Gross Placenta Characteristics in Pre-eclampsia/Eclampsia and Normotensive Pregnancies. A Comparative Study

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Abstract

Background: *Preeclampsia/eclampsia is a leading cause of maternal and perinatal mortality; the prevailing theory is that it is a consequence of disordered placentations which are manifested as vascular and villous abnormalities with consequences in the developing foetus.*

Objective: *To evaluate and study gross changes in the placentae of women with preeclampsia/eclampsia and normotensive mothers and correlate with pregnancy outcome and neonatal morbidity and mortality.*

Methods: *This was a comparative(prospective) study of pathologic lesions in the placentae of 146 pregnant women; 73 were normotensive (control group) while the other 73 women were preeclamptic /eclamptic (study group). The placental findings in the two groups were further examined for association with severity of the hypertensive disease and neonatal mortality.*

Results: *The mean placental weight was lower in the study group compared to the control (556.82 grams ± 169.72 vs. 649.93 grams ± 116.38, p<0.001). Placenta weight was significantly lower at gestational ages of 31-36.6weeks. The study group had a significantly higher percentage of abnormal cord insertions than the control group. There was no significant association between gross parameters and disease severity. Gross infarcts were only seen in placentae of study group and the difference was statistically significant. Gross infarcts and membrane colour were significantly associated with perinatal mortality. The study group had 11% neonatal mortality while there were*

no neonatal deaths in the control group.

Conclusion: *There were distinct gross pathological changes in the placentae of mothers with preeclampsia/eclampsia several of these pathological changes occurred more in the severe and eclamptic cases. There was also association with perinatal mortality.*

Introduction

Pre-eclampsia (PE) is a pregnancy related hypertensive disease, it is one of the 5 major causes of maternal mortality in Nigeria. Nigeria has one of the highest maternal mortality rates in the world. Pre-eclampsia accounts for about 50000 -60000 maternal deaths per year worldwide.[1,2,3] It has a prevalence rate of 5-8% of pregnancies worldwide with higher prevalence in sub-SaharanAfrica. Studies have reported an incidence of between 2 and 16% in Nigeria[1,3].

Pre-eclampsia is defined as the presence of new onset of raised blood pressure after 20weeks gestational period, with presence of either ≥ 2+ on dipstick or ≥300gm/24hours proteinuria[1]

It is one of the main causes of maternal and perinatal morbidity and mortality globally and it is associated with an increased risk of the mother and her child developing cardiovascular complications and diabetes mellitus later in life[3,4,5,6].

Eclampsia is an extreme complication in the spectrum of preeclamptic disease which, progresses from mild to severe and may culminate in generalized tonic- clonic seizures which is called eclampsia[2,3].

Pre-eclampsia is generally divided into two main types, early- and late-onset PE. The late onset comprises>80% of pre-eclampsia[1]. In early onset PE clinical signs appear before 33 weeks gestation, while they occur after 34 weeks gestation in the late onset type[1]. It is the early-onset type that is responsible for most of the high maternal and foetal mortality and morbidity rate[1].

Pre-eclampsia is a multi-systemic syndrome, involving genetic and environmental factors in its pathogenesis and pathophysiology which are still poorly understood. There are however several theories and hypothesis about its aetiopathogenesis[1]. Pre-eclampsia begins to abate with the delivery of the baby and particularly the placenta and indeed the only known treatment of PE is delivery of the placenta[1,7].

Pre-eclampsia can occur in the absence of a fetus, in the presence of only trophoblast tissue as in hydatidiform moles[7]. It is therefore generally accepted that PE is associated with disorders of the placenta. Several gross and macroscopic placenta lesions have been identified in relation to PE. It has also been associated with morphological, biochemical and functional abnormalities in the umbilical cord[8,9].

Abnormal cord insertion particularly marginal cord insertion has been associated with PE[9,10,11]. Central and eccentric cord insertions are classified as normal while marginal and velamentous as abnormal insertions. Velamentous cord insertion (VCI) occurs when blood vessels from the cord traverse foetal membranes before reaching the placenta margin and inserting peripherally thereby leaving the vessels exposed and unprotected and vulnerable to injury and pressure during pregnancy, labour and delivery[11, 12,13]. In marginal cord insertion (MCI), the cord inserts at the edge of the placenta, but still arises directly from the placental mass. The prevalence of MCI varies between 6.3% and 7% in singleton pregnancies[9-13]. Other abnormalities in length, diameter, knots, coils most of which have limited studies in our environment, have also been associated with hypertensive disorders in pregnancy[14].

The placenta is the most accurate record of the prenatal events of pregnancy especially as it affects the neonate[6].Histopathological and microbiological examination of the placenta can reveal the aetiology of many conditions[15], Placental examination reveals abnormal findings in almost all cases of foetal death or abnormalities[14], and histopathology can diagnose the cause of death in about one-third of cases in which it could not be determined clinically. It may also offer essential evidence in medical liability cases and may provide defence against allegations of malpractice[15,16,17]. Knowledge of placental changes that are associated with certain disease conditions may form a basis for radiological identification of the lesions.

The placenta is not thoroughly studied in our environment. This may partly be because of the cultural beliefs about the sacredness of the placenta. The placenta is usually demanded for and given to the father or close family members for immediate culturally accepted disposal, as it is believed that mishandling of the placenta by evil people endangers the life or .future of the child[18,19].

The study examined the gross placental abnormalities found in PE and the association of the findings with severity of the disease and perinatal outcome.

Materials and Methods

The study was comparative study involving pre-eclamptic/eclamptic and normotensive pregnant women between the ages of 18 and 40 years and gestational ages of 28weeks and 41weeks, who presented at the University of Ilorin Teaching hospital. The hospital is a tertiary health facility at the outskirts of Ilorin, the capital city of Kwara state and located in the North central geopolitical zone of Nigeria. There is an average of 43 deliveries per week in the hospital. The study spanned from January to November 2018. Patients were recruited from the labour ward, antenatal, emergency wards and operating theatres of the Obstetrics and Gynaecology unit while laboratory analyses was done in the anatomic pathology laboratory. The study group (pre-eclamptics/eclamptics) were pregnant women with high blood pressure after 20weeks gestational age with associated significant proteinuria. An equal number of controls (normotensives) matched for age and gestational age were recruited. Purposive non-probability sampling was employed. The sample size was calculated using the formula[20]

$$n = \frac{z^2 pq}{d^2}$$

Where: n =sample size
z = standard normal deviation (a constant which is 1.96 at 95% confidence interval)
p = prevalence of preeclampsia at the study site i.e. 0.05 (5%)[21]
d = observed difference at 0.05(5%) level of significance.

$q = 1 - p = 1 - 0.05 = 0.95$

$n = \frac{1.96^2 \times 0.05 \times 0.95}{(0.05)^2} = 73$

Thus, a minimum sample size of 73 was recruited into each arm of the study to give a total number of 146 participants.
The research instrument was a proforma which was used to record the biodata and on which all the other findings on clinical and laboratory examination were recorded. At delivery, birth weights and Apgar scores were noted and recorded. The placentae were washed to remove blood clots, weighed and carefully examined for completeness, gross abnormalities in the umbilical cord (insertions, twists, thrombosis etc.), foetal membranes

(extrachorial placentations, and meconium staining) and abnormalities in the placenta disc (infarction, calcification, retroplacentalhaemorrhage and fibrin deposition).

Analysis was performed using SPSS version 23.0 (IBM, Armonk, NY, USA) and $p<0.05$ was termed significant.

Ethical approval was obtained from the ethical review committee of the University of Ilorin Teaching Hospital (Approval number:NHREC/02/05/2010. Date: 11th January, 2017) and a written informed consent was obtained from all participants.

Results

The results of the research are presented in this section.

Table 1: Distribution of the socio-demographic characteristics of participants.

Variables	Study group n (%)	Control group n(%)	χ2/t	ρ
Age groups			2.359	0.670
≤ 24	7 (9.6)	9 (12.3)		
25 – 29	25 (34.2)	30 (41.1)		
30 – 34	26 (35.6)	18 (24.7)		
35 – 39	13 (17.8)	13 (17.8)		
≥40	2 (2.7)	3 (4.1)		
Mean ± SD	30.04 ± 4.67	29.86 ± 4.81	0.227	0.821
Range	20 – 40	20 – 40		
Marital Status			1.007	0.316
Single	0 (0.0)	1 (1.4)		
Married	73 (100.0)	72 (98.6)		
Level of Education			1.215	0.749
No formal education	3 (4.1)	1 (1.4)		
Primary	3 (4.1)	4 (5.5)		
Secondary	15 (20.5)	14 (19.2)		
Tertiary	52 (71.2)	54 (74.0)		
Occupation			5.084	0.279
Unemployed	4 (5.5)	5 (6.8)		
Student	4 (5.5)	12 (16.4)		
Trader	29 (39.7)	25 (34.2)		
Artisan	9 (12.3)	6 (8.2)		
Civil servant	27 (37.0)	25 (34.2)		

χ2*:* Chi Square test; t: T test

Table 1 shows the sociodemographic characteristics of the participants of the control and the study groups. There was no statistical difference in any of the sociodemographic parameters. The mean age of the study and control group were 30.04± 4.67 years and 29.86 ± 4.81 years respectively. Majority were married 73(100%) in the study group and 72(98.6%) in the control group. Most participants in both groups had tertiary level of education; 52(71.2%) in the study and 54(74%) in the control groups. The most common occupation amongst the two groups was trading and work as civil servants; 29(39.7%) and 27(37.0%) for the study group and 25(34.2%) and 25(34.2%) for the control group respectively.

Table 2: Gross placenta parameters

Macroscopic parameters	Study group n (%)	Control n (%)	χ2/t	P
Foetal weight	2.66 ± 0.77	3.21 ± 0.43	5.306	< 0.001*
Placental characteristics				
Placental weight	556.82 ± 169.72	649.93 ± 116.38	-3.866	< 0.001*
Foetal/Placental weight ratio	4.87 ± 0.88	5.01 ± 0.67	-1.077	0.283
Cord insertion			8.078[y]	0.044*
Central	23 (31.50)	33 (45.2)		
Eccentric	36 (49.3)	38 (52.1)		
Marginal	10 (13.7)	1 (1.4)		
Velamentous	4 (5.5)	1 (1.4)		
Membranes			1.007	0.316
Marginal	72 (98.6)	73 (100.0)		
Circumvallate	1 (1.4)	0 (0.0)		
Membrane colour			1.833[y]	0.399
Green	0 (0.0)	2 (2.7)		
Opaque	3 (4.1)	0 (0.0)		
Normal	70 (95.9)	71 (97.3)		
Gross abnormalities			13.075	< 0.001*
Infarction	12 (16.4)	0 (0.0)		
None	61 (83.6)	73 (100.0)		

χ2*:* Chi Square test; t: T test. *= *p < 0.050 (statistically significant)*[y]*=Yates Corrected Chi square result*

Table 2 shows the gross placental features seen during examination of the placentae. The mean placental weight in the control group was 649.93±116.38kg while that of the study group was 556.82±169.72.

The most common placental insertion type was the eccentric which was 36(49%) in the study group and 38(52.1%) in the control group. The next most common type was central insertion which occurred in 23(31.50%) of study group and 33(45%) of the control group. The abnormal insertion sites were the marginal and the velamentous insertion and these occurred with more frequency among those in the study group. Of marginal insertion, 10(13.7%) of the study group placentae and 1(1.4%) of the control group placentae had this kind of insertion. The difference in frequency was statistically significant. The least common insertion type was velamentous insertion which occurred in 4(5.5%) and 1(1.4%) of study and control groups respectively. Gross placenta infarction was found in 12(16.4%) placentae of the study group, but there were no gross placental abnormalities in the control group.

Table 3: Placenta Weight comparison based on Gestational age

Variables	Gestational Age at delivery (Weeks)					
	Very preterm ≤ 31 weeks (%)		Moderate preterm 31 – < 37 weeks (%)		Term ≥ 37 weeks (%)	
Placental Weight	Subjects	Control	Subjects	Control	Subjects	Control
< 300	0 (0.0)	0 (0.0)	3 (9.4)	0 (0.0)	0 (0.0)	0 (0.0)
300 – 399.9	2 (50.0)	0 (0.0)	5 (15.6)	0 (0.0)	0 (0.0)	0 (0.0)
400 – 499.9	1 (25.0)	0 (0.0)	11 (34.4)	1 (5.0)	7 (18.9)	6 (11.3)
500 – 599.9	1 (25.0)	0 (0.0)	7 (21.9)	5 (25.0)	7 (18.9)	10 (18.9)
≥ 600	0 (0.0)	0 (0.0)	6 (18.8)	14 (70.0)	23 (62.2)	37 (69.8)
	χ^2 =0.625 ρ= 0.960[y]		χ^2 =12.861ρ= 0.012[y]		χ^2 =1.062	ρ= 0.588

[y]=*Yates corrected p-valuesp< 0.050 (statistically significant)*

Placental weights in the groups were further compared according to gestational age and a statistically significant difference was observed for preterm deliveries between the gestational ages of 31 to about 36weeks 6day. This is shown in table 3.

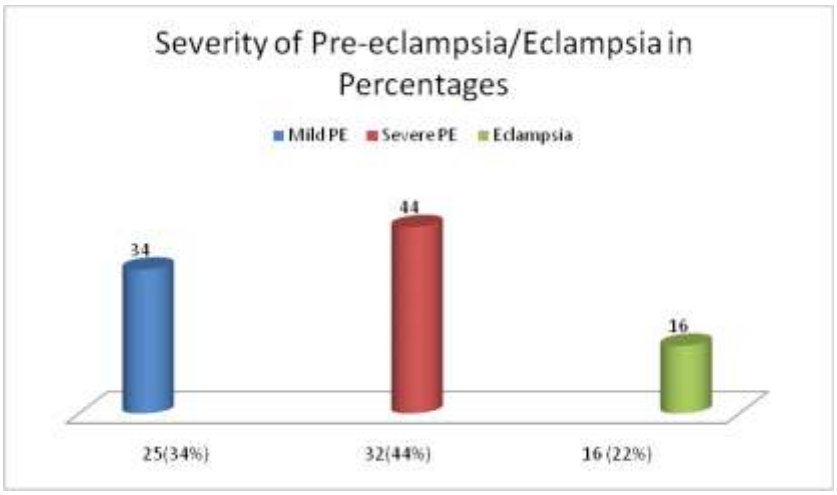

Figure 1 shows varying severity of the diseasein percentages.
Severe pre-eclampsia was most common form of the hypertensive disease followed by the mild form.

Table 4: Gross placenta parameters with disease severity and Foetal Mortality

	Severity of Disease					Fetal outcome			
Variables	Mild	Severe	Eclampsia	χ2/t		Alive	Dead	χ2/t	P
Cord insertion				2.615[y]	0.855			0.234[y]	0.971
Central	10 (43.5)	9 (39.1)	4 (17.4)			20 (87.0)	3 (13.0)		
Eccentric	9 (25.0)	17 (47.2)	10 (27.8)			33 (91.7)	3 (8.3)		
Marginal	3 (30.0)	5 (50.0)	2 (20.0)			8(80.0)	2(20.0)		
Velamentous	3 (75.00)	1 (25.0)	0 (0.0)			4(100)	0(0.0)		
Membranes				0.447[y]	0.799			0.125[y]	0.724
Marginal	25 (34.7)	31 (43.1)	16 (22.2)			64(88.9)	8(11.1)		

Circumvallate	0 (0.0)	1 (100.0)	0 (0.0)			1(100)	0(0.0)		
Membrane colour				0.293[y]	0.990			16.79[y]	<0.001
Green	0 (0.0)	0 (0.0)	0 (0.0)			0(0.0)	0(0.0)		
Opaque	1 (33.3)	2 (66.70)	0 (0.0)			0(0.0)	3(100)		
Normal	24 (34.3)	30 (42.9)	16 (22.9)			65(92.9)	5(7.1)		
Gross abnormalities				3.132[y]	0.209			4.879[y]	0.027
Foci of infarction	1 (8.3)	8 (66.7)	3 (25.0)			8(66.7)	4(33.3)		
None	24 (39.3)	24 (39.3)	13 (21.3)			57(93.4)	4(6.6)		

$\chi 2$:Chi Square test; t: T test. *p< 0.050 (statistically significant)*[y]*=Yates Corrected Chi square result*

The presence of macroscopic abnormalities were compared in the severity of the disease and foetal mortality in Table 4. There were no statistically significant gross abnormalities associated with severity of the disease. The most common site of placenta insertion in the live babies was eccentric insertion. All eight of the dead babies had marginal membranes which was also the more common membrane type. There was only one case of circumvallate membrane in the study group. Most membranes were normal coloured, only three were opaque, and all three had perinatal mortality.

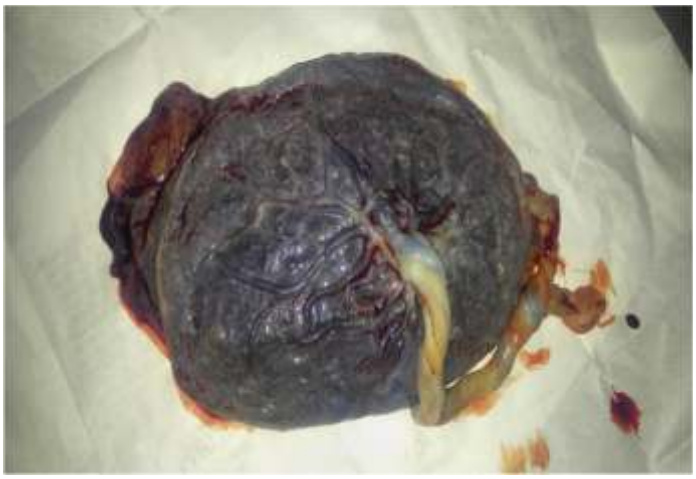

Figure 2a: Gross picture of a placenta with central cord insertion

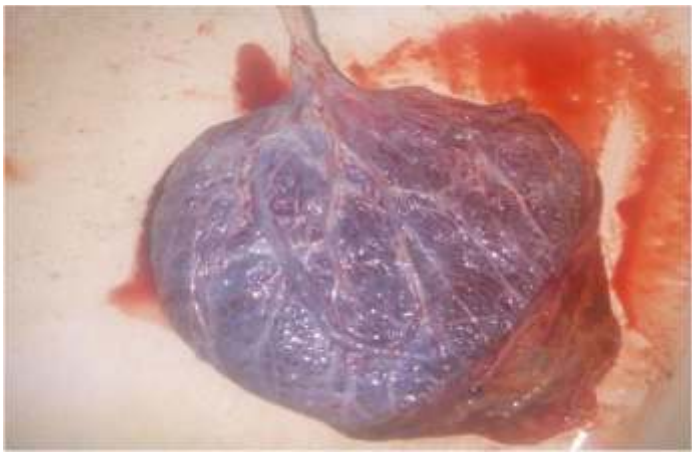

Figure 2b: Gross picture of a placenta with marginal cord insertion

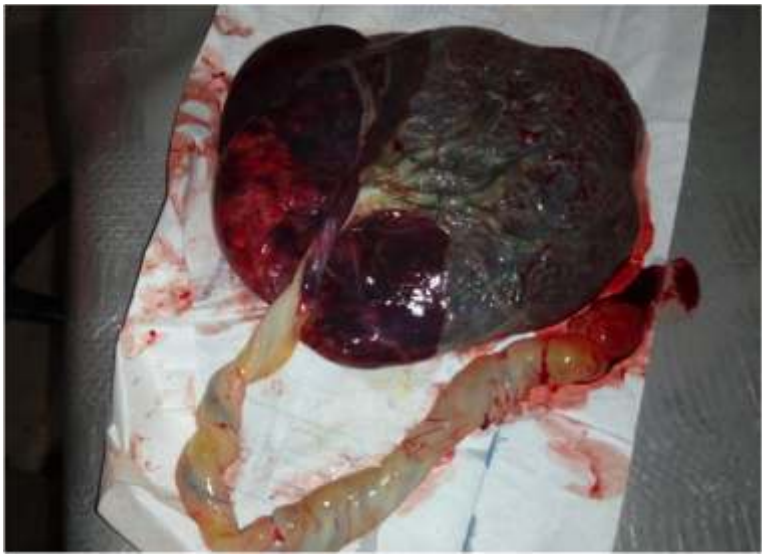

Figure 2c: Gross picture of a placenta with velamentous cord insertion (partly detached). Figures 2a,b and c show three different types of placenta insertions.

Discussion

The mean placenta weight of the study group was significantly lower than that of the control group, this was similar to the study by Salmaniet al[23]. Predoi et al also revealed significantly lower weights in the PE placentae[22]. This is believed to occur as a result of placenta ischemia.A key factor in the pathogenesis of PE is failure of cytotrophoblastic invasion of spiral arteries this in turn causes decreased placental perfusion and placenta ischemia[23]. The foetalplacenta weight ratio was also less in the study group than the control group but not significantly so and this suggests a corresponding decrease in the foetal weight thereby resulting in a constant foetalplacenta weight ratio. This is different from what was obtained inthe studies cited above which revealed a significantly decreased fetal placenta weight ratio[22,23]. Other factors that can affect foetalplacenta ratio include the gestational age at delivery, as the foetalplacental weight ratio differs at different gestational ages and maternal nutrition and race. Some studies have reported hypertrophy of placenta in hypertensive cases in response to chronic hypoxia[24], this together with the often associated low birthweight of the fetuses results in a low fetoplacenta ratio.

Majority of the placentae in both the study and control groups showed normal cord insertion. There were more eccentric cord insertions followed by central cord insertion, however 14(19.2%) placentae in study group had abnormal cord insertion, of which 10(13.7%) were marginal and 4(5.5%) velamentous, and this difference was statistically significant. Of the marginal insertions three were in mild cases of preeclampsia, five in severe and two in eclamptics. Velamentous cord insertion into the placenta was found in three cases of mild and one of severe pre-eclampsia. The abnormal cord insertions are associated with abnormal development of placenta and with increased risk of an adverse perinatal outcome. These risks are greater for velamentous than for marginal insertion and could possibly contribute to the high perinatal mortality and negative outcome in these PEgroup[12,13].

Majority of the placenta membrane appeared normal (translucent) in both groups, there were three opaque membranes in the study group. Opacity is most often caused by acute

chorioamnionitis or meconium staining.[25]Acute chorioamnionitis is the inflammation of the membranes and chorion of the placenta and is often caused by ascending bacterial infection, however sterile acute chorioamnionitis can occur in the absence of demonstrable microorganisms and can be induced by substances released under conditions of cellular stress, injury or death. The type of acute chorioamnionitis in these study cases was not actually determined. The study by Kim et al found the prevalence of chronic chorioamnionitis to be 23 and 16% in term and preterm PE cases respectively in their own study[26]. All three neonates with opaque placenta membranes in this study had perinatal mortality.

There were 12 cases of placenta infarcts seenon gross examination of the placenta and all were seen in the study group placenta, eight of these were found in severe pre-eclampsia, three in eclamptic cases and one in mild PE. Placenta infarcts may occur in uncomplicated pregnancies and has been reported in up to 20% of such[22], it however appears in this study to be related to presence and severity of PE. This is supported by Predoi et al's study which revealed that placenta infarcts could be documented in 70% and 40% of severe and mild PE respectively[22]. Other gross placenta abnormalities such as calcifications, retroplacental hematoma, abnormal umbilical coils were not seen.

This study revealed distinct gross pathological changes in the placentas of mothers with preeclampsia/eclampsia. Several of the pathological changes occurred more in the severe and eclamptic cases but the association was not statistically significant, there were however some significant association with adverse perinatal outcomes.Use of advanced ultrasound with Doppler studies to determine insertion of cord and placenta infarcts and other gross features may be helpful in determining the degree of severity of the disease and timing and mode of delivery. Studies also suggest that the identification of placental lesions with ultrasound in the absence of fetal growth restriction may be managed by antithrombotic treatment such as low molecular-weight heparin and aspirin[22]. Intrauterine fetal testing and monitoring may help to correctly identify the appropriate time for fetal birth and avoid in utero fetal demise.

The importance of examination and identification of placenta lesions in disease situations and the significance of such pathologic changes cannot be over emphasized. Early identification of pathological changes may assist in management which may lead to significant improvement in the pregnancy outcome. It may also play animportantrole in resolution of medicolegal situations.

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