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Comparison of Some Haemostatic Parameters in Preeclampsia Patients with Normal Pregnancy and Non-pregnant Women

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Abstract

Preeclampsia is the development of gestational hypertension and significant proteinuria after 20th week of gestation, during labour or within 48 hours of delivery. This was a case control study carried out on preeclampsia patients accessing treatment at the department of obstetrics and gyneacology in the University of Port Harcourt Teaching Hospital.

Aim: The study aimed to identify possible abnormal changes in haemostatic parameters associated with established preeclampsia in pregnant women and comparing it with normal pregnancy and non-pregnant women.

Materials and Methods: A total of 90 women grouped into three participated in the study, 30 women in each group. The healthy pregnant and non- pregnant women has a systolic blood pressure between 90 and 120 mmHg and diastolic blood patients between 60 and 90 mmHg with or without protein in the urine. The preeclampsia patient had a systolic blood pressure between 140 and 190 mmHg and diastolic blood pressure 90 and 120 mmHg with or without protein in urine. Data were analyzed using Graph- Pad Prism 5.0 (ANOVA) version to get the mean and standard deviation of patients with preeclampsia, normal pregnant group and the non-pregnant group.

Results: Results were presented as means $\pm$ standard deviation. The mean of prothrombin (PT) and activated partial thromboplastin time of preeclampsia patients were significantly prolonged (P = 0.0001). There was no significant difference in mean value of fibrinogen in preeclampsia patients when compared to healthy pregnant and non-pregnant women. The result points towards a hypercoagulable state. Routine check of these parameters from the 20th week in pregnancy could be helpful to avoid the occurrence of disseminated intravascular coagulation in pregnant women.

Keywords: Preeclampsia. Blood pressure, Proteinuria, Haemostastic parameters

1. Introduction

Preeclampsia is the development of gestational hypertension and significant proteinuria after 20th weeks of gestation or during labour within 48 hours of delivery [9]. It is also known as toxemia or pregnancy-induced hypertension (PIH) usually appears in the latter part of the second trimester or the third trimester [11]. It is characterized by hypertension and proteinuria. Hypertension is a condition of high blood pressure, usually 140/90 and higher [10]. Proteinuria is a condition in which the urine contains abnormally high level of protein. Preeclampsia affects 2 to 7% of pregnant women. Up to 25 % of cases develop postpartum, most often within the first 4 days but sometimes up to 6 weeks of postpartum. If not properly recognized and managed preeclampsia can lead to eclampsia. Eclampsia is defined as seizure that cannot be attributed to other causes in women with preeclampsia. The word eclampsia dates from the 17th century. The first known description of the condition was by Hippocrates in the 5th century BC. Hippocrates noted that headaches, convulsions and drowsiness are ominous signs in association with pregnancy. In this book GynaecologyVarandeous, he coined the term eclampsia in 1619 [17]. At the end of the 18th century and through the 19th century, the classification of pre-eclampsia continued to become more refined as the classic signs and symptoms of preeclampsia became more readily recognized.

Preeclampsia is one of the leading causes of maternal and prenatal morbidity and mortality worldwide [13]. It is a potentially life-threatening multi-system disorder. Nearly one-tenth of all maternal deaths in Africa and Asia and one quarter in Latin America are associated with hypertensive diseases in pregnancy, a category that encompasses preeclampsia [9].

Preeclampsia affects approximately 2-5% of all pregnancies world-wide [15]. According to the World Health Organization (WHO) its incidence is seven times higher in developing countries (2.8% of still births) than in developed countries (0.4%)[9].Preeclampsia is much more common in women who are pregnant for the first time [16].Women have previously been diagnosed with preeclampsia are also more likely to experience preeclampsia in subsequent pregnancies delivery [14].Preeclampsia is also more common in women who have preexisting hypertension, obesity, diabetes, autoimmune diseases such as lupus, various inherited thrombophilia such as Factor V Leiden, renal disease, multiple gestation (twins or multiple birth), and advanced Pathophysiology of preeclampsia is complex and poorly understood. Factors may include poorly developed uterine placental spiral arterioles (which decrease utero placental blood flow during late pregnancy), a genetic abnormality on chromosome 13, immunologic abnormalities, environmental factors and placental ischemia, also lipid peroxidation of cell membranes induced by free radicals may contribute [1].

Preeclampsia is a two-stage disease. The first stage is asymptomatic, characterized by abnormal placental development during the first trimester resulting in placental insufficiency and the release of excessive amounts of placental materials into the maternal circulation. This in turn leads to the second, symptomatic stage, wherein the pregnant woman develops characteristic hypertension, renal impairment, and proteinuria and is at risk for the haemolysis elevated liver function enzymes and low platelets referred to as (HELLP syndrome), eclampsia, and other end-organ damage [1].

Normal pregnancy is associated with a range of alterations to the haemostatic components, in preeclampsia pregnancy these alterations can be rapidly increased which can combine to give an increased risk of haemorrhage and thrombosis. The knowledge of these changes in preeclampsia and normal pregnancy provides a sound basis for rational approach to obstetric complication associated with abnormalities in haemostatic. Bleeding during child birth has been and still remains a major cause of maternal morbidity and death [12] Because of this realization, the study aimed at investigating the changes in prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, platelet count including and blood pressure in preeclampsia pregnancy, normal pregnancy and non - pregnant women in Port-Harcourt city.

2. Materials and Method

2.1 Study area and Design

This study was a case-control and comparative study carried in University of Port -Harcourt Teaching Hospital among pregnant women with 20 weeks gestation or more who were admitted into the Department of Obstetrics and Gynecology or were attended to at antenatal care unit. The blood pressure and urinalysis of these women were determined by the Nurses working in the antenatal care unit clinic. The bio data and medical history of all pregnant women were obtained from their folder while a structured questionnaire was used to obtain the bio data of the control group. All subjects were recruited within three months from December 2017-February 2018.

2.2 Study Population

Pregnant women for the study were within the age range of 20-40yrs. A total of 60 pregnant women, Thirty (30) patients diagnosed with both mild or severe preeclampsia and 30 patients with normal pregnancies as control. Thirty (30) healthy non- pregnant women were included, to know the normal range of coagulation parameters in women, their non-pregnant status was confirmed by pregnancy test. The bio data and medical history of all pregnant women were obtained from their folder.

2.3 Eligibility Criteria

Pregnant women diagnosed with preeclampsia by a clinician with blood pressure of ⩾140 /90 mm Hg detected from 20 weeks gestation, combined with protieniuria of ⩾2g /24h or without protein in urine and no manifestation of multiple organ damage or dysfunction. Patients with known bleeding disorder and history of thrombosis or anticoagulant drug /oral contraceptive use were excluded from the study.

2.4 Sample Collection and Processing

Eight milliliters (8ml) of blood sample was taken from the antecubital vein mostly between 8-10am from each participant. 4.5ml of blood, was dispensed into a covered bottle containing 0.5ml of 3.8% trisodium citrate, the sample was mixed thoroughly and centrifuged at 2000g for 10 minutes and the plasma separated into another clean tube used within 6 hours of collection. The control blood samples were treated alike.

2.5 Sample Analysis

Samples for prothrombin (PT), activated partial thromboplastin time (APTT) and fibrinogen were analysed by using the Helena C-1 (single channel coagulometer) using the Agappe (PT, APPT and Fibrinogen assay kit) Diagnostics Switzerland GmbH.Determination of Prothrombin time test was performed using Agappe reagent kit (Agappe Diagnostics Switzerland GmbH) Lotexpiry 2018/12. Determination of Activated Thromboplastin Time (APTT)test was performed using Agappe reagent kit(Agappe Diagnostics Switzerland GmbH)Lotexpiry 2018/12 and Determination of Fibrinogen assay was performed using Agappe reagent kit (Agappe Diagnostics Switzerland GmbH) Lot expiry 2019/12.Each batch of coagulation screening tests and assays, a repeatability control was simultaneously processed. Standard operating procedures as described by the Kit manufacturer was employed during the analysis.

2.6 Statistical Analysis

Data were analyzed using Graph- Pad Prism 5.0 (ANOVA) version to get the mean and standard deviation of patients with preeclampsia, normal pregnant group and the non pregnant group. Results were presented as means ± standard deviation. The analysis also gave the P-value between the study group and the control group from two tail sample t-test and p-values of < 0.05 were considered to be statistically significant. Results were presented in Tables.

3. Results

3.1 Demographic Details of Participants

A total of sixty (60) pregnant women were recruited for the study, thirty (30) patients were diagnosed with either mild or severe preeclampsia with 20 weeks of gestation or more. Thirty (30) healthy normal pregnant women were used as control study. Also, thirty (30) non-pregnant were also included to serve as reference range for the pregnant groups. All women for the studies were within the age range of 20-40years and are residents

of Port Harcourt City. Table 1 shows the demographic details of those recruited in the study.

Table 1: Demographic Details of Participants in the Studies

PARAMETER	PREECLAMPSIA PREGNANCY	NORMAL PREGNANCY	NON-PREGNANCY
Number of Patients	30	30	30
Age Range (Years)	20 - 40	20 - 40	20 - 40
Systolic(mmHg(upper)	150 -190	90 - 120	100 - 120
Diastolic(mmHg) lower)	80 - 100	60 - 90	60 - 90

3.2 Haemostatic Parameters in Preeclampsia Pregnancy, Normal Pregnancy and Non - Pregnancy group

Table 2. This table show the comparison of haemostatic parameters between the patients with preeclampsia, normal pregnant control group and non- pregnant group. There was no significant difference between the test group, control group and non- pregnant group in the mean value of fibrinogen. Whereas there was significant mean value of Prothrombin time (PT) and activated partial thromboplastin time (APTT) in preeclampsia patients. The value of Fibrinogen (Table 2) showed no significant ($P \leqslant 0.05$) variation between the non- pregnant control group (249.20 ± 4.89) and the normal pregnant group (249.30 ± 78.43) when compared with preeclampsia group (215.05 ± 78.43). A significant ($P \leqslant 0.05$) difference does not exist between the preeclampsia group and the two control groups. The Prothrombin time of preeclampsia (table 2) was significantly ($P \leqslant 0.05$) prolonged (19.35 ± 5.18 sec) when compared with normal pregnant (13.58 ± 2.21 sec). There was no significant different between the normal pregnant group and the non- pregnant group (13.09 ± 1.60 sec). The activated partial thromboplastin time of preeclampsia was significantly ($P \leqslant 0.05$)prolonged (37.57 ± 4.81sec) when compared with normal pregnant group (34.69 ± 3.73 sec). There was no significant different between the normal pregnant group and the non- pregnant group (31.70 ± 5.51).

Table 2: Comparison of Haemostatic Parameter in Preeclampsia Patients with Normal Pregnancy and Non - Pregnancy Group

Parameters/ Units	Preeclampsia Pregnancy	Normal Pregnancy	Non-Pregnancy	Df	P-Value (ANOVA)
Fibrinogen (mg/dl)	**215.05 ± 78.43**	**249.30 ± 78.43**	**239.20 ± 4.89**	**2.55**	**0.0840(NS)**
Range	**100.00 - 350.00**	**50.00 - 400.00**	**180.00 - 310.00**		
Prothrombin	**19.35 ± 5.18**	**13.58 ± 2.21**	**13.09 ± 1.60**	**31.69**	**0.0001(S)**
(Second)Range	**11.90 - 31.10**	**11.90 - 22.60**	**11.80 - 17.10**		
APTT (seconds)	**37.57 ± 4.81**	**34.69 ± 3.73**	**31.70 ± 5.511**	**0.54**	**0.0001(S)**
Range	**20.30 - 43.00**	**20.30 - 23.00**	**20.70 - 39.00**		

NS - Non-Significant P > 0.05, S - Significant P<0.05

3.3 Percentage of Haemostatic Parameter in Preeclampsia Patients Based on Age Range

The difference in age of preeclampsia patient compare to the two-control group was high in the age range of 30-39 with 56.7%. This probably indicates that preeclampsia increases with the age of patients or can be seen more in older pregnant women compare to younger pregnant women as seen in table 3.

Table 3 :Percentage of haemostatic parameter in preeclampsia patients based on age range

AGE RANGE (YEARS)	PREECLAMPSIA PREGNANCY (N%)		NORMAL PREGNANCY (N%)		NON PREGNANCY (N%)	
20 -29	7	23.3	19	63.3	18	60
30 – 39	17	56.7	8	26.7	7	23.3
40 – ABOVE	6	20	3	10	5	16.7
Total	**30**	**100%**	**30**	**100%**	**30**	**100%**

4. Discussion

Preeclampsia is a complication of the second half trimester of pregnancy, labour or can develop up to 6 weeks after delivery, it can also develop during labour or up to 6 weeks after delivery. It is one of the leading causes of maternal mortality world-wide with a potentially life threatening multi system disorder.

Comparison was made on some haemostatic parameters among preeclampsia pregnant women non eclampsia pregnant women and non-pregnant women. Preeclampsia group values was significantly higher or prolonged when compared to normal pregnant group and non-pregnant group in the Prothrombin time (PT) and Activated Partial Thromboplastin Time (APTT).Prothrombin time is used to determine the clothing tendency of blood. It is one of many plasma protein involved in the clotting process which is important to prevent bleeding. Activated partial thromboplastin is also a test used in measuring the time it takes for blood to clot. The finding in this study agrees with the finding of [3][15]. They observed a prolonged PT and APTT in their finding. The study showed that the prothrombin time and activated partial thromboplastin time are prolonged in preeclampsia and this could cause excessive bleeding? Although the scope of this study was limited to PT, APTT and fibrinogen analysis, it could be said that the patients may also be suffering from vitamin K deficiency or deficiency in plasma clotting factors like factor II, VII, IX and X as well as factors of the common pathway which include; fibrinogen, prothrombin, factor V and X, which depends on vitamin K for their synthesis. If a patient does not produce enough vitamin K, there will be deficiency in some of the plasma clotting factors and they may not be produced in adequate amount needed by the patients, which may result in excessive bleeding during pregnancy or during delivery. Prothrombin time is a widely used laboratory assay for the detection of inherited or acquired coagulation defects related to extrinsic pathway of coagulation while activated thromboplastin time is used to detect congenital and acquired abnormalities of the intrinsic coagulation pathway. Fibrinogen levels in this study were low compared to the two control groups, although there was no significant difference. This study did not agree with the findings of [5][8]. In one of the findings only severe preeclampsia patients were recruited [3] and in the other only eclampsia patients were included [8]. In this study mild and severe preeclampsia patients were recruited and there was no significant difference between fibrinogen level in preeclampsia patients and the controls, this agrees with the finding where they observed no significant difference between fibrinogen level in preeclampsia groups and control groups[19]. There was significant increase in value of fibrinogen in preeclampsia when compared to normal pregnancy and non- pregnancy group according to their studies [3][8]. Report shows increase in plasma fibrinogen concentration in pregnancy. Increased fibrinogen level has been postulated to enhance thrombus formation by altering the kinetic of coagulation cascade and thereby resulting in increased formation augmenting platelet interaction by increased binding to the glycoprotein II / IIIa and increasing plasma viscosity [7]. These physiological changes support the growing uterus and fetus to withstand labour and postpartum course. During pregnancy hyperfibrinogenaemia is a normal requirement for maintaining placental implantation. Progressively raised fibrinogen concentration observed in all the trimesters during pregnancy, is part of the hypercoagulability of pregnancy. So, decreased or

excessive increase level of fibrinogen indicates haemostatic disorder [19][2].

Platelet aggregation depends on fibrinogen binding to activated platelet via the fibrinogen receptor gpIIb-IIIa. Fibrin adhesion to stimulated platelet is also important in thrombus formation. Increased fibrinogen level may be due to continuous increased synthesis by liver hepatocytes to cope with increased utilization in utero placental circulation. This may serve to protect the patient from hazard of bleeding imposed by placentation and delivery. The increase might also be due to depressed fibrinolytic system. Raised fibrinogen concentration is well established risk factor for thrombotic episodes in disseminated coagulation in pregnancy.

5. Conclusion

The study showed that the prothrombin time and activated partial thromboplastin time are prolonged in preeclampsia pregnancy compared to normal pregnancy and non - pregnant women. Prothrombin ($P < 0.05$), activated partial thromboplastin ($P < 0.05$). Prolonged prothrombin time and activated partial thromboplastin time can cause excessive bleeding. The patients may be suffering from vitamin K deficiency or deficiency in plasma clotting factors. Prothrombin and other clotting factors in blood cannot be produced in adequate amount.

Conclusively prolonged prothrombin time (PT) and activated thromboplastin time (APTT) in preeclampsia group are the haemostatic changes that occur in preeclampsia, which makes the patients prone to bleeding before or during delivery. These parameters can be used to monitor patients to avoid disseminated intravascular coagulation in pregnancy. Prothrombin time and Activated thromboplastin time can be used as a simple and rapid procedure for detection of haemostatic changes in preeclampsia. Effective monitoring of the haemostasis is necessary to prevent eclampsia and dissemination intravascular coagulation to reduce maternal mortality. Also, the study has shown that maternal age can be predisposed to preeclampsia.

Conflict of Interest

The authors report no form of conflict of interest in this work. No form of funding was received from any funding organization /agency for this work.

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