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Studies of Some Haemostatic Variables in Preeclamptic Women in Owerri, Imo State, Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Preeclampsia is a serious and life-threatening pregnancy complication. In this study, the levels of haemostatic parameters were measured in preeclamptic women in Owerri, Imo State. A total of 120 pregnant women aged 18-45 years at 20-40 weeks of pregnancy were recruited; 60 were preeclamptic women (test group) while 60 were normotensive pregnant women (control group). Preeclampsia was determined by the presence of \geq 2+ protein in the urine using combi 2 dipstick for urinalysis and sphygmomanometer blood pressure reading of \geq 140/90 mmHg. From the demographic data obtained in the studied subject through questionnaire, it showed that nulliparity and family history of high blood pressure were the most dominant risk factor of preeclampsia. The mean haemostatic parameters (PT, APTT, Fibrinogen, D-dimer and t-PA) of the test group were 12.3±0.94sec, 32.17±3.38sec, 627.31±106.93mg/ld, 2.23±0.50mg/l, 2.65±0.57ng/ml respectively, while the control group were 11.76±0.97sec, 28.69±2.64sec, 554±124.81 mg/dl, 1.89±0.44mg/l and 2.37±0.66 ng/ml respectively. There was a significant difference between the haemostatic parameter of the test group when compared with the control group. The results indicated that

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although anaemia and activation of coagulation and fibrinolysis occur within the peripheral circulation of both preeclamptic and normotensive pregnancy, an abnormal pattern of haemostasis occurs more in preeclamptic women.

Keywords: Preeclampsia; pregnant women; PT; APTT; Fibrinogen; D-dimer; t-PA.

1. INTRODUCTION

Preeclampsia is universally defined as significant hypertension and proteinuria developed at or after 20weeks of pregnancy in an otherwise normotensive woman [1,2,3,4]. Gestational hypertension is the presence of new hypertension (usually systolic BP > 140 mmHg and/or diastolic BP > 90 mmHg) occurring in the second half of pregnancy, while preeclampsia is the combination of gestational hypertension in the new proteinuria [5,6]. In the absence of proteinuria, hypertension together with evidence of systemic disease such as thrombocytopenia or elevated levels of liver transaminase is required for diagnosis [7].

Worldwide, preeclampsia affects estimated 2-10% pregnant women [8,9]. More than 4 million women across the world develop this disorder every year and an estimated 50,000 - 76,000 women and 500,000 infants die of this condition every year (National Heart, Lung and Blood Institute, 2000). In Nigeria, it is estimated that 3-10% are complicated by Hypertensive Disorder in Pregnancy (HDP) [10,11].

Haemostasis is the regulation of blood loss in the case of injury to the vein and artery and the dissolution of excessive blood clot in cases of thromboembolism. Profound changes in coagulation and fibrinolytic mechanisms resulting in hypercoagulable state occur during normal human pregnancy and it is a physiologic adaptation to prevent major haemorrhage during and after placental separation [12]. According to Rune, [13], alterations in blood coagulation and fibrinolysis are believed to play an important role in the pathogenesis of preeclampsia. The abnormalities of coagulation parameters like prothrombin partial time (PT), activated thromboplastin time (aPTT) and fibrinogen levels are usually observed in preeclampsia and even in the presence of normal platelet count [14]. According to Jahromi et al. [15], the measurement of aPTT seems to be important for early detection of coagulation abnormalities in patients with preeclampsia who have normal platelet counts. Similarly, preeclampsia is with microvasculature associated fibrin deposition [16] and endothelial dysfunction [12].

D-dimer and tissue plasminogen activator (t-PA) have been used as a marker to access production/degradation of fibrin in vivo and endothelial dysfunction respectively. Several studies have shown increased D-dimer and elevated t-PA antigen in preeclampsia when compared to normotensive pregnant subjects [17,16,18,12].

This study will be done to provide data on the level of haemostatic variables in pregnant women with preeclampsia in Owerri, South-East of Nigeria, Africa. I believe these findings will contribute to the body of knowledge on the effects of this disorder on pregnant women residing in this area. This will help reduce the risk of complications from preeclampsia that could result in maternal and perinatal morbidity and mortality in Nigeria.

The study is aimed at determining the levels of some haemostatic parameters in preeclampsia and normotensive pregnant women in Owerri, Imo State, Nigeria.

2. MATERIALS AND METHODS

2.1 The Study Area

This study was carried out in Federal Medical Centre Owerri in Imo State, Nigeria.

2.2 Study Population and Sample Size

A total of 120 subjects all women aged from 18-45 years were recruited for the study. Sixty pregnant women clinically diagnosed as preeclampsia and 60 normotensive pregnant women, all in their third trimester (28-40 weeks) between the ages of 18-45 years attending maternity clinic of Federal medical Centre Owerri, Vaden Specialist Hospital Owerri, Life-Spring Specialist Hospital Owerri and Emekuku Specialist Hospital Owerri were recruited for the study. The sample size was obtained using the formula by Naing *et al.*, (2006). Prevalence rate of preeclampsia is 3.4% [11].

 $n = z^2 \times P (1-P)/d^2$

Emeka-Obi et al.; JPRI, 33(42B): 39-48, 2021; Article no.JPRI.72826

Where n = Sample size p = prevalence rate 3.4% z = confidence interval 95% - 1.96 d = Degree of accuracy- 0.05 N = $1.96^2 \times 0.034(1-0.034)/0.05^2 = 50$

Therefore, the minimum sample size was 50. Considering 10% attrition, a sample size of 60 was used for the study. The control subjects for this study were randomly selected and were appropriately matched for maternal and gestational age with those of the test group.

2.3 Study Design

A case-control study was carried out on 2 groups.

Group 1 = 60 Preeclamptic Pregnant Subjects, Group 2 =60 Normotensive Pregnant Subjects,

A structured questionnaire was administered to all respondents who were also part of clinical study.

2.4 Inclusion Criteria

- Pregnant women who were diagnosed of preeclampsia in their third trimester between the ages of 18-45 years. Preeclampsia is defined as hypertension with significant proteinuria after 20 weeks of gestation. Hypertension: Blood pressure of >140/90 mmHg on at least two occasions 6 hours apart; Significant Proteinuria: urinary protein excretion of >300 mg/day quantitatively or ≥2+ on dipstick examination
- Normotensive pregnant women in their third trimester between the ages of 18-45 years.

2.5 Exclusion Criteria

Those that were excluded from the study were:

- Pregnant women with evidence of chronic infection like HIV, chronic renal disease, tuberculosis and other inflammatory disease.
- Pregnant women who have past history of diabetes, systemic or endocrine disorder.
- Pregnant women with previous history of hypertension.

- Pregnant women who were in active labour.
- Pregnant women using any kind of anticoagulant drugs.
- Pregnant women who smokes and drink alcohols.
- Pregnant women who did not give their informed consent.
- Pregnant women in need of emergency care or having an at-risk pregnancy such as gestational diabetes; gestational hypertension.

2.6 Sample Collection

About 8mls of participants venous blood was drawn from the ante cubital vein of the lower arm by the researchers for tests.

2.7 Laboratory Procedures

All reagents were commercially purchased and the manufacturer's Standard Operating Procedures (SOP) will be strictly followed. The analysis of the parameter was done at the Medical Laboratory Unit of Federal Medical Centre, Owerri by three medical laboratory Scientists in the laboratory with the researcher observing and assisting in the analysis.

2.8 Dipstick Urinalysis

Medi-Test Coombi 2 urine test stripe was used.

Procedure: The test stripe was completely immersed in a well mixed sample of urine for a short period of time, and was then extracted from the container. Supporting the edge of the stripe over the mouth of the container, the excess urine was removed. The stripe was then left to stand for the time necessary for the reactions to occur (1 to 2 minutes), and finally the colours that appear was compared against the chromatic scale provided by the manufacturer.

2.9 Prothrombin Time Estimation

Commercial Kit by Diagen Diagnostics was used

Procedure: All reagents were prewarmed at 37° C. Hundred (100μ L) of trisodium citrate anticoagulated blood was dispense in a plastic tube. It was incubated for 2 minutes at 37° C. 200 μ L of reagent was added. Time taken to clot was read and recorded.

2.10 Activated Partial Thromboplastin Time Estimation

Commercial Kit by Diagen Diagnostics was used

Procedure: All reagents were prewarmed at 37° C. Hundred (100μ L) of trisodium citrate anticoagulated blood was dispensed in a plastic tube. 100μ L of reagent was added and mixed together. It was incubated for 4 minutes at 37° C. 100μ L of calcium chloride was added. Time taken to clot was read and recorded.

2.11 Fibrinogen Assay

As modified by GIESSE Diagnostics was used

Procedure: Samples and controls were diluted 1:10 with imidazole buffer $(50\mu L + 450\mu L)$. 200 μL of prediluted samples were pipetted into a plastic tube and incubated for a period of 5 minutes at 37^{0} C. 100 μ L of Bovine thrombin was added and the time taken to clot was recorded.

2.13 D-Dimer Parameter Estimation

Finecare[™] D-Dimer Rapid Quantitative Test along with Finecare[™] FIA Meter was used.

Procedure: The d-dimer ID Chip was inserted into the Finecare[™] FIA meter. Using a transfer pipette, 10µL of plasma was added to the buffer tube. The sample was properly mixed with the buffer for 1minute by inverting the tube. After mixing, 75µL of sample mixture was loaded onto the sample well of the Test Cartridge. The Test Cartridge was inserted onto the Test Cartridge Holder in the Finecare[™] FIA meter and the "Test" button was clicked. After 5 minutes, the test result was shown in the display and the print out was obtained when the click "Print" was pressed.

2.14 Tissue Plasminogen Activator Antigen

Commercial ELISA Kit by MELSIN Medical Co., Limited was used

Procedure: Dilutions of standard were prepared to get a concentration of 24 ng/mL, 12ng/mL, 6ng/mL, 3ng/mL, 1.5ng/mL and 0ng/mL. Fifty (50µl) of standard was added to the well, 10µl of testing sample was added into another well .Then sample diluent 40µl was added to testing sample well. 100µl of HRP-conjugate reagent

was added to each well, and cover with an adhesive strip and incubate for 60 minutes at 37°C. 5. Each well was aspirated and wash, repeating the process four times for a total of five washes. Each well was wash by filling with Wash Solution (400µl) using a squirt bottle, manifold dispenser or autowasher. Complete removal of liquid at each step is essential to good performance. After the last wash, the remaining Wash Solution was removed by aspirating or decanting. The plate was inverted and blotted it against clean paper towels, 50µl of chromogen solution A and 50µl chromogen solution B was added to each well and gently mixed and incubated for 15 minutes at 37°C. Protecting it from light. Then 50µl Stop Solution was added to each well. The color in the wells should changes from blue to yellow. Optical density of the samples was read in a microtiter plate reader at 450nm wavelength within 15 minute.

3. RESULTS

Table 1 shows the demographic data of study and control subjects. The subjects ranged from 18 to 45years with the mean ± SD lower in test (30.19±4.76years) group than control (30.33±5.79) and the difference was not statistically significant (P>0.05). In both the study and control group, the age group 36⁺ years had the highest number of subjects recruited for the study 24 (40.0%) and 20 (33.3%) respectively. The least number was seen in the age group 18-(13.3%) preeclampsia 8 24years. while normotensive had 10(16.7%).

Gestational age was found to be lower in test group $(32.90\pm3.46week)$ compared with the control (34.68+3.32weeks) and the difference was not statistically significant (p>0.05). Those in the gestational age 32 to 36 weeks were highest in both groups, preeclampsia had 28(46.7%) while 30 (50.0%) were recruited in the control group. With respect to parity, most of the subjects in the test group were nulliparious 28(46.7%), followed by multiparious 23(38.3%) while 9(15.0%) were secondigravidae. When compared with the control group, it was found to be statistically significant (χ^2 =7.948, P=0.018).

According to marital status, most of the study participants in both test and control group were married (90.0% and 95.0%) respectively. There was no statistical significant difference among the groups (p=0.901). Majority of the subject were Christians, accounting for 96.7% and 98.3% of study test and control group

respectively. There was no significant association between them (χ^2 =0.087, P= 0.768).

Most of the subjects recruited for the study were self employed, accounting for 58.3% and 65.0% of the test and control subject respectively. The least among them were students (unemployed) accounting for 8.0% and 6.0% of test and control subject respectively. There was no significant association between the study group in respect to occupation (χ^2 =0.53%, P=0.765). More of the test subject had family history of HBP, (65.0%) while less of the control subjects had family history of HBP (36.7%). There was a significant association between both group (χ^2 =9.190, P= 0.002). Most of the tests and control subjects attended care (96.2% and 95.0% respectively).

Table 2 shows the mean ± SD of RBC, Hb, PCV and Red cell indices of Test and Control group.

From the table, the red blood cell of test subjects (3.21±0.35x10¹²/I) was lower than control $(3.63\pm0.4\times10^{12}/I)$ and their difference was significant (P=0.001). Haemoglobin and PCV value of Test subjects (9.7±0.9 g/dl, and 29.33±2.51% respectively) were lower than control (10.52±1.20g/dl and 32.54±3.76% respectively) and their difference was statistically significant (P=0.0001). MCV, MCH and MCHC of Test group were (88.17±4.32fl, 29.79±22.11pg and 33.37±1.61g/dl respectively while that of control group were 86.19±4.199fl, 29.23±2.82pg and 31.81±96q/dl respectively. The difference between the groups was significant in MCV (P =0.028), MCHC (P=0.001) while MCH was not significant (p=0.239).

RDW of test subjects $(15.54\pm1.25\%)$ was significantly (P=0.029) higher when compared with control $(14.91\pm1.71\%)$.

Variables	Preeclamptic Women N(%)	Normotensive Pregnant Women N (%	Chi Square (X ²)	P-Value
Age Group (years)				
18-24	8 (13.3)	10 (16.7)		
25-30	16 (26.7)	18 (30.0)		
31-35	12 (20.0)	12 (20.0)		
36 ⁺	24 (40.0)	20 (33.3)		
Mean±SD (years)	30.19±4.76	30.33±5.79	0.704	0.872 ^{ns}
Gestational Age (weeks)				
28-31	15 (25.0)	12 (20.0)		
32-36	28(46.7)	30 (50.0)		
37-40	17(28.3)	18 (30.0)		
Mean±SD (years)	32.90±3.46	34.68±3.32	0.431	0.807 ^{ns}
Parity				
Nulli	28(46.7)	24(40.0)		
Second	9(15.0)	22(36.7)		
Multi	23(38.3)	14(23.3)	7.948	0.018*
Religion	()	()		
Christianity	58(96.7)	59(98.3)		
Muslims	2(3.3)	1(1.7)	0.3419	0.559 ^{ns}
Family History of HBP	()	()		
Yes	39(65.0)	22(36.7)		
No	21(35.0)	38(63.3)	9.636	0.002*
Antenatal Visit	x y	()		
Yes	58(96.2)	57(95.0)		
No	2 (3.8)	3(5.0)	0.2087	0.647 ^{ns}
Occupation		. ,		
Student	8(13.3)	6(10.0)		
Civil Servant	17(28.3)	15(25.0)		
Self Employed	35(58.3)	39(65.0)	0.627	0.731 ^{ns}
Marital Status	- (/		-	-
Single	6(10.0)	3(5.0)		
Married	54(90.0)	57(95.0)	0.015	0.901 ^{ns}

Table 2. Comparison of Platelet and Platelet Indices of Studied Subjects

Table 2 shows mean ± SD of prothrombin and activated partial thromboplastin time, fibrinogen. d-dimer and t-PA of the test and control group. Prothombin time of test (12.32±0.94sec) subject was higher than that of control (11.76±0.97sec) and the difference was significant (P=0.003). Activated partial thromboplastin time of test subjects (32.17±3.38 sec) was higher than control (28.69±2.64sec) and the difference was significantly higher (p=0.0001). Fibrinogen and ddimer of Test group (637.31±106.39mg/dl and 2.23±0.50mg/l respectively) were significant higher (p=0.0001) when compared with the control (554.45±124.81mg/dl and 1.89±0.44mg/l respectively). Tissue plasmmogen activator antigen of test subjects (2.65±0.57ng/ml) was higher than control subject (2.37±0.66ng/ml) and the difference was significant (P=0.014).

4. DISCUSSION

The socio-demographic data obtained from the studied subject showed that majority of the preeclamptic women recruited for the study were above 35 years of age (40%). Preeclampsia has been linked to multiple risk factors, one of the suggested risk factors is advanced maternal age. The result from this study agrees with the findings of previous researchers [19] [20], who stated that maternal age is a risk factor in preeclampsia. Increased age of women is an important risk factor due to increased villous reaction leading to preeclampsia in a woman greater than 30years [21].

In relation to parity, the prevalence of preeclampsia was higher in nulliparious women (46.7%) when compared to multiparous women. Several studies have shown preeclampsia to be

commonly encountered in nulliparous women. This is because nulliparity is due to initial trophoblastic invasion and how the mother reacts to it. The failure of the normal invasion of trophoblastic cells leads to mal adaptation of the spiral arterioles, which are related to the causation of preeclampsia [3]. The result in this study is in accordance with the findings from similar studies in Nigeria and other countries [22] [23].

It was observed in this study that family history of hypertension was a major risk factor for preeclampsia. A significant number of the preeclamptic women had family history of hypertension, (65.0%) while less of the normotensive pregnant women (36.7 %.) had family history of hypertension. It has been noted that family history of hypertension was the most dominant risk factor for preeclampsia in pregnant women. This finding was in keeping with the findings from other studies [24] [21]. Moreso, from this study 8 (13%) of test subjects have had previous history of preeclampsia. History of preeclampsia has always been implicated as a risk factor in the development of preeclampsia in multiparous women. This is in accoradance with the findings from other studies (Hernandez-Diaz et al., 2009, [25,26].

Pregnancy is associated with changes in haemostasis, including an increase in the majority of clotting factors, a decrease in the quantity of natural anticoagulants and a reduction in fibrinolytic activity [27]. These changes result in a state of hypercoagulability, likely due to hormonal changes (Satter et al., 1999) and this increases the risk of thromboembolism. From this study, there is an increase in PT, APTT and fibrinoaen in preeclamptic women when normotensive compared with pregnant

Parameter	Test (n=60)	Control (n=60)	T-Test	P-Value
PT (sec)	12.32±0.94	11.76±0.97	3.066	0.003**
APTT (sec)	32.17±3.38	28.69±2.64	6.124	0.0001***
Fibrinogen (mg/dl)	627.31±106.93	554±124.81	3.291	0.001**
D-dimer (mg/l)	2.23±0.50	1.89±0.44	3.989	0.0001***
t-PA (ng/ml)	2.65±0.57	2.37±0.66	2.488	0.014*

Table 2. Comparison of haemostatic parameters of study subjects using students t-test

Significant level *P<0.05, **P<0.001, ***P<0.0001.Ns Not significant (P>0.05)

KEY:

PT- Prothrombin Time APTT Activated Partial Thromboplastin Time tPA Tissue Plasmmogen Activator Antigen women. In preeclampsia, the coagulationfibrinolytic system is thought to be one of the most seriously affected systems by maternal inflammatory reactions and immune dysfunction [16]. The abnormalities of coagulation parameters like prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen levels has been observed in preeclampsia (Chaware et al., 2015, [28]. In a study by Jambhulkar et al., [29], and Pratibha et al., [17], there was a significant increase in partial thromboplastin time activated with Kaolin (PTTK) and thrombin time (TT) in preeclampsia. The aPTT and the PT reflect the function of endogenous and exogenous coagulation pathways respectively.

There is a significantly elevated d-dimer level in preeclampsia when compare to normotensive pregnant women in this study. D-dimer is a specific degradative product resulting from the hydrolysis of the fibrin monomer and is considered to be an indirect marker for thrombosis and fibrinolytic activity. The maternal d-dimer concentration in normal pregnancy increases progressively from conception to delivery [30]. D-dimer is increased in normal pregnancy because of compensated state of low grade intravascular coagulation; Moreover, this increase shows that, inspite of the marked impairment in fibrinolytic potential; the fibrinolytic system remains functionally active. Previous research showed higher d-dimer concentrations in pregnant women with preeclampsia compared with normotensive pregnant women [18] [31] [32]. D-dimer is involved in the dynamic balance between plasminogen activators (t-PA and uPA) and plasminogen inhibitor (PAI-1) in women with preeclampsia therefore. [33] d-dimer concentration can reflect the dynamic changes in both the super-hypercoagulable status and the activated fibrinolytic state in preeclamptic patients [34] [35] [36].

It is known that the pathogenesis of preeclampsia is associated with endothelial cell (EC) dysfunction. This tends to increase the expression of endothelial- derived fibrinolytic its inhibitor and products proteins. in preeclampsia more than in normotensive pregnant women. This is supported by the finding in the present study in which plasma levels of endothelially derived tPA were significantly higher in preeclampsia than controls. Luis et al., [12], Tharmin et al., [37] and Oladosu-olayiwola et al., [32], found an elevated t-PA antigen in preeclampsia when compared to normotensive

pregnant women. These findings are in keeping with the result obtained in this study. Many authors suggest these products may serve as an early marker of coagulopathy and the aggressive management towards early delivery may result in decreasing morbidity and mortality [38-41].

5. CONCLUSION

Pregnancy has been described as a state of 'mild' controlled inflammation. However when this inflammatory response becomes exaggerated it results in the development of preeclampsia. A role has been suggested for inflammatory mediators in the pathogenesis and pathology of preeclampsia. The results obtained from this study also showed a significant difference in the haemostasis parameters of preeclamptic women. This abnormality in haemostatic parameters has been documented to be the leading cause of death in women with preeclampsia as such women are prone to developing haemostatic disorders.

A keen observation and monitoring of the haematological and haemostatic parameters in preeclamptic women is vital.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

ETHICAL APPROVAL

A letter of introduction was secured from the Head of Department, Medical Laboratory Science of Nnamdi Azikiwe University, Awka. The letter together with a written proposal on the study was submitted to the ethical committee of Federal Medical Centre Owerri to seek for ethical approval to carry out the study. After all considerations the Ethical committee approved my request.

CONSENT

An oral consent was gotten from the patients. Participants were recruited among pregnant women who were booked for antenatal care. Thereafter demographic information which includes age, parity, place of residence, education, socio-economic status and medical and obstetrical history was collected using a questionnaire. The second group comprising of normotensive pregnant women as control (appropriately matched for marternal age and gestational age) was randomly selected from pregnant women attending antenatal clinic in the hospital.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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