances, both of which are implicated in the pathophysiology of preeclampsia. The interplay between elevated cortisol and other biomarkers, such as inflammatory cytokines and oxidative stress markers, further underscores its role in disease progression (11). The potential utility of cortisol as a biomarker for preeclampsia has gained attention. Elevated cortisol levels in maternal plasma or saliva during early pregnancy may predict the development of preeclampsia. Moreover, the cortisol-to-cortisone ratio, reflecting the activity of 11β-hydroxysteroid dehydrogenase enzymes, has been proposed as a more specific marker of HPA axis dysregulation in preeclamptic pregnancies. These findings highlight the need for longitudinal studies to validate cortisol's diagnostic and prognostic value (12). Targeting cortisol dysregulation in preeclampsia remains an area of ongoing research. Glucocorticoid receptor antagonists and other interventions that modulate the HPA axis are being explored for their potential therapeutic benefits. However, the safety and efficacy of such approaches require further

investigation. Understanding the mechanisms linking cortisol to preeclampsia may pave the way for personalized treatment strategies aimed at mitigating maternal and fetal complications (13).

3. MATERIALS AND METHODS

Geographical Description of the Study Area

This research was carried out among Third Trimester Pregnant women in St. Philomina Catholic Hospital, Edo State , Nigeria.

lies longitudinally at 04ºE and 43ºE and Latitude 05º44ºN and 07º34ºN. It geopolitical location is the South South and it has a population of 3.5 million people. Oredo land, Benin City, the State capital, is 100 km long. Edo State, South-South, Nigeria. Oredo is a Local Government Area of Edo State, Nigeria. Its headquarters are in the town, Benin city. It has an area of 502 km² and a population of 500,000 at the 2006 census.

Majority of which are civil servants, traders, businessmen/women, transporter, farmers, teachers/lecturers and students by occupation. Oredo, since after its designation as headquarters and as the host of Oba of Benin Palace, the town has grown into an urban center.

Research Design

Forty (40) consenting pregnant subjects were recruited from St. Philomina Catholic Hospital, Edo State. These subjects consisted of twenty (20) normotensive pregnant women in their third trimester of pregnancy with blood pressure between 120/80mmHg to 130/90 mm/Hg without presence of proteinuria and twenty (20) preeclamptic women in their third trimester of pregnancy classified as having preeclampsia according to their blood pressure measured was above 130/90 mm/Hg with the presence of proteinuria taken two consecutive times at presentation at the antenatal clinic of the hospital

Sample Size

The Population of study was determined using the formula;

$N= Z^2pq/d^2$

Where N= the desired sample size (when population is greater than 10,000)

Z= is a constant given as 1.96 (or more simply at 2.0) which corresponds to the 95% confidence level.

P= previous survery prevalence of 2.23%

q= 1.0-p

d= acceptable error 5%.

Where N= sample size, Z=1.96, p=0.1% (0.01) and d=5% (0.05)

N= 39.8 subject.

Therefore, the sample for this study is 40 respondents who are normotensive and preeclamptic pregnant women from Oredo town, Benin City.

Ethical Approval and Informed Consent

Ethical clearance (REC Approval No:RECC/10/2023(07)) was obtained from the Research Ethics Committee of St. Philomina Catholic Hospital, Edo State. Written informed consent was obtained from subjects prior to commencement of the study.

Blood Sampling

10 milliliters (10 ml) of venous blood was drawn from consenting participants and placed in a lithium heparin sample bottles. Blood samples was spun in a bucket centrifuge at 2500 RPM (rounds per minute) for 10 minutes after which plasma was collected and stored frozen in plain sample bottles and was analyzed for Stress Marker (cortisol)

Experimental Protocols

After the subjects were identified and recruited into the study, they were taken to the lab where their vital signs was taken, after which blood samples were collected by venipuncture and taken to the chemistry laboratory for analysis.

Study Area/Population

The study were conducted for three months at St. Philomina Catholic Hospital, Edo State, Nigeria.

Inclusion Criteria

Normotensive and Preeclamptic pregnant women in the third trimester of pregnancy, within the age range of 25 to 35years was used for this study. Pregnant women were recruited for this study and women who had given birth before and were pregnant for the second time.

Exclusion Criteria

Normotensive and Preeclamptic pregnant women who were on drugs and with a known history of hyperlipidemia, gestational Diabetes and other comorbidity.

Biochemical Examination

Measurement of Stress Marker (cortisol): Cortisol hormone level was determined according to the method of Tiez and Andresen, (1986) using ELISA TECO kit for cortisol.

Principle

The cortisol ELISA Kit is a solid phase enzyme-linked immunosorbent assay (ELISA), based on the principle of competitive binding. The microtiter wells are coated with an antibody directed towards an unique antigenic site on the cortisol molecule. Endogenous cortisol of a patient sample competes with a cortisol horseradish peroxidase conjugate for binding to the coated antibody. After incubation the unbound conjugate is washed off. The amount of bound peroxidase conjugate is reverse proportional to the concentration of cortisol in the sample. After addition of the substrate solution, the intensity of colour developed is reverse proportional to the concentration of cortisol in the patient sample.

Kit components

1. Microtiter wells, 12x8 (break apart) Strips, 96 wells coated with mouse monoclonal anti-cortisol antibody
2. Standard (Standard 0-6), 7 vials, 1 ml, ready to use concentrations: 0 - 0.2 - 0.5 .1 .2 . 6 - 16 ng/ml Conversion: 1 ng/ml = 3.467 nmol/l
3. Enzyme conjugate, 1 vial, 25 ml, ready to use cortisol conjugated to horseradish peroxidase
4. Substrate solution, 1 vial, 25 ml

5. Stop Solution, 1 vial, 14 ml, ready to use contains 0.5M H_2SO_4 avoid contact with the stop solution. It may cause skin irritations and burns.
6. Wash Solution, 1 vial, 30 ml (40X concentrated)

Assay procedure

All samples and reagents was allowed to reach at room temperature ~25°C). Reagents was mixed by gentle inversion before use. Standards, controls and samples assayed in duplicate.

1. Microtitration Strip was marked to be used.
2. Twenty-five µL of the standards, controls and samples were added into each appropriate well.
3. Two hundred µL of Conjugate Reagent were added into each well using a precision pipette.
4. The wells were mixed for 10 seconds.
5. The wells were incubated for 60 minute at room temperature (~25°C).
6. Each well was aspirated and washed 3 times by added 400 µL of working Wash Solution.
7. Two hundred µL of substrate solution were added into each well using a precision pipette and gently mixed for 10 seconds.
8. The wells were incubated in the dark for 15 minute at room temperature (~25°C).
9. One hundred µL of Stop Solution were added into each well using a precision pipette and mixed for 10-20 seconds.
10. The absorbances of the solution in each well were read at 450 nm.

Calculation

The absorbance for each standard, control, or samples were obtained, and then the standard curve prepared by plotted the absorbance readings for each of the standards along the Y-axis versus standard concentrations in ng/mL along the X-axis, the mean absorbance values for each sample were determined the corresponding concentration of cortisol in ng/mL from the standard curve.

Data Analysis

Data obtained from this study were analysed using Graph Pad Prism 9. Results generated were expressed as mean ± SEM and a P-value of ≤ 0.05 were considered satistically significant. The significance of difference among the groups were used to assess the repeated-measures

analysis of variance (ANOVA). Independent students' t-test were used to compare normotensive and preelclamptic pregnant women groups.

4. RESULT AND DISCUSSION

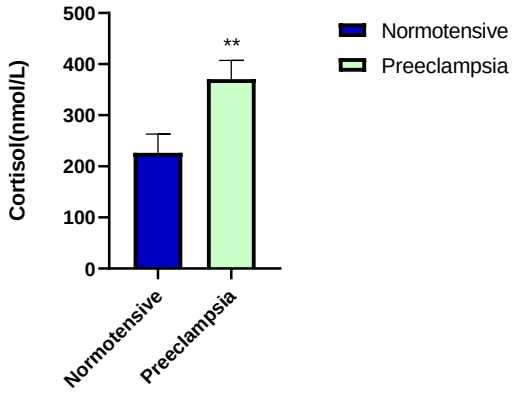

Figure 1: Mean ± SEM of Cortisol level in normotensive (n=20) and preeclampsia (n=20). The t-test was carried out to access any significant difference. ** represents p<0.01

Figure 1 shows the levels of Cortisol in Normotensive and pre-eclamptic women in their third trimester of pregnancy. Cortisol level increased from 226.4 ± 36.53nmol/L in Normotensive women to 370.7 ± 36.47nmol/L in pre-eclamptic women. This increase was found to be statistically significant ($p<0.05$; <0.0081).

5. DISCUSSION

Cortisol, a stress hormone produced by the adrenal glands, is released in response to various physiological and psychological stressors. Figure 1 cortisol levels were significantly higher in pre-eclamptic pregnant women compared to normotensive women, suggesting increase in cortisol level may be directly proportional to oxidative stress abnormal cascade in preeclampsia, in line with other previous Studies which consistently reported elevated cortisol levels in women with preeclampsia compared to normotensive pregnant women [1]. Moreover, increase cortisol levels in early pregnancy have been associated with an increased risk of developing preeclampsia later in pregnancy [6]. Therefore, monitoring cortisol levels during pregnancy, particularly in the third trimester, may provide valuable information for identifying women at risk of developing preeclampsia and guiding clinical management [7]. Elevated cortisol levels are associated with conditions characterized by increased stress and inflammation, such as preeclampsia, which is

known to be linked to maternal stress and activation of the hypothalamic-pituitary-adrenal (HPA) axis [8]. Cortisol's effects on placental function, vascular regulation, and immune response have also been implicated in the pathogenesis of preeclampsia [8].

CONCLUSION

The present study showed that there was statistically significant increase in Cortisol levels was observed in preeclamptic women compared to normotensive pregnant women, comparatively there is underlying pathophysiological processes such as oxidative stress abnormal cascade activation in preeclampsia.

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