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CLINICAL AND HEMATOLOGICAL PROFILES OF PRE-ECLAMPTIC VERSUS NORMOTENSIVE PREGNANT WOMEN IN SOUTHERN NIGERIAN ANTENATAL CLINICS

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Abstract
Pre-eclampsia is an obstetric disorder that affects a tenth of pregnancies worldwide. It has a growing burden in Nigeria with a prevalence ranging from 5-10%. Normal pregnancy is associated with changes in haematological indices. This hospital-based case-control observational study was carried out to determine the clinical characteristics and peripheral blood film picture in pre-eclamptic patients at diagnosis and suitably matched controls. It involved 65 pre-eclamptic women as the test group, and 65 age, trimester and parity matched normotensive, non-proteinuric pregnant women as control group. The test group was classified clinically as having mild or severe pre-eclampsia using the American College of Obstetricians and Gynecologists classification. Clinical information of pregnant women was obtained from their electronic medical records with respective patient's consent. The LB-1270 compound biological trinocular digital microscope with camera and software (5.0MP), LCD and Infinite Optical System was used to visualize peripheral blood films. The result of the study shows that the BMI of pregnant females with pre-eclampsia (25.99±2.3) and normotensive pregnant females (25.21±1.9) were within the reference interval for trimester-matched Body mass index (BMI) and there was no evidence of fetal compromise. Seventeen (13.1%) of the participants were pale at presentation, and 24.6% of pre-eclamptic subjects in the second trimester had features of microangiopathic haemolytic anaemia (MAHA). In conclusion, pre-eclampsia had significant haemolytic changes and altered physiological balance characterized by marked changes in clinical features.

Keywords: Pre-eclampsia, Blood film, normotensive, clinical features

INTRODUCTION

The burden of pre-eclampsia is high in Nigeria with a prevalence ranging from 2.0% - 16.7% [1]. Haemostatic disorders have been implicated in the pathogenesis of pre-eclampsia with varying severity and attendant complications, thus necessitating several treatment options. There are still no satisfactory preventive measures globally, largely due to the several factors implicated in its pathogenesis. There is however, paucity of information on the possible predictive value of the markers of severity of pre-eclampsia, which can be used to monitor the progress of pregnancies with associated pre-eclampsia and prevent complications [2]. Pre-eclampsia is a pregnancyspecific syndrome with multisystem affectation [3, 4]. It is characterized by new-onset hypertension and proteinuria at ≥20 weeks of gestation in a previously normotensive woman. Hypertension is the presence of systolic blood pressure (SBP) greater than or equal to 140 mm Hg or diastolic blood pressure (DBP) greater than or equal to 90 mm Hg or higher, on two occasions at least 4 hours apart in a previously normotensive patient, or an SBP greater than or equal to

160 mm Hg or a DBP greater than or equal to 110 mm Hg or higher [5]. Proteinuria is the presence of protein in urine of greater than or equal to 0.3 grams in a 24-hour urine specimen. A protein (mg/dL)/creatinine (mg/dL) ratio of 0.3 or higher, or a urine dipstick protein of 1+ (if a quantitative measurement is unavailable) is required to make diagnosis of pre-eclampsia. In the absence of proteinuria, diagnosis requires the presence of hypertension together with evidence of systemic disease (such as thrombocytopenia, elevated levels of liver transaminases, renal insufficiency, pulmonary oedema, and visual or cerebral disturbances [6]. Historically, pre-eclampsia was introduced as a state preceding eclampsia, which was first recognized as a convulsive disorder of pregnancy, which subsequently led to blood pressure and urine check amongst pregnant women
[7].

The global incidence of pre-eclampsia is affected by race, ethnic group, and genetic predisposition, ranging up to 5 percent in white, 9 percent in Hispanic, and as high as 11 percent in women of African-American descent [8]. It is a leading cause of maternal and perinatal morbidity and mortality [9]. Ten to fifteen percent of maternal deaths annually are directly associated with preeclampsia and eclampsia [3]. Pre-eclampsia is said to occur more frequently in young women having their first pregnancy [10]. The immune mechanism has been attributed to this as immune tolerance develops following exposure of the maternal immune system to paternal alloantigens [11]. With prolonged exposure to semen, there is a decrease in the risk of developing pre-eclampsia possibly explaining the increased risk of this condition in women with a short interval between first coitus and conception, assisted reproductive technologies involving artificial insemination, barrier methods of contraception, and in multiparous women who have changed partner since the previous pregnancy [9]. Twin studies estimates of the heritability of pre-eclampsia range from 22% to 47% [12].

Haematological abnormalities seen in pre-eclamptic women include; haemolysis due largely from microangiopathic haemolytic anaemia (MAHA), thrombocytopaenia, and decrease in the concentration of clotting factors which may lead to disseminated intravascular coagulopathy (DIC) [13]. Microangiopathic haemolytic anaemia (MAHA) is caused by endothelial disruption, adhesion of platelet, and deposition of fibrin. Alterations in the serum lipids lead to morphological changes characterized by the presence of spherocytes, schistocytes, echinocytes, and reticulocytosis in the peripheral blood [13]. Red cell distribution width (RDW) which is a marker for anisocytosis as well as an inflammation marker in hypertension and cardiovascular diseases, increases in severe pre-eclampsia [14]. A high percentage of patients with hypertensive disorders of pregnancy show some morphologic alterations mostly in erythrocytes as seen in peripheral blood smear [15]. Also, study of blood smear can assist in identifying patients who are likely to develop complications of severe pre-eclampsia [16]. Thrombocytopenia is a common haematological problem in pregnant women and it is mostly gestational thrombocytopenia, which is usually mild, not associated with any bleeding tendency, and resolves spontaneously after delivery. Thrombocytopenia results from platelet activation, aggregation, and consumption that is accompanied by

increased mean platelet volume and decreased life span. The level of thrombocytopenia is dependent on the severity and duration of pre-eclampsia syndrome [13]. Platelet aggregation is decreased compared with the normal increase seen in pregnancy. This decrease is due to platelet exhaustion following in-vivo activation, immunological processes, and platelet deposition at sites of endothelial damage [17]. HELLP syndrome may be difficult to discern from primary thrombotic microangiopathies such as thrombotic thrombocytopenic purpura (TTP) and the atypical haemolytic uremic syndrome, which are not unique to pregnancy but can occur with increased frequency in preeclamptics [18]. However, the time of onset of thrombocytopenia, associated haematological and other manifestations must be considered to rule out these differential diagnoses. Though thrombocytopenic disorders may severely compromise the outcomes of some pregnancies, prompt diagnosis and appropriate therapy often lead to successful pregnancy outcomes [18].

SUBJECTS AND METHODS

This was a hospital-based, case-control observational study. The age, haemoglobin genotype, trimester, and parity of pre-eclamptic pregnant females were matched with normotensive pregnant women as controls in the antenatal clinic of the department of Obstetrics and Gynaecology of Irrua Specialist Teaching Hospital. Irrua is situated in Esan Central local government area of Edo state, in the South-South geopolitical zone of Nigeria. It is located on a Latitude of 6.5438 and a Longitude of 5.8987 and has boundaries with Kogi state to the northeast and east, Anambra state to the east, Delta state to the southeast and south, and Ondo state to the west and northwest. Irrua Specialist Teaching Hospital, Irrua is a 375 bed tertiary institution located in Irrua, Esan Central Local Government Area, Edo State, Nigeria.

The study population was made up of pregnant women attending antenatal clinic of the Obstetrics and Gynaecology department and the controls were age and gestation-matched non-pre-eclamptic patients from January to December, 2021. Samples collected from these patients were analyzed in the Departments of Haematology of Irrua Specialist Teaching Hospital which is equipped with standard electrophoresis machine.

Procedure

The study population comprised pregnant women, for which the study group (those) with preeclampsia and controls (normotensive and non-proteinuric pregnant women) were recruited from the antenatal clinic using simple random sampling. The list of all the pregnant women attending the clinic for that day was retrieved and separated into two; that is, those who met the criteria for pre-eclampsia and those with normal blood pressure. From both lists, those patients and controls that met the inclusion criteria were recruited by simple random sampling. This was done for every antenatal clinic until the sample size was met. The recruited study subjects were further divided into two groups based on their severity status for pre-eclampsia using their clinical signs and symptoms; into non-severe and severe groups. The sample size was calculated using the difference in proportion formula for case-control studies [19].

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$$n = \left(\frac{r+1}{r}\right)\frac{(\bar{p})(1-\bar{p})(Z_{\beta}+Z_{\alpha/2})^2}{(p_1-p_2)^2}$$

Where;

n = sample size in the case-control group

r = ratio of controls to cases

Z_{β} = Represents the desired power (typically 0.84 for 80% power)

Z_{α} = Represents the desired level of statistical significance (typically 1.96).

$P_1 - P_2$ Þ = A measure of variability (similar to standard deviation) (_____) 2

$(P_1 - P_2)^2$ = Effect Size (the difference in proportions)

P_1 is the proportion of cases exposed.

P_2 is the proportion of exposed cases in the control group which is 10% (0.1) [20].

P_1

To get the proportion of cases exposed, P_1 = OR_____

$P_1(OR-1)+1$

The odds ratio (OR) for those exposed in the control group is 4.0. [20]

Therefore, $P_1 = \frac{(0.1)}{1(4.0-1)+1}$ (4.0)

0.

$P_1 = 0.31$

P_1+P_2 0.31+0.1

Þ = _____ = = 0.21

2 2

1+1 (0.21)(1−0.21)(0.84+1.96) 2

Therefore, n = ___ _____

1 (0.31−0.1)(0.31−0.1)

n = 59

To calculate 10% attrition rate, which is 10% of n, i.e. 10% of 59 = 6

Therefore 59 + 6 = 65

From the result of the calculation of the sample size, 65 patients with pre-eclampsia who meet the selection criteria described above were enrolled in the study while 65 age, trimester and paritymatched normotensive and non-proteinuric pregnant women who also meet the selection criteria above, were recruited as controls.

Women who were diagnosed with pre-eclampsia according to the criteria of the National Blood Pressure Education Program Working Group as blood pressure of 140/90mmHg and confirmed proteinuria (0.3g/L/24h) with or without previous evidence of an underlying hypertensive disorder were recruited. Age-matched pregnant women with gestational age > 20 weeks were recruited as controls.

Ethical clearance was obtained from the Ethics and Research Committee of the Irrua Specialist Teaching Hospital with the ethics committee protocol number ISTH/HREC/20200308/078. Written permission was

sought and obtained from the Heads of the Department of Haematology and Blood Transfusion and Obstetrics and Gynaecology. Written informed consent was obtained from the patients after explaining the aim of the study and the procedures involved in the best language they understood. The participants were not required to make payment for any of the investigations required.

A structured proforma (questionnaire) was researcher-administered to the patient, this was used to collect data that included socio-demographic data, past medical history, reproductive history, and medical history. A general examination including their weight and blood pressure check was also carried out before specimen collection. Patients noted to have any need for immediate care, were referred to the managing consultant for treatment.

The symphysis-fundal height of all participants were measured using a measuring tape from the pubic symphysis to the top of the uterus and recorded in centimeters. The fetal heart rates were measured using a Pinard stethoscope and recorded in rate per minute. All procedures were carried out in the presence of female chaperones.

Each patient was seated comfortably with a forearm extended and a tourniquet applied to the arm to distend the antecubital vein. Using the standard sterile procedure, four milliliters of venous blood was taken by the standard sterile procedure and dispensed into a bottle containing ethylene diamine tetraacetic acid (EDTA), and then gently and thoroughly mixed. The sample in the EDTA bottle was used for the preparation of peripheral blood film, and genotype determination. The same method of blood collection, preparation, and storage was done for the controls.

Thin smears consist of blood spread in a layer such that the thickness decreases progressively toward the feathered edge. In the feathered edge, the cells should be in a monolayer, not touching one another [21]. A clean and unscratched microscope glass slide measuring 75mm by 25 mm and approximately 1 mm thick, was labelled with a pencil on the frosted end, with the sample number and details and then the slide labels were checked to ensure they corresponded with the sample bottles. A small drop of the sample blood was placed on one end of the slide, using the end of another slide at an angle of approximately 30° to the first, the small drop of blood was allowed to move along the first slide to spread the blood drop into one continuous thin film. The smear was air dried, fixed in absolute methanol (acetone-free) for 15 minutes and air dried again before staining, and the fixed films were transferred into a staining jar containing May–Grunwald stain and allowed to stain for about 15 minutes. They were transferred without washing into another jar containing Giemsa stain, staining for 15 minutes, then transferred into a jar containing buffered water (pH 6.8), rapidly washed in three or four changes of water, and finally allowed to stand undisturbed in water for 2–5 minutes (for differentiation to take place). The slides were drained in a vertical position and allowed to air dry, following which, they are viewed under a microscope. Data generated was analyzed using the SPSS version 26 statistical software packages and the level of significance was put at p-value <0.05.

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RESULTS

A total of 65 patients with pre-eclampsia and 65 normotensive pregnant women were sampled for this study, and the mean comparison of the anthropometry of pregnant women at the antenatal clinic Irrua and fetal characteristics in the second and third trimesters are shown in table 1. All subjects were within the reference interval for trimester-matched Body mass index (BMI) and there was no evidence of fetal compromise.

Table 1: Mean comparison of anthropometry of pregnant women at the antenatal clinic Irrua and fetal characteristics in the second and third trimesters

	Pre-eclampsia (n=65) Mean±SD	**Normotensive (n=65) Mean±SD**	**t-value**	**P**
		Second trimester		
Weight (kg)	76.09±8.8	73.35±5.9	2.080	**0.039***
Height (m)	1.71±0.1	1.70±0.1	0.449	0.654
BMI (kg/m^2)	25.99±2.3	25.21±1.9	2.073	**0.040***
		Third trimester		
Weight (kg)	82.32±8.8	80.81±6.1	1.131	0.260
BMI (kg/m^2)	28.10±2.3	27.77±2.0	0.892	0.374
Temperature (^{o}C)	36.60±0.2	36.62±0.3	-0.494	0.622
Symphysis fundal height (cm)	26.05±1.9	24.69±1.2	4.825	**<0.001***
Foetal heart rate (beats/min)	155.82±6.2	168.45±8.7	-9.545	**<0.001***

The distribution of pre-eclamptics and normotensive pregnant women visiting the antenatal clinic Irrua according to their haemoglobin electrophoresis, previous surgery and obstetric characteristics is shown on table 2. Only two (0.5%) of the subjects had sickle cell disease while thirty five (26.9%) had sickle cell trait. Fifty-two (40%) of the subjects had carried a pregnancy to age of viability (parity - 1) before index pregnancy.

Table 2: Distribution of pregnant women at the antenatal clinic Irrua between the pre-eclamptics and normotensive pregnant women according to their medical characteristics (Haemoglobin electrophoresis, previous surgery and obstetric characteristics).

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	Preeclampsia (n=65) n(%)	Normotensive (n=65) n(%)	Total (n=355) n(%)	χ^2	p-value
Genotype					
AA	47(72.3)	45(69.2)	92(70.8)	1.072	0.784
AC	0(0.0)	1(1.5)	1(0.8)		
AS	17(26.2)	18(27.7)	35(26.9)		
SS	1(1.5)	1(1.5)	2(1.5)		
Previous surgery					
Yes	4(6.2)	4(6.2)	8(6.2)	0.000	1.000
No	61(93.8)	61(93.8)	122(93.8)		
Gravidity					
None	15(23.1)	11(16.9)	26(20.0)	5.751	0.124
1	20(30.8)	33(50.8)	53(40.8)		
2	16(24.6)	13(20.0)	29(22.3)		
≥3	14(21.5)	8(12.3)	22(16.9)		
Parity					
None	15(23.1)	12(18.5)	27(20.8)	2.179	0.536
1	23(35.4)	29(44.6)	52(40.0)		
2	12(18.5)	14(21.5)	26(20.0)		
≥3	15(23.1)	10(15.4)	25(19.2)		
Gestational age at recruitment (Weeks)	25.66±1.3	25.58±1.2		0.394*	0.384

*Independent student t-test

Severity of pre-eclampsia among pregnant women at the antenatal clinic Irrua between the preeclamptics and normotensive pregnant women. Thirty-four (52.3%) of the subjects had severe preeclampsia while 31(47.7%) had mild pre-eclampsia as shown in Figure 1.

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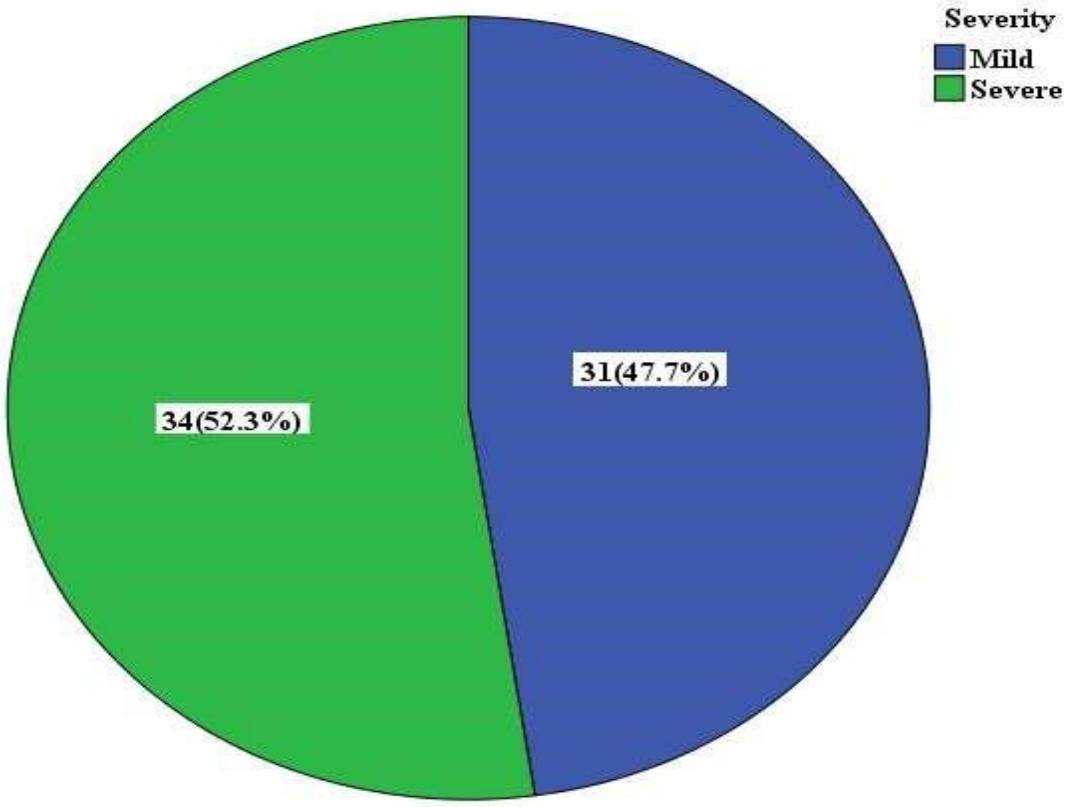

Figure 1: Severity of pre-eclampsia among pregnant women at the antenatal clinic Irrua between the pre-eclamptics and normotensive pregnant women.

Table 3 shows the peripheral blood film findings among the subjects in the second trimester, where 44(33.8%) had normocytic hypochromic blood picture and 16(24.6%) had features of microangiopathic haemolytic anaemia (MAHA) from the pre-eclamptics.

Table 3: Peripheral blood film findings among subjects in the second trimester

	Preeclampsia (n=65)	**Normotensive (n=65)**	**Total (n=130)**		
	n(%)	**n(%)**	**n(%)**	**χ^2**	**p-value**
NN	6(9.2)	16(24.6)	22(16.9)	5.471	0.019*
NH	8(13.8)	35(53.8)	44(33.8)	23.224	<0.001*
MH	13(20.0)	10(15.4)	23(17.7)	0.475	0.491
Dimorphic	0(0.0)	4(6.2)	4(3.1)	4.127	0.042
MAHA	16(24.6)	0(0.0)	16(12.3)	18.246	<0.001*

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Macrocytic	0(0)	0(0)	0(0)	0(0)	
Leucoerythrobastic	1(1.5)	1(1.5)	2(1.5)	0.000	1.000

KEY: NN – Normocytic normochromic
NH – Normocytic hypochromic
MH – Macrocytic hypochromic
MAHA – Microangiopathic haemolytic anaemia

Table 4 shows the peripheral blood film finding among the subjects in the third trimester, where 23(17.7%) had macrocytic hypochromic blood picture and 16(24.6%) also had features of microangiopathic haemolytic anaemia (MAHA) for the pre-eclamptics, similar to the second trimester.

Table 4: Peripheral blood film findings among participants in the third trimester

	Preeclampsia (n=65)	**Normotensive (n=65)**	**Total (n=130)**		
	n(%)	**n(%)**	**n(%)**	**χ^2**	**p-value**
NN	6(9.2)	16(24.6)	22(16.9)	5.471	0.019
NH	9(13.8)	35(53.8)	44(33.8)	23.224	<0.001*
MH	13(20.0)	10(15.4)	23(17.7)	0.475	0.491
Dimorphic	0(0.0)	4(6.2)	4(3.1)	4.127	0.042*
MAHA	16(24.6)	0(0.0)	16(12.3)	18.246	<0.001*
Macrocytic	0(0.0)	1(1.5)	1(0.8)	1.008	0.315
Leucoerythrobastic	1(1.5)	1(1.5)	2(1.5)	0.000	1.000

KEY: NN – Normocytic normochromic
NH – Normocytic hypochromic
MH – Macrocytic hypochromic
MAHA – Microangiopathic haemolytic anaemia

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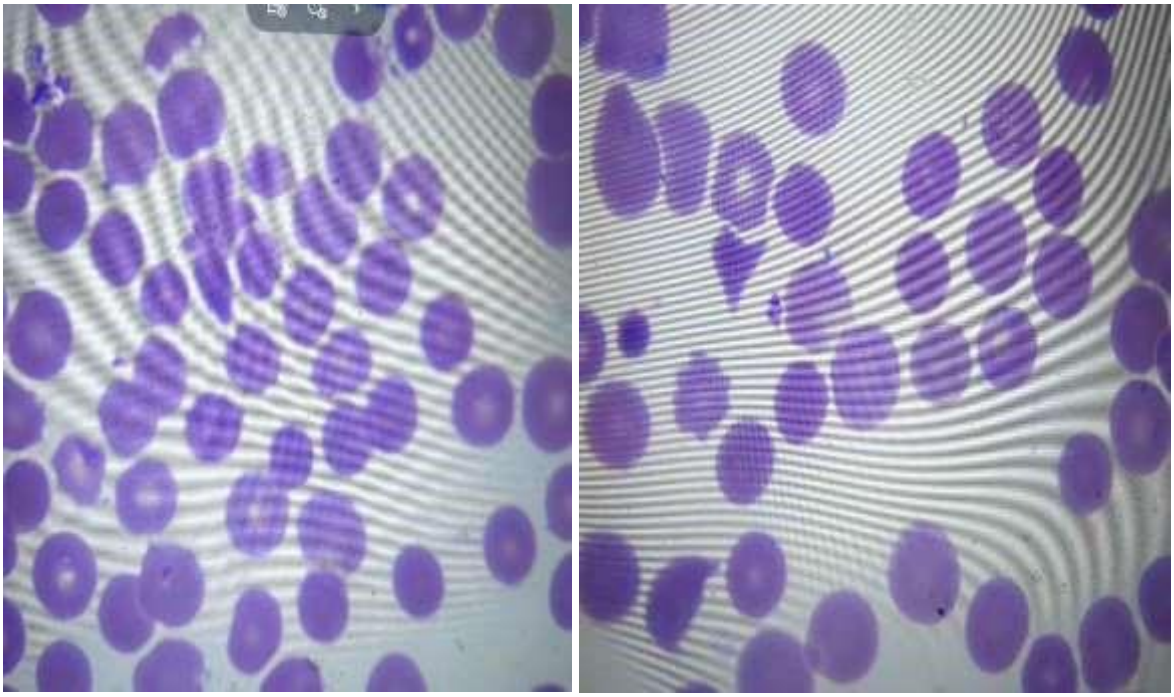

Figure 2a & 2b: Peripheral Blood Film of pregnant women with Pre-eclampsia showing Schistocytes

DISCUSSION

Pre-eclampsia has been daubed a disease of many theories as the aetiology remains unclear. However, abnormal trophoblastic invasion of uterine vessels as a result of placental implantation has been central in the aetiology of the condition. Others include: immunological maladaptive tolerance between maternal, paternal (placental), and fetal tissues; maladaptation to cardiovascular or inflammatory changes of normal pregnancy by the mother via endothelial cell activation; genetic factors including inherited predisposing genes, epigenetic influences and parity [22]. The present study found primiparity to be a risk factor for the development of pre-eclampsia as seen in several other studies [23, 24].

This study observed that all subjects were within the reference interval for trimester-matched normal body mass index (BMI), and this finding aligns with the report of Ogugua & Iwuagwu which reported an a verage BMI of 25kg/m^2 amongst pregnant women with pre-eclampsia in a multispecialty hospital in Southeastern Nigeria [25].

The haemoglobin genotype AA which occurs when an individual inherits the A gene, was the most occurring genotype in the study population, it was the most occurring haemoglobin genotype among pre-eclamptic women. This may indicate a hereditary interaction between the pre-eclamptic gene and other haematological genes. Heredity predisposes to pre-eclampsia likely from interactions of hundreds of inherited genes from maternal and paternal or both that control many enzymatic and metabolic functions throughout every organ system [26]. The evidence of the incidence of pre-eclampsia is higher in women with African-American decent than those of Latin America due to the interaction of American Indians and

white race genes [27]. Racial-ethnic differences have been observed in the distribution of mid-trimester maternal levels of placental growth factor and soluble endoglin and the associations with early-onset pre-eclampsia [28].

The morphology of the peripheral blood film of the subjects was largely of normocytic hypochromic red blood cells. However, there was associated microangiopathic haemolytic anaemia amongst the severe pre-eclamptics evidenced by the presence of schistocytes. This is probably due to endothelial dysfunction which is associated with pre-eclampsia. This is similar to the findings of Hernandez-Hernandez *et al*, who looked at the peripheral blood films of women with hypertensive disorders during pregnancy and showed a high percentage of morphologic alterations of red blood cells [15]. Also, in the study by Shetty *et al*, the diagnosis of patients with HELLP syndrome was confirmed by finding of burr cells, schistocytes, and polychromasia on peripheral smear [16]. The women in this current study with features of microangiopathic haemolytic anemia had not developed HELLP syndrome; however, it cannot be ruled out at the time of the investigation.

CONCLUSION

The current study has established that there are significant changes in clinical features such as palor, oedema, headache and abdominal pain in pregnant women with pre-eclampsia. Although these are common symptoms in commonly ill pregnant and non-pregnant patients, a presentation of one or more of the clinical features in pregnancy should raise concerns and trigger a further evaluation for pre-eclampsia. Combining these clinical features with peripheral blood film showing microangiopathic haemolytic anaemia evidenced by the presence of schistocytes in pregnant women with raised blood pressure could be sufficient diagnosis for pre-eclampsia.

Limitations of the Study

The study was restricted to antenatal clinic patients only. There is a tendency of missing out on a certain population of women who presented with symptoms at the emergency unit. Non-pregnant women were not included in this study, hence they were not investigated. This would have afforded the opportunity of substantiating the findings of the various parameters concerning the normotensive non-pregnant women.

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Conflicts of interest

There are no conflicts of interest

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