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# **The Relationship between Placenta Location with Occurrence of Pre-Eclampsia: A Single Centre Study in Port Harcourt, Nigeria**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. Author ND conceptualized, design and wrote the initial draft of the manuscript as well as literature review. Author GB contributed in the intellectual content of the study design and protocol, statistical analysis and review of the manuscript. Author EWU took part in the study design, data collection, intellectual content and review of the manuscript. All authors read and approve of the final version of the manuscript.*

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## **ABSTRACT**

**Background:** Over the years, several screening tests have been developed, yet none is clinically useful for the prediction of pre-eclampsia. Currently, biochemical and biophysical markers of abnormal placentation are being studied as a link to the pathogenesis of pre-eclampsia.

**Objectives:** The aim of the study was to determine the relationship between the type of placental location determined by the use of ultrasound scan and occurrence of pre-eclampsia.

**Methodology:** The study was carried out at the department of Obstetrics and Gynaecology of the University of Port Harcourt Teaching Hospital (UPTH). Women admitted with the diagnosis of pre-eclampsia as well as those without pre-eclampsia at 28 to 42 weeks of gestation who satisfied the eligibility criteria, and consented for the study were enrolled. A structured proforma was used to obtain relevant information from the participants. Data was entered and analysed with SPSS

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Statistics for windows, version 20. Results were presented infrequency tables. Chi square and student 't' test were used to respectively compare discrete and continuous variables with p value < 0.05 set as significant.

**Results:** The results showed that majority 41 (75%) of women with pre-eclampsia had the severe form of the disorder and majority 35 (65%) were referrals from peripheral health centres. Generally, the most common 42 (38.2%) placenta location was anterior placenta. The majority 26 (47.27%) of women without pre-eclampsia had anterior placenta and the relationship was significant,  $p = 0.0049$ , (OR 0.45; 95% CI 0.20 – 1.00). While the majority 18 (32.73%) of women with pre-eclampsia had posterior placenta,  $p = 0.1298$ , (OR 1.94; 95% CI: 0.81 – 4.63). Lateral placenta was observed in 9 (16.3%) of women with pre-eclampsia, and the association with pre-eclampsia was significant,  $p = 0.0017$ .

**Conclusion:** Ultrasound location of the placenta is relatively safe and cost effective. Lateral placenta may be another risk factor for pre-eclampsia and its detection may raise the index of suspicion for the risk of pre-eclampsia. This may enhance early and prompt institution of preventive measures in order to improve outcome.

*Keywords: Placenta location; preeclampsia; Port Harcourt.*

## 1. INTRODUCTION

Pre-eclampsia is a pregnancy specific syndrome that can affect virtually every organ system, characterized by hypertension and proteinuria after 20 weeks of gestation [1]. Globally, pre-eclampsia complicates 2–10% of pregnancies, and the incidence is about seven-fold higher in developing countries than developed countries [2,3]. A prevalence of 3.3% and 5.6% were reported from Enugu and Benin respectively [4,5].

Pre-eclampsia and eclampsia are among the leading causes of maternal morbidity and mortality as shown in the recent World Health Organization systematic analysis and the world health statistics 2014 [6,7]. A similar trend had been reported at the University of Port Harcourt Teaching Hospital [8]. Perinatal morbidity and mortality are worse in pre-eclamptic patients than the normal populace [5].

Over the years, tremendous efforts had been made in the search for simple, cost-effective and valid tests to predict pre-eclampsia. This has however remained challenging; necessitating more research in this area to establish possible predictors of pre-eclampsia, and hence its prevention. A variety of biological, biochemical and biophysical markers implicated in the pathophysiology of pre-eclampsia had been proposed to predict its development [9]. Some of these tests to predict the development of pre-eclampsia include; roll-over test, isometric exercise test, angiotensin-2 infusion test, mid-trimester mean arterial pressure, 24-hour ambulatory blood pressure monitoring, uterine artery Doppler velocimetry, pregnancy

associated protein-A, placental protein-13, serum uric acid, urinary kallikrein and vascular endothelial growth factor-1. Efforts to identify early makers of abnormal placentation and impaired placental perfusion, endothelial cell activation and dysfunction, and activation of coagulation involved in pathogenesis of pre-eclampsia have also been done [10]. The World Health Organization systemic review of screening tests for pre-eclampsia assessed the usefulness of clinical, biophysical and biochemical tests in the prediction of pre-eclampsia and concluded that there is no clinically useful screening test to predict the development of pre-eclampsia [11]. Poon and co-workers reported in their study that the combination of maternal characteristics (personal or family history of pre-eclampsia, racial origin, body mass index [BMI]), biophysical (mean arterial pressure [MAP], uterine artery pulsatility index [UtAPI]) and biochemical markers (pregnancy – associated plasma protein A [PAPP-A], placental growth factor [PlGF]) increase the prediction rate of pre-eclampsia to greater than 90% [12].

The placenta is cardinal to the development of pre-eclampsia and abnormal placentation characterized by faulty implantation and subsequent trophoblastic invasion of spiral arteries herald the emergence of the disease. The determination of placenta location by ultrasonography is one of the various tests that have been studied to predict pre-eclampsia. It has been observed that lateral location of placenta was associated with increased risk for development of pre-eclampsia [13].

Ultrasonography is a simple procedure that is reliable, non-invasive, widely acceptable and

relatively cheap. Unlike biochemical tests which are invasive, ultrasonography is devoid of risk of blood borne infection, pain and discomfort. This is the first study at the university of Port Harcourt teaching hospital comparing the relationship between placenta location and its association with preeclampsia. This study sought to determine the relationship if any between placenta location and pre-eclampsia and irrespective of the outcome, findings from this study will contribute to the body of knowledge regarding the relationship between placenta location and pre-eclampsia.

## 2. METHODOLOGY

This was a hospital based prospective cross-sectional study involving 55 women with pre-eclampsia and 55 pregnant mothers without pre-eclampsia attending antenatal clinic at the University of Port Harcourt Teaching Hospital who consented to take part in the study and their pregnancies were between 28 to 42 weeks of gestation. The study was conducted between January and August 2018.

Women with multiple gestation, parturient with pregnancy below 28 weeks or above 42 weeks of gestation and those who refuse to give consent were excluded from the study.

The sample size was calculated using the formula for cross-sectional studies [14]  $n = z^2 p(1-p)/d^2$  with a prevalence (p) from a previous study of 5.6% and with an attrition rate of 10% gave a sample size of 55 participants for each arm of the study. Systematic sampling technique was employed to select the participants in this study with a sampling interval of [2]. The sampling interval was determined by dividing the number of patients with pre-eclampsia admitted weekly at UPTH which is [4] divided by the desired number of participants to be recruited weekly which is [2,15]. The first participant was selected by simple random sampling using ballot technique thereafter the sampling interval of [2] was applied and thus the 3rd, 5th, 7th participant with pre-eclampsia were consecutively selected until the required sample size was obtained. This was similarly carried out for the control arm that is those without pre-eclampsia.

Following the admission of patients with pre-eclampsia into the antenatal ward or labour ward, the Principal Investigator was notified by the staff on duty, besides the constant checks on both wards for such patients by the Principal

Investigator. Gestational age was calculated based on last menstrual period (LMP) for those who were certain of their LMP or with the first trimester ultrasound scan, where last menstrual period was uncertain. Where disparity occurred, gestational age derived from ultrasound scan was used. Other relevant information obtained from the participants were age, occupation, levels of education, marital status, ethnic group and parity. History of previous medical disorders, pre-eclampsia and uterine surgery were also obtained. General and systemic examinations, including obstetric examination were performed on the participants. Blood pressure was measured with a manual mercury sphygmomanometer attached with an adult sized fitting cuff. The patients were made to relax in sitting position, the arm and sphygmomanometer at the level of the heart when measuring the blood pressure. Foley's catheter specimen of urine collected under aseptic condition was used for dipstick analysis for proteinuria.

The patients were categorized as having mild or severe pre-eclampsia based on the severity of hypertension and proteinuria. The patients were managed according to standard protocol including, use of antihypertensive drugs, magnesium sulphate for seizure prophylaxis and timely delivery of the fetus.

A trans-abdominal ultrasonography was done by the same consultant sonologist, at the patient's bedside, using the same 2-dimensional ultrasound scan machine Sonarock SR-2. The findings on placenta location such as fundal placenta, placenta praevia, lateral placenta, anterior or posterior placenta, were recorded in the proforma for each participant. Ultrasound scan was performed for both participants with pre-eclampsia and those without pre-eclampsia. The sonologist was blinded as to which arm of the study the participant belonged to.

All data obtained including ultrasonographic placenta location were entered and analysed using SPSS statistical package for window version 20 (Armonk, NY, USA). Results were presented in simple frequency tables. Comparison between women with pre-eclampsia and women without pre-eclampsia was made with Chi square and Fisher's exact test for discrete variables and student's t-test for means of continuous variables and p value less than 0.05 was considered significant. Odds ratio (OR) was used to calculate the risk of association.

### 3. RESULTS

There were fifty-five participants enrolled into each arm of the study that is cases (parturients with pre-eclampsia) and control (parturients without pre-eclampsia) respectively. Majority 35 (64%) of the participants with pre-eclampsia were referred from peripheral health centres. Twelve (22%) were unbooked (did not receive formal antenatal care) and 8 (14%) were booked (received antenatal care) in the study centre. All the 55 (100%) parturients in the control group were booked in the study centre.

The socio-demographic characteristics were similar between the 2 groups. Three participants among those with pre-eclampsia had primary level of education while thirty-five participants had tertiary level of education whereas one and forty-one participants respectively had primary and tertiary level of education among the control group. Primary level of education was not significantly associated with pre-eclampsia ( $x=1.04$ ,  $p=0.38$ ,  $OR=3.2$ ) though women with primary level of education were three times more likely to develop pre-eclampsia. Tertiary level of education was not significantly associated with pre-eclampsia ( $x=1.53$ ,  $p= 0.215$ ,  $OR=0.6$ ) One hundred and eight (98.2%) participants were Christians while 2(1.8%) were Moslems. One(0.9%) of the women was single, others were married (table 1). Majority 46(41.8%) were in the 30-34 age groups. Majority 67(60.9%) have had 1-4 previous deliveries and 51(46.36%) were in their 28-33 weeks of gestation on admission.

Pre-eclampsia was more in the 30 – 34 age groups followed by those aged 35 or older however, these were not statistically significant. The association of the age groups 20 - 24 with pre-eclampsia was statistically significant ( $p = 0.0148$ )(Table2) The mean age between both groups was similar. Pre-eclampsia was observed in the majority 37 (67.27%) of parous women who had given birth 1 – 4 times. Eighteen (32.73%) of the case group were nulliparous. Although, these were not statistically significant,  $p = 0.1713$  and  $p = 0.2389$  respectively (Table 2).

The mean gestational ages for the case and control groups were  $33.8 \pm 4.0$  and  $34.0 \pm 4.4$  respectively. The relationship between gestational age and pre-eclampsia, was not statistically significant,  $P > 0.05$  (Table 3).

In the case group, 41 (75%) patients had severe pre-eclampsia while, mild pre-eclampsia occurred in 14 (25%). Of all the locations of placenta, anterior placenta was the commonest 42 (38.2%) and the least location was placenta praevia 1 (0.9%) in the study population. In the control group, anterior placenta location was also the most common 26 (47.3%) and the relationship was significant,  $p = 0.0049$ , ( $OR 0.45$ ; 95%  $CI 0.20 - 1.00$ ). The posterior placenta was most common 18 (32.7%) among the case group and the relationship was not significant statistically,  $p = 0.1298$ , ( $OR 1.94$ ;  $CI 0.81 - 4.63$ ). Lateral placenta location was observed in 9 (16.4%) of the case group, and none in the control. The difference was statistically significant,  $p = 0.0017$  (Table 4).

**Table 1. Socio-demographic characteristics of the study population**

Variable		Frequency (n = 110)	Percent (%)
Education	Primary	4	3.64
	Secondary	30	27.27
	Tertiary	76	69.09
Religion	Christian	108	98.18
	Islam	2	1.82
Marital status	Married	109	99.01
	Single	1	0.90
Agegroup (years)	<20	1	0.90
	20 -24	9	9.18
	25 -39	21	19.09
	30 – 34	46	41.82
	≥ 35	33	30.0
Gestational age (weeks) on admission	28 – 33	51	46.36
	34 – 36	28	25.45
	37 – 42	31	28.19
parity	0	42	38.18
	1 – 4	67	60.91
	≥5	1	0.91

Chronic hypertension and diabetes mellitus were observed among the participants. Nine (16.4%) of the case group had history of chronic hypertension. This was statistically significant, P = 0.0017. Three (5.5%) in the case group had history of diabetes mellitus, this was not significant, p = 0.0790 (Table 5).

**4. DISCUSSION**

Majority 76 (69.1%) of the participants in this study had tertiary level of education. This finding was at variance with the report from Enugu that showed that secondary education was commoner (46.7%) among the study group.4 The demographic characteristics of the studied population showed that women with primary level of education were three times more likely to develop pre-eclampsia (evident by the significant odds ratio) when compared with higher levels of education. Conversely, other reports have shown that maternal higher level of education was associated with lower risk for pre-eclampsia [16,17].

This study showed that majority 46 (41.8%) of participants were in the age group 30 – 34 years followed by the elderly gravidae (≥ 35 years) but their association with pre-eclampsia was not statistically significant. However, frequency of pre-eclampsia in the age group 20 – 24 years was 8 (14.5%) and was statistically significant (p value = 0.0148). These findings were in agreement with studies done in Enugu and Benin but at variance with earlier report that maternal age ≥ 35 years is a risk factor of pre-eclampsia.4,5,9 Some other characteristics in the women may be responsible for this disparity. This disparity may be related to their parity as

nulliparity is associated with pre-eclampsia and young persons aged 20 – 24 years are likely to be of low parity.

The gestational ages of the participants ranged between 28 – 42 weeks, and majority 51 (46.36%) were in the gestational age range between 28 – 33 weeks. Even among the case group, the occurrence of pre-eclampsia was more 26 (47.27%) at 28 – 33 weeks of gestation. At term (37 – 42 weeks), 15 (27.3%) of the cases had pre-eclampsia. This observation showed that the occurrence of pre-eclampsia has an inverse relationship with gestational age and as gestational age increases, pre-eclampsia decreases with fewer cases diagnosed at term. Comparing this with findings at Enugu where the commonest gestational age range was between 34 – 36 weeks, the commonest gestational age range in this study was lower [4]. This implied that more women may develop pre-eclampsia at a lower gestational age, and the management is faced with challenges, bothering on prolongation of the pregnancy and delivery of a premature infant.

Majority 67 (60.9%) of participants in this study were parous women (para 1 – 4) and nulliparity was not significantly associated with pre-eclampsia in this study. This was different from findings of previous studies in which majority of cases were nulliparous [4,5]. Moreover, nulliparity (para 0) had been suggested as a risk factor of pre-eclampsia because of their strong association [9,18,19] This inconsistency may suggest that pre-eclampsia may occur in women irrespective of their parity. Moreover, parous women may be of advanced maternal age which is associated with risk for diabetes mellitus and

**Table 2. Relationship of age groups and parity with pre-eclampsia**

Age Groups (years)	Case (n=55)	Control (n =55)	Chi-square (p-value)	P-value
<20	0 (0.0%)	1 (1.82%)	1.00	0.5000 <sup>†</sup>
20 -24	8 (14.55%)	1 (1.82%)	5.92	0.0148*
25 -39	8 (14.55%)	13 (23.64%)	1.47	0.2251
30 – 34	23 (41.82%)	23 (41.82%)	0.04	0.5765
≥ 35	16 (29.09%)	17 (30.91%)	0.04	0.8351
Mean Age	31.8±5.1 <sup>a</sup>	31.8±4.8		
Parity				
0	18 (32.73%)	24(43.64%)	1.38	0.2389
1 – 4	37 (67.27%)	30(54.55%)	1.87	0.1713
≥5	0 (0.0%)	1 (1.82%)	1.01	0.5000 <sup>†</sup>
Mean Parity (±SD)	3.6 ±2.0 <sup>a</sup>	3.1 ±1.2		

<sup>†</sup>Fischer's exact value, <sup>a</sup> Difference in the mean age of both groups was not statistically significant (T test =0.9, p=0.26),

\*Association of age group and pre-eclampsia was statistically significant

<sup>a</sup>Difference between the groups was not statistically significant (p > 0.05), <sup>†</sup> Fischer's exact value, <sup>a</sup> T-test showing difference between group mean parity was statistically significant, (T test=2.7, p=0.0002)

**Table 3. Relationship of gestational age and pre-eclampsia**

Gestational Age (weeks)	Case (n=55)	Control (n = 55)	Chi-square (p-value)
28 – 33	26 (47.27%)	24 (43.64%)	0.14 (0.7017)
34 – 36	14 (25.45%)	11 (20.00%)	0.46 (0.4948)
37 – 42	15 (27.27%)	20 (36.36%)	1.04 (0.3060)
Mean	33.8±4.0 <sup>b</sup>	34.0±4.4	

Association of gestational age and pre-eclampsia was not statistically significant ( $p > 0.05$ ), <sup>b</sup>Difference in mean gestational age was not significant ( $p > 0.05$ )

**Table 4. Relationship of placenta location and pre-eclampsia**

Placenta location	Case (n, %)	Control (n, %)	Chi-square (p - value)	OR (95%CI)
Anterior	16 (29.09)	26 (47.27)	3.85 (0.0049)**	0.45 (0.20 – 1.00)
Fundal	12 (21.82)	17 (30.91)	1.17 (0.2792)	0.62 (0.26 – 1.47)
Placenta praevia	0 (0.0)	1 (1.82)	1.01 (0.5000) <sup>†</sup>	NA
Posterior	18 (32.73)	11 (20.0)	2.29 (0.1298)	1.94 (0.81 – 4.63)
Lateral	9 (16.36)	0 (0.0)	9.80 (0.0017)**	NA
Total	55 (100.0)	55 (100.0)		

<sup>†</sup>Fischer's exact value, OR: Odd ratio (95% confidence interval), NA: not applicable\*Difference between both groups was statistically significant

**Table5. Relationship of medical history and pre-eclampsia**

Medical history	Case		Control		Chi-square (p-value)
	No (%)	Yes (%)	No (%)	Yes (%)	
Autoimmune disorders	55 (100.0)	0 (0.0)	55 (100.0)	0 (0.0)	NA
Bronchial asthma	55 (100.0)	0 (0.0)	55 (100.0)	0 (0.0)	NA
Renal disease	55 (100.0)	0 (0.0)	55 (100.0)	0 (0.0)	NA
Diabetes mellitus	52 (94.5)	3 (5.5)	55 (100.0)	0 (0.0)	3.08 (0.0790)
Thyroid disorders	55 (100.0)	0 (0.0)	55 (100.0)	0 (0.0)	NA
Chronic hypertension	46 (83.6)	9(16.4)	55(100.0)	0 (0.0)	9.80 (0.0017)**
Previous pre-eclampsia	55 (100)	0 (0.0)	55 (100)	0 (0.0)	NA

NA: Analysis not applicable. \*association was statistically significant

chronic hypertension, and subsequent risk for pre-eclampsia. On the contrary, parous women impregnated by a new partner may have an increased risk of pre-eclampsia.

The results of this study showed that majority of women with pre-eclampsia have the severe form. Out of 55 pre-eclamptic women majority 41 (75%) had severe pre-eclampsia. This corroborated the report by Dolea and AbouZahr, in which about 7-fold higher incidence of pre-eclampsia occurred in developing countries.<sup>3</sup> Another study done at Enugu, Southeast Nigeria reported 3.3% prevalence of severe pre-eclampsia.<sup>4</sup> On the contrary, a higher prevalence of 25% was reported for severe pre-eclampsia in the United States of America [17]. That notwithstanding, women with severe pre-eclampsia are usually admitted in the hospital for treatment and delivery. Therefore, majority of women on admission were likely to have severe pre-eclampsia as was observed in this study.

The findings from many studies have suggested possible role of abnormal placentation in the aetiology of pre-eclampsia. The location of

placenta had been suggested by many studies to either lower or increase the risk of pre-eclampsia [13,16,19-21]. This study showed that a relationship exist between placenta location and occurrence of pre-eclampsia. This study demonstrated that generally, anterior placenta was the commonest placenta location amongst the entire study population. In the women without pre-eclampsia, anterior placenta was more common 26 (47.3%) and the association was statistically significant;  $p = 0.0049$ , (OR = 0.45; 95% CI: 0.20–1.00). This implies that women with anterior placenta location may be at lower risk for pre-eclampsia. This finding agreed with previous study, in which anterior placenta location was the commonest amongst participants studied [22] Although, that study evaluated women at term (37–42 weeks) therefore, majority of the women who were less than 37 weeks gestation were excluded. This current study may be more representative, as it included women at 28 – 42 weeks of gestation.

Interestingly, no lateral placenta location was found in the 55 women without pre-eclampsia

while 9 out of 55 women with pre-eclampsia had lateral placenta location and the difference was statistically significant ( $p = 0.0017$ ). This finding was corroborated by the study conducted by Bhalerao et al in which laterally located placenta had significantly associated risk of developing pregnancy induced-hypertension ( $p = 0.00002$ , OR = 5.09; 95% CI: 2.40 - 10.80) [20]. However, the study by Bhalerao was done in the second trimester at 18 – 24 weeks of gestation and as such sensitivity of ultrasonography for placenta location may be less. Despite that, sensitivity between 73% - 75% and specificity between 81% - 86% were also reported from studies by many investigators [13,19,23]. Furthermore, in women with pre-eclampsia it was found that posterior placenta location was most common 18 (32.72%). However, the association with pre-eclampsia was not significant statistically;  $p = 0.1298$ , (OR 1.94; 95% CI: 0.81 – 4.63). This is at variance with results of an earlier study indicating that posterior placenta was not the most common placenta location [22]. Also, among the pre-eclamptic participants there was none with placenta praeviawhile on the contrary, placenta praevia was found in 1 (1.8%) of the women without pre-eclampsia. However, this difference was not statistically significant ( $p$  value = 0.5000). Reports have been inconsistent regarding the role of placenta praevia in pre-eclampsia, while some authors have suggested the protective effect of placenta praevia on the developments of preeclampsia, others have refuted such claim [16,18,24].

Chronic hypertension was demonstrated in this study to be significantly associated with pre-eclampsia although findings regarding diabetes mellitus was at variance with other reports which showed diabetes mellitus as a risk factor for pre-eclampsia [17,18]. Consequently, patients with chronic hypertension require increased surveillance during the antenatal period to ensure early detection of superimposed pre-eclampsia in order to improve outcome.

## 5. CONCLUSION

Ultrasound location of a laterally located placenta may be another risk factor for pre-eclampsia while anteriorly located placenta may seem protective. The detection of lateral placenta may raise the index of suspicion for the risk of pre-eclampsia. This may enhance early identification and management of high-risk women.

## 6. RECOMMENDATION

The use of ultrasonography to locate the placenta should be encouraged as part of the routine sonography in pregnancy. This could detect women with lateral placenta. Lateral placenta location should be considered a risk factor for developing pre-eclampsia and should trigger surveillance for monitoring these women.

## 7. LIMITATION OF THE STUDY

The sample size in the study was small and this may affect the power of the study. Also, being a single centre study, our findings may not completely reflect findings in the general population. A multi-centered study is required to buttress our findings.

## CONSENT

The antenatal records of eligible participants were reviewed and informed consent obtained for participation in the study.

## ETHICAL APPROVAL

Ethical approval was obtained from the Ethics committee of the hospital for the conduct of this research.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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