PLACENTAL CHANGES IN PATIENTS WITH PREECLAMPSIA AND ECLAMPSIA AS SEEN IN IRRUA SPECIALIST TEACHING HOSPITAL, IRRUA EDO STATE

A DISERTATION SUBMITTED TO THE NATIONAL POSTGRADUATE MEDICAL COLLEGE OF NIGERIA FOR THE PART TWO FELLOWSHIP EXAMINATION OF THE FACULTY OF OBSTETRICS AND GYNAECOLOGY.

BY

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MBBS (BENIN)

2008
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DECLARATION

I hereby declare that this work is original unless otherwise acknowledged. It has neither been presented to any college, faculty or school for the award of a degree, diploma or fellowship nor has it been submitted elsewhere for publication.

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Signature and Date---------------------------------
CERTIFICATION

I hereby certify that this work was carried out by Dr. Gbejegbe, Emmanuel Hero of the department of obstetrics and Gynaecology, Irrua Specialist Teaching Hospital, Irrua, under supervision of under listed consultants

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2. Dr. S.A. Okogbenin, MBBS, FWACS.
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DEDICATION

This work is dedicated to the Almighty God, Jehovah for His loving kindness over me. It is also dedicated to my parents who instil in me love for academics. Lastly, it is dedicated to my loving wife for her support and my children Rume and Tejiri for the happiness they brought me.
ACKNOWLEDGEMENT

Special thanks go to Dr. J.O. Eigbefoh, Dr. S.A. Okogbenin and Dr. O. Ohiosimuan for the idea of this study and the motivation to carry out this work.

I also want to acknowledge Dr. Odike. Head of Department Pathology Ambrose Alli University, Ekpoma for his support. I also want to acknowledge all the consultants and residents in the department of Obstetrics and Gynaecology, of Irrua Specialist Teaching Hospital for their constructive criticisms and suggestions. I will always remain grateful.
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ABSTRACT

Context: Preeclampsia and eclampsia are common complications of pregnancy with attendant adverse maternal and fetal outcome. Studies done in different parts of the world had indicated that the pathology is at the placental bed. However, no such study has been published from our area.

Objective: To determine the pattern of placenta histopathological changes in preeclampsia and eclampsia among Nigerians in Irrua, and correlate these with the clinical severity as well as the maternal and perinatal outcome.

Design: One point descriptive cross sectional study.

Setting: Department of Obstetrics and Gynaecology, Irrua Specialist Teaching Hospital, Irrua, Edo State, Nigeria.

Subject: Placental pathologies were evaluated in thirty-three preeclamptic and five eclamptic patients and were compared with forty women (matched for age, parity and gestational age) without pregnancy complications as control.

Result: Preeclampsia and eclampsia were associated with significant placental infarcts with about 40% of maternal surface area affected in 60% of patients. Placental stromal fibrosis (79 %) and acute atherosis (74%) were the more consistent histopathological findings with severe disease (p< 0.05, 0.001 respectively). Histopathological lesions has no direct correlation to the clinical severity ( proteinuria p< 0.6385, blob pressure p< 0.0743).

Conclusion: Preeclampsia and eclampsia in Nigerians at Irrua are associated with similar placental changes as in other parts of the world. Histopathological lesions were worse with severe disease, however, the lesions were much less severe compared to those in western countries.
INTRODUCTION

Preeclampsia and eclampsia are important causes of perinatal and maternal mortality and morbidity in most countries of the world\(^1\). In spite of the advances made in the reduction of maternal and perinatal mortality, the contribution due to preeclampsia/eclampsia has remained significantly high and assuming a relative increase compared to other causes of mortality.\(^2\)\(^3\) Recent studies on maternal mortality rate in Nigeria shows that preeclampsia and eclampsia are now the leading causes of maternal mortality rate.\(^4\)

The exact aetiology of preeclampsia is not fully understood.\(^5\)\(^-\)\(^10\) However, different theories have been proposed, but none has explained all the pathological changes observed in this disease. The established disease is characterized by high vascular resistance.\(^6\) The clinical syndrome is characterized by the onset of hypertension and proteinuria in the second half of pregnancy.\(^11\)\(^12\) However, changes such as increased sensitivity to vasopressors, reduced plasma volume altered proximal renal tubular function and activation of the coagulation cascade antedate overt hypertension, and suggest that hypertension may not be central to the pathogenesis of preeclampsia rather a fallout.\(^3\)\(^4\)\(^10\)\(^-\)\(^12\) Approximately, 20% of eclampsia and 15% of patient with the haemolysis, elevated liver enzyme and low platelet (HELLP) syndrome are normotensive.\(^13\)

Various studies show defective or abnormal implantation of placenta as a result of failure of the second wave of trophoblastic invasion to be the central cause of the pathophysiological changes observed in preeclampsia and Eclampsia.\(^14\)\(^15\) As a result,
the placentae of preeclamptic and eclamptic patients have been subject of intense research.

Most of the studies of placental changes used to assess the disease severity were done on Caucasians and Negroids living in western countries. These findings have been applied to patients in developing countries Nigeria inclusive, who live under different conditions. Apparently, the same pathological changes will be expected irrespective of the nationality. However, in view of the diverse aetiology of this disease, genetic, immunological, environmental and social cultural modification of the pathology cannot be ruled out convincingly without evidence based on research. These factors have been shown to have effects on placental functions, birth weight and fetal mortality.\textsuperscript{16-31} Therefore, there is a need to for local studies to evaluate the placentae of these patients and develop indigenous data based information for patients’ evaluation. The emerging legal climate as regard litigation makes it imperative to re-evaluate what we do with the placental postpartum as it may be the only reliable witness although it is often neglected.\textsuperscript{31}

This descriptive cross sectional study therefore is to determine the pathological changes in the placenta of Negroid women with preeclampsia/eclampsia. This will be compared with findings from various regions of the world. The findings will assist in designing evidence-based strategies for reducing the mortality and morbidity associated with preeclampsia/eclampsia, especially in Nigeria.
LITERATURE REVIEW

Preeclampsia/eclampsia constitutes severe forms of hypertensive disorders of pregnancy with high maternal and perinatal morbidity and mortality.\textsuperscript{2-3, 5-8} Maternal and perinatal mortality in the West African Sub-region is one of the highest in the World over.\textsuperscript{1} Pre-eclampsia is a hypertensive disorder unique to pregnancy. It is the occurrence of hypertension and proteinuria developing usually after the 20\textsuperscript{th} week of pregnancy, during labour and the puerperium in a previously normotensive, non-proteinuric woman,\textsuperscript{11} while eclampsia is defined as the occurrence of generalized tonic-clonic convulsion usually after the 20\textsuperscript{th} week of pregnancy, during labour and the first 14 days of the puerperium, in absence of epilepsy and other cerebral causes of convulsion.\textsuperscript{11}

Various risk factors have been identified in women with preeclampsia. These include genetic, obstetric and medical factors. Women whose mothers had preeclampsia, have a relative risk of 4 of developing preeclampsia while sisters of women with preeclampsia have a relative risk of 7 of developing preeclampsia compared to the general population.\textsuperscript{20} Also African-Americans (Negroids) have an increased risk compared to their Caucasian counterparts.\textsuperscript{20} The obstetric risk factors include primigravidity or nullipara, multiple gestation, previous preeclampsia, hydrops fetalis with a large placenta and hydatidiform mole. The medical risk factors are chronic hypertension, chronic renal disease, diabetes mellitus, anti-phospholipid syndrome and connective tissue disorder.\textsuperscript{20, 21} Also low socio-economic status have been identified by some authors as a risk factor.\textsuperscript{21}

The exact aetiology of pre-eclampsia remains unknown.\textsuperscript{11, 24} Different theories have been proposed, but none has explained all the pathological features of the disease.\textsuperscript{11,}
These theories include increased vascular reactivity, genetic and immunologic susceptibility, disseminated intravascular coagulation, imbalance of prostanoids production, abnormal production, abnormal trophoblastic invasion and excessive production of free radicals and lipid peroxides. However, it is believed that there is a genetic predisposition, which leads to a failure of the usual tolerance between the fetal allograft and the maternal decidua. This immunological intolerance leads to a failure of the second wave of cytotrophoblastic invasion of the maternal myometrial spiral arteries. As a result the myometrial spiral arteries remain muscular, undilated and responsive to vasomotor influences. The uteroplacental blood flow is therefore reduced as observed from Doppler volumetric studies. The resulting hypoxia leads to oxidative stress with the release of circulating factors from the placenta bed. The precise nature of these circulating factors remain speculative but are believed to include lipid peroxidation products, reactive oxygen species (superoxide anion and hydroxyl radicals), cytokines (tumour necrosis factor α and Interleukin 6), placental syncytiotrophoblast membrane, and vascular endothelial growth factors. All these circulating factors lead to widespread vascular endothelial damage. Vascular endothelial damage remains the key factor to the pathogenesis of preeclampsia, with the multi-systemic manifestation of the disease arising from this singular event. The endothelium is important in the modulation of vascular tone. Damaged endothelium leads to a reduction in the production of prostacycline and nitric oxide which are major vessel dilators while the production of thromboxane A2 and endothelin 1, which are vasoconstrictors, are increased.

The endothelial vascular damage leads to the multisystemic manifestation of the disease. The systemic vasoconstriction due to increased production of vasoconstrictions
leads to systemic hypertension. Thrombocytopenia and coagulopathy occurs as a result of platelet aggregation and fibrin mesh-work formation on the damaged endothelium. Altered vascular permeability leads to peripheral and pulmonary oedema. In the kidneys, the endothelial damage leads to proteinuria and acute renal failure. In the central nervous system, the increase vascular resistance and vasoconstriction leads to hypoxia with associated oedema – which causes the seizure, cerebrovascular accident, cortical blindness and retinal detachment. At the placenta bed, the reduction in the blood supply due to the increase vascular resistance lead to fetal growth restriction, hypoxia and abruption placenta.

Preeclampsia/eclampsia is associated with some changes in the placenta. Macroscopically the weight of the placenta is reduced or may be within normal limit. The oxygen supply of the villi is derived from the maternal blood. Little or no mixing of blood from individual maternal decidual arterioles occurs. Therefore these arterioles are end arteries. Occlusion of such blood vessel lead to infarction. Most placental infarcts are due to thrombotic occlusion of the maternal arteries. Infarction also occurs when the blood flow through the placental tissue overlying a retro-placental haematoma cut off by the latter. Extensive placental infarcts involving 60-70% of patients are commonly seen. In severe preeclampsia, more than 50% of the maternal surface area of placenta may be involved. Retro-placental clots may be present. Histological findings include accelerated maturation, reduced vascularity of the villi with fibromuscular hyperplasia and obliterator endarteritis of the fetal stem arteries. Oedema, stromal fibrosis, prominent and increased numbers of syncytial knots, cytotrophoblastic hyperplasia, trophoblastic basement membrane thickening, and excessive fibrinoid necrosis may also
be seen.\(^\text{13, 32}\) The basic and most consistent lesion is acute atherosis in the basal arteries in the decidual basalis and the spiral arteries in decidual parietalis. This is characterised by fibrinoid necrosis and lipid macrophages in the vessel wall and perivascular lymphocytic infiltration. A plausible immunopathological basis for this is the deposition of immunoglobulin-M (IgM), fibrinoid and complement factor 3 (C3) in the involved arteries.\(^\text{31-33}\) Although some investigators claim to have observed acute atherosis in chronic hypertension, systemic lupus erythematosis (SLE), diabetes mellitus (DM) and intrauterine growth restriction (IUGR),\(^\text{34,35}\) it appears that from a practical point of view, acute atherosis can be considered diagnostic of preeclampsia.\(^\text{32}\)

Some researchers here observed similar pathologies especially with placenta of fetus of IUGR without hypertension. There is elevation in interleukin-10, placental atrial natriuritic peptide, and plasma endothelin–1 concentration\(^\text{36}\). These findings suggest a possible role for abnormal immune activation and abnormal placentation in the genesis of this condition.\(^\text{37, 38}\) Fetal growth restriction alone or when coexisting with pre-eclampsia contributes towards significant reductions in volumetric and surface area of terminal villous and vascular features. IUGR is found to be associated with significant difference in volume, surface areas, length, diameters and shape of terminal and intermediate villi.\(^\text{39}\) Since IUGR can result from preeclampsia, the findings are difficult to interpret.\(^\text{39}\) The findings of these change in IUGR complicated by preeclampsia is obvious.\(^\text{39}\) How when preeclampsia is not present, there occurrence have been speculative. Same aetiologies have been found for these conditions, but why some develop only IUGR without preeclampsia have been elusive.\(^\text{14}\)
In chronic hypertension, the placenta shows the same findings as described for preeclampsia, with three exceptions: (1) the maternal vasculative in the decidua shows medial thickening and intimal hyperplasia – acute atherosis is seldom seen in chronic hypertension, (2) there is no excess of fibronoid necrosis of villi, and (3) the frequency and severity of obliteratorative endarteritis of system villi are less markers than in preeclampsia (therefore, the prominence of syncytial knots and should fibrosis of villi is also less marked). 40

The histopathologised changes observed in placenta of maternal diabetic patients include among others edema, variable maturity (normal in 9%, delayed or accelerated in 30% each), thickening of the trophoblastic basement membrane, variable vascularity (normal, hypovascularity or choriangiosis), and excessive fibrinoid necrosis of villi. The fetal stem arteries show thrombosis in about 10% of cases. 32 Obliteratorative endarteritis is also seen in 25% of class. No lesions are present in the decidual maternal arteries unless diabetes is complicated by pre-existing hypertension or super imposed preeclampsia.

In the HELLP syndrome, characterized by haemolysis, elevated liver enzymes, and low platelets which is more commonly seen in white women, 41 the placenta lesions are similar to those in preeclampsia. The lesions may be more severe, and the incidence of thrombosis of maternal arteries may be more frequent. A systematic description of placental findings in the HELLP syndrome is rare if not lacking in the hiteroture. 1, 13, 32 As a result, patients diagnosed or suspected to have HELLP syndrome were excluded from this study.

The outcome is worse for the mother and baby if preeclampsia/eclampsia occurs at a lower gestational age. Haemolysis, elevated liver enzymes and low platelet count
(HELLP) syndrome, disseminated intravascular coagulopathy (DIC) and IUGR are other complications related to the severity of the disease.\textsuperscript{31, 42} There is therefore every reason for early recognition of this condition and prompt intervention. The disease can progress very fast; therefore the management principle is often stabilisation and delivery by the most expeditious route.\textsuperscript{43} However, for patients that develop it at early gestation, the perinatal outcome is poor because of prematurity. Therefore some authorities advocate conservative management with antihypertensive and steroids. This practice is yet to gain wide acceptance.\textsuperscript{44, 45} Histological infarction is common in placentas from pregnancies complicated by severe PET but the prevalence is significantly greater in cases requiring delivery at earlier gestations, even when similar clinical indications for delivery were applied.\textsuperscript{46}

Preeclampsia/eclampsia is considered to be a disease with its origin at the placenta bed.\textsuperscript{32, 45} Most of the studies conducted were mainly on Caucasians.\textsuperscript{32, 45} This study was therefore designed to evaluate the placentae of Nigerian women with preeclampsia and eclampsia in Irrua. The study also determined the pattern of lesions in placentae of such women as related to the severity of the condition clinically.

**AIMS AND OBJECTIVES**

**The primary objectives are:**

1. To determine the pattern of placenta histopathological changes in preeclampsia and eclampsia among Nigerians in Irrua.

2. To determine the correlation between placenta histopathological findings and maternal and perinatal outcome.
The secondary objective is:

To compare this histopathological changes with those in previous studies which were in western countries.

MATERIALS AND METHOD

STUDY DESIGN - This was one point descriptive cross sectional study conducted in the Department of Obstetrics and Gynaecology of the Irrua Specialist Teaching Hospital. It is a tertiary care hospital and a referral centre for parts of Edo, Delta, Kogi and Ondo states. The department has 42 gynaecological and 48 obstetric beds and undertakes about 1,200 deliveries annually.

SAMPLE SIZE

The sample size was calculated based on a preeclampsia/eclampsia prevalence of about 2.5% in this environment using the statistical formula \( N = \frac{PQ}{(E/1.96)^2} \), which is used for cross sectional study.

\[
N = \frac{PQ}{(E/1.96)^2}
\]

Where:

N is sample size

P is a maximum known prevalence of the disease

q is 1-p (proportion of persons free from the disease)

E is the error margin allowable (0.05).

\[
0.025 \times 0.975
\]

\[
N = \frac{0.025 \times 0.975}{(0.05/1.96)^2} = 37
\]
Seventy eight (78) patients were recruited, 38 cases of preeclampsia/eclampsia and 40 cases of women with normal deliveries as control were recruited within 18 months the study was conducted. The control group was matched for age, parity and gestational age. This allowed for proper comparison of results.

**ETHICAL CONSIDERATION**

Approval for the study was obtained from the ethical committee of the Irrua Specialist Teaching Hospital. The study was carefully explained to the patients or the relations and their informed consent (consent form- appendix 1) obtained before being recruited into the study. The rights of the patients to participate or not were respected.

**METHOD**

Preeclampsia was defined as blood pressure (BP) equal to or greater than 140/90mmHg with proteinuria on a catheterised urine specimen of at least 1+, or a clean catch midstream urine 1+, (after patient had received standardized verbal instruction). Mild preeclampsia was defined as BP of 140/90mmHg and above but less than 160/110mmHg. Severe preeclampsia was defined as BP of 160/110mmHg and above with 2+ or more proteinuria. Eclampsia was defined as occurrence of convulsion in pregnant women after 20 weeks gestation in the absence of medical causes in a patient who is not a known epileptic.

**STUDY POPULATION**

**INCLUSION CRITERIA**

Placental tissue samples were collected immediately after delivery from all women diagnosed with preeclampsia or eclampsia during the period of the study. Informed consent was also obtained from the patients or the patient’s relation when the clinical
condition of the patient precluded obtaining informed consent. Only women with gestational ages greater than 20 weeks at delivery were recruited into the study. Placental samples were collected after vaginal or Caesarean delivery.

EXCLUSION CRITERIA

Exclusion criteria included non Nigerian and those of mixed races, chorioamnionitis, chronic hypertension, gestational diabetes, multiple gestation, pre-gestational diabetes (known diabetes), chronic renal disease, systemic lupus erythematosiis, sickle cell disease, antiphospholipid antibody syndrome, thyroid disease, cardiac disease, acute asthma requiring medication during pregnancy, pre-existing seizure disorder. Also all fragmented placentae were excluded.

The placentae were examined within 10 minutes of delivery, using a modified ‘American Family Physician’ (1998)\textsuperscript{48} guideline for placental examination (appendix 2). The placental membranes were trimmed to the edge of the placental disc and blood clots were removed from the maternal surface. The placentae were then placed into labelled plastic containers, containing 10% formaldehyde solution. The entire specimen remained submerged for a minimum of 24 hours to prevent autolysis from taking place. The specimens were then sent for pathological examination. A repeat macroscopic examination included weight, presence of infarcts, and haematoma. These findings were compared with previous examination in the delivery room. Cut sections were made and the cut surface examined.

LABORATORY PROCESSING OF SPECIMEN

Small sections of about 2cm ×2cm of specimen were taken from the different parts of the placenta. Care was taken to include section of membrane rolled edge and
maternal surface in the hope of finding an adequate number of maternal arteries [the
central portion, the edge including the membrane and the fetal surface]. These were
passed through alcohol solution of varying percentages to effect dehydration [70% for 3
hours then 90% for 3 hours and 10% absolute for 3 hours] the tissues were then
transferred into toluene solution for about 1 hour as clearing agent to remove the alcohol.
The tissues were then transferred from the clearing agent to a bath of molten paraffin wax
in an embedding oven. The clearing agent was eliminated from the tissues by diffusion
into the surrounding melted wax and the wax in turn diffuses into the tissues to replace
the molten paraffin and to ensure complete elimination of the clearing agent, this process
took about 24 hours. The tissues were then transferred into moulds {stainless steel} for
embedding with paraffin wax. Moulds of suitable size were used, tissues were carefully
positioned and plastic cassettes were placed and paraffin wax was poured until it reaches
the top. After cooling the mould was removed and tissues were sectioned using
microtome. Section was done into a floating out bath made up of 20% alcohol. Cut
section were picked up with hot plates {slides} for 30-60 minutes and placed in hot air
oven for 1-2 hours. The tissues were then passed through 2 jars of toluene solution to
remove the wax and washed in water before passing through 90% alcohol solution for 3
minutes and 100% alcohol for 2 minutes. The tissues were subsequently washed in water
for 2 minutes.

The tissues were then stained using haematoxylin and Eosin. Haematoxylin was
added for 5 minutes and washed in water. Then 1 % HCL was subsequently used to stain
for 3 minutes and washed in water. “Clearing” was done with xyline solution. The
specimen was mounted on slide and allowed to dry before viewing. The slides were examined under light microscope at magnification of 4, 10 and 40.\textsuperscript{49}

**DATA ANALYSIS**

Data were entered and stored in Microsoft excel Software and analysed by using excel statistical package. Proportions were compared by Chi-square where appropriate and the statistical significance of P-value will be P<0.05. Patients were excluded from the analysis where clinical information / specimens were not available.

**RESULTS**

There were a total of 38 patients recruited, out of these 33 (87%) patients had preeclampsia while 5 (13%) had eclampsia. The control group consisted of 40 women without pregnancy complications.

Table 1 shows the age distribution of the patients in relationship to diseased and control groups. Sixty-eight percent (26) were in their twenties (20-29 years) and only 5% (2) were below 20 years. The control group was selected to reflect similar age distribution. About half (45%) were primigravida while only 5.2% of the patients were grandmultiparous (table 2). There was no significant statistical relationship between the control and disease groups in relation to age.

Thirty three (87%) of the patients delivered at term (table 3). There was no case of post term delivery. Thirty five (87.5%) in the control group delivered at term. This was to allow for favourable comparism. The mean birth weight was 3.09 kg for the study group who delivered at term while that for the control group was 3.22 kg. The overall mean weight were 2.75 kg and 2.86 kg for diseased and control groups respectively. There was
no statistical difference in mean birth weight (p=0.25). The mean placental weight was 0.49 kg and 0.50 kg for study and control group respectively. The fetal/placental weight ratio showed a marginal reduction in the diseased group delivered at term, but no statistical difference. A mean ratio of 5.6:1 and 5.7:1 were obtained for diseased and control group respectively.

The macroscopic (gross) features of the placentae was as shown in table 4. Six (16%) of the placentae had no obvious macroscopic abnormalities. Thirty two (84.21%) of the placentae in the diseased group had both infarcts and haematoma (table 4) and the infarcts covered about 40% of the maternal surface area of the placentae in 60% of patients (table 5). There were significant statistical relationship between the presence of haematoma and infarcts in diseased and control groups (p<0.01 and 0.001). Only 10% of the control group had infarcts, these covered less than 5% of the maternal surface area.

All the placentae of the diseased group had histological abnormalities; mainly stromal fibrosis (79%) and acute atherosis (74%) (table 6). Stromal fibrosis, syncytial knots and acute atherosis were found more in the diseased group than in the control group, and were statistical significant on analysis (p<0.05, <0.01 and <0.001 respectively).

The relationship between the clinical severity of disease and the histological findings was as presented in table 7. Generally, the placentae in diseased group showed varying degree of pathological changes that were evaluated. The severity of proteinuria did not correlate with the histological changes. Patients with plus (+) proteinuria had similar histological changes as plus (++) and plus (+++). There was no statistical significance in the placental lesions (p=0.6385) (table7b1). Also, with regard to the
severity of the blood pressure, there were similar histological changes in mild and severe pre-eclampsia (P=0.0743) (table 7b2i). However, patients with eclampsia had severe histological changes. There were significant statistical relationship between severe preeclampsia and eclampsia (P=0.03) (table 7b2ii). Severe forms of placental changes (Table 7b2iii) were seen with severe preeclampsia and eclampsia. Stroma fibrosis and acute atherosis were the most common lesions. Placental infarcts and stromal fibrosis were present in all eclamptics.

There was a maternal mortality and a macerated still birth, both in the eclamptic group.

Table 1: PATIENT’S AGE

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TABLE 3: RELATIONSHIP BETWEEN GESTATIONAL AGE, MEAN BIRTH WEIGHT, MEAN PLACENTAL WEIGHT & BIRTH WIEGHT/ PLACENTAL RATIO

<table>
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<th>Disease</th>
<th>Control</th>
<th>Mean birth weight</th>
<th>Mean placental weight</th>
<th>BW/PW ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
<td>DX</td>
</tr>
<tr>
<td>20-29</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30-34</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>2.15</td>
</tr>
<tr>
<td>35-36</td>
<td>3</td>
<td>8</td>
<td>3</td>
<td>7.5</td>
<td>3.02</td>
</tr>
<tr>
<td>37-42</td>
<td>33</td>
<td>87</td>
<td>35</td>
<td>87.5</td>
<td>3.09</td>
</tr>
<tr>
<td>&gt;42</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>OVERALL MEAN</td>
<td>2.75</td>
<td>2.86</td>
<td>0.49</td>
<td>0.50</td>
<td>5.6</td>
</tr>
</tbody>
</table>

P=0.25 (overall mean birth weight)

Key- DX= Diseased, CONT= control
Table 4: MACROSCOPIC FEATURES OF PLACENTAE OF THE DISEASE AND CONTROL GROUP

<table>
<thead>
<tr>
<th>Features</th>
<th>Disease</th>
<th>Control</th>
<th>X²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct &amp; haematoma</td>
<td>32 (84.21%)</td>
<td>4 (10%)</td>
<td>9.4793</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Infarcts only</td>
<td>20 (52.63%)</td>
<td>4 (10%)</td>
<td>9.7228</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>No infarcts no haematoma</td>
<td>6 (16%)</td>
<td>36 (90%)</td>
<td>9.4793</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 5: DEGREE OF INFARCTS IN RELATION TO MATERNAL PLACENTAL SURFACE AREA

<table>
<thead>
<tr>
<th>Degree of infarcts in percentage of maternal surface area (%)</th>
<th>Disease</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>10 – 29</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>30 – 49</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>≥ 50</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 6: MICROSCOPIC FEATURES OF PLACENTAE IN DISEASED AND CONTROL GROUPS

<table>
<thead>
<tr>
<th>Histology</th>
<th>Disease</th>
<th>Control</th>
<th>X²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Stromal oedema</td>
<td>20</td>
<td>53</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>0.0002</td>
<td>&gt;0.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stromal Fibrosis</td>
<td>30</td>
<td>79</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>6.9824</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncytial knots</td>
<td>26</td>
<td>68</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>9.1020</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute atherosis</td>
<td>28</td>
<td>74</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>9.9746</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test of statistical significance- p <0.05

Table 7(a) EFFECTS OF THE SEVERITY OF PREECLAMPSIA/ECLAMPSIA ON THE PLACENTAE. (NUMBER OF PLACENTA AFFECTED AS A PERCENTAGE OF THE TOTAL WITH THE SAME CLINICAL STATE).

<table>
<thead>
<tr>
<th>Clinical state</th>
<th>Infarcts</th>
<th>haematoma</th>
<th>Stromal oedema</th>
<th>Stromal fibrosis</th>
<th>Syncytial knots</th>
<th>Acute atherosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>20</td>
<td>50</td>
<td>25</td>
<td>40</td>
<td>70</td>
<td>60</td>
</tr>
<tr>
<td>++</td>
<td>14</td>
<td>50</td>
<td>36</td>
<td>71</td>
<td>93</td>
<td>79</td>
</tr>
<tr>
<td>+++</td>
<td>4</td>
<td>75</td>
<td>50</td>
<td>50</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>--</td>
<td>---</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>15</td>
<td>47</td>
<td>27</td>
<td>53</td>
<td>80</td>
<td>73</td>
</tr>
<tr>
<td>Severe</td>
<td>18</td>
<td>44</td>
<td>33</td>
<td>50</td>
<td>72</td>
<td>67</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>5</td>
<td>100</td>
<td>40</td>
<td>60</td>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
Table 7(b1). DEGREE OF PROTEINURIA AND PLACENTAL CHANGES

<table>
<thead>
<tr>
<th>Degree of proteinuria</th>
<th>with infarcts</th>
<th>Without infarcts</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>++</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>+++</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

P= 0.6385

Table 7(b2i). Severity of blood pressure (bp) and placental changes

<table>
<thead>
<tr>
<th>Severity of BP</th>
<th>Infarcts</th>
<th>No infarcts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Severe</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

P=0.0743

Table 7(b2ii). Severity of blood pressure (bp) and placental changes

<table>
<thead>
<tr>
<th></th>
<th>Infarcts</th>
<th>No infarcts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

P=0.03

Table 7(b2iii) Severity of blood pressure (BP) and placental changes

<table>
<thead>
<tr>
<th></th>
<th>Acute atherosis</th>
<th>No acute atherosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

P=0.604


DISCUSSION

A total of 38 patients with preeclampsia/eclampsia were evaluated. The demographic variables presented are as in tables 1-3. The peak age range was 20-29 years (68%), primigravidae contributed the commonest parity (45%) and the peak gestational age was at term (87%). Primigravidae or nulliparous are known to be at high risk of developing preeclampsia.\textsuperscript{49-52} In a study conducted on 4302 nulliparous women who delivered at or beyond 20 weeks’ gestation, a fourth developed a pregnancy-related hypertensive disorder, and of all nulliparae, preeclampsia was diagnosed in 7.6 percent and severe disease developed in 3.3 percent.\textsuperscript{45}

The peak age of 20-29 years may be reflective of the fact that most deliveries in this environment occur at that age, and not necessarily of any special contribution of this age bracket to the aetiology of the disease. Thirty three (87%) of the patients in the diseased group delivered at term and no patient delivered before 30 weeks gestation (table 3. This confirms the fact that majority of the patients developed the disease in the late third trimester. Late onset of preeclampsia is associated with better outcome for the mother and the fetus.\textsuperscript{45} There was no case of post term delivery. Thirty five (87.5%) in the control group delivered at term. The mean birth weight was 3.09 kg for the study group who delivered at term while that for the control group was 3.22kg. The overall mean weight were 2.75kg and 2.86kg for diseased and control groups respectively. There was no statistical difference in mean birth weight (p=0.25). The weight of the fetus is often related to the maternal nutrition and utero-placental placental blood flow.\textsuperscript{45} In preeclampsia, the utero-placental blood flow is compromised and is the proposed mechanism of fetal growth restriction.\textsuperscript{13, 23, 31, 34} However, when preeclampsia develop in
late pregnancy, there will be no effect on birth weight. The mean placental weight was 0.49 kg and 0.50 kg for study and control group respectively. The fetal/placental weight ratio showed a marginal reduction in the diseased group delivered at term, but no statistical difference. A mean ratio of 5.6:1 and 5.7:1 were obtained for diseased and control groups respectively. This has been observed when preeclampsia developed close to term.

About 25% of normal term placenta contained infarcts involving <5% of the placental parenchyma, but their frequency of occurrence is increased in preeclampsia and extensive infarcts being present in 60-70% of patients with severe disease. In preeclampsia/eclampsia, 50% of placentae parenchyma may show infarcts however in this study 32 (84.21%) of placentae of patients with preeclampsia/eclampsia had infarcts. This is similar to what was found in various studies done in western countries. Also, the degree of infarcts (maternal surface area covered with infarcts) was less as infarcts covered only 30-50% of maternal surface area of placentae in majority of cases. Only 20% of patients had infarcts covering 50% or more of the surface area of their placentae in this study. From studies done in western countries however, majority had 50% of the surface area covered with infarcts. This may be due to the fact that the disease developed close to or at term. Early onset disease is associated with severe placental changes. Term preeclampsia is associated with minimal histopathological placental features regardless of clinical severity. Haematoma is not a consistent finding in isolation as none of the placentae had haematoma without infarcts. Haematoma and intervillous thrombi have been found to be the least common lesion in preeclampsia and eclampsia. The control group had infarcts in 10% of the placentae,
and this covered less than 5% of the maternal surface area. Minimal infarcts are not unusual findings in placentae delivered at term, and they are considered to be due to placental “aging”. In preeclampsia/eclampsia however, there is accelerated “aging”, and widespread infarcts are common findings. There are however, no histological or ultrastructural changes in the villi that can be considered as indicative of an aging process according to some authorities. 55, 56

Microscopic features observable under the light microscope include oedema, stromal fibrosis, syncytial knots and acute atherosis among others. 31, 32, 35, 45, 34 These changes were observed in more than 50% of placentae that were examined. Stromal fibrosis and acute atherosis respectively, were present in 79% and 74% of placentae of preeclamptic patients. Stromal fibrosis, syncytial knots and acute atherosis all showed statistical significance on analysis (p<0.05, <0.01 and <0.001 respectively). Placental oedema was the least observed microscopic lesion. Some of these features have been observed to a variable degree in other clinical conditions such as chronic hypertension, systemic lupus erythomatosus (SLE), diabetes mellitus (DM) and intrauterine growth restriction, 34, 35, but all of these conditions have not been described together in any of these deseases, 31 nevertheless they were excluded from the study to eliminate bias. The presence of these changes therefore is indicative of being induced by preeclampsia/eclampsia. In fact, from practical point of view, acute atherosis have been considered to be diagnostic of preeclampsia. 32

The level of proteinuria did not appear to have a direct relationship with the histological findings 57-59 Conventionally, significant proteinuria is defined as the presence of 2+ or more protein in midstream or catheter specimen urine, or 1+ proteinuria
on dipstike when the specific gravity is less than 1030.\textsuperscript{49} The use of dipstick may be a factor and it have been associated with significant false negative result.\textsuperscript{60} Diagnosis is significantly accurate when 24-hour urine protein excretion or protein/creatinine ratio are used.\textsuperscript{60} However, minimal proteinuria in the presence of severe hypertension is usually not ignored.\textsuperscript{37-59} The severity of proteinuria did not correlate with the histological changes. Plus (+) proteinuria had similar histological changes as plus (++) and plus (+++). There was no statistical significance in the placental lesions (p=0.6385, fisher’s exact) (table7b1). This study has shown the need for proper evaluation for proteinuria and minimal proteinuria should not be trivialized. Proteinuria is a late feature of the disease and is usually preceded by changes at the placental bed and eclampsia may occur without proteinuria.\textsuperscript{45} Most patients with proteinuria will have glumeruloendotheliosis on kidney biopsy.\textsuperscript{45, 61} Proteinuria is a reflection of renal tubular epithelial cell injury.\textsuperscript{62}

Although hypertension is a requisite to diagnosing preeclampsia, absolute blood pressure alone is not always a dependable indicator of its severity.\textsuperscript{45, 61} The histological findings in mild and severe preeclampsia were similar. This finding have been noted by other researchers especially when preeclampsia occurs closed to or at term.\textsuperscript{46} The differentiation between mild and severe preeclampsia therefore can be misleading because in clinical practice a mild disease may progress rapidly to severe disease.\textsuperscript{61, 63}

Most placental infarcts are due to thrombotic occlusion of the maternal arteries. Infarction also occurs when the blood flow through the placental tissue overlying a retro-placental haematomas is cut off by the latter. In uncomplicated pregnancy, with good placental reserve, no compromise of placental function may be seen when as much as 30\% of the placental tissues is infarcted,\textsuperscript{64} however, a diseased placenta , such as in
preeclampsia, can withstand the loss of only 15-20% of the villi due to infarction.\textsuperscript{40} Fetal compromise therefore is generally the rule and perinatal mortality is high as reflected in a maternal mortality and a perinatal mortality recorded among the eclamptics. This gave a mortality ratio 2800/100,000, which is unacceptably high. If the mortality is expressed per number of eclamptic patients it will be one death for every five eclamptics. There is increased incidence of interventional delivery and this has been noted to be contributory to the morbidity and mortality for both mother and baby.\textsuperscript{63,65-69} It is obvious therefore that preeclampsia and eclampsia are major contributors to maternal and perinatal mortality in developed and developing countries.\textsuperscript{3,5-763,65-70}

This study has shown that preeclampsia/eclampsia is associated with significant macroscopic and microscopic changes in the placenta. These changes are similar in forms and pattern to those observed among Caucasians. There was no obvious reduction in placental size in the study group; this could be due to the facts that most of the patients had late onset disease.\textsuperscript{53} Also, the severity of infarcts which was noted to be less could be due to the same reason,\textsuperscript{53} this however does not translate to a better pregnancy outcome. The ultra structural changes were similar. However, the effects of other variables such the neonatal facility, level of maternal care and socio-demographic status of the patients were not evaluated in this study. A study of associations between the incidences of placentas bearing each of the three common focal macroscopic placental lesions, infarcts, intervillous fibrin plaques (IVFP), and intervillous thrombi (IVT) and 31 socio-demographic and pregnancy-related factors showed no associations.\textsuperscript{71}

The main limitation in this study was the small sample size. A sample size of about a thousand or more will enable a definite conclusion to be drawn. Also, financial
grant would have reduced the burden on the researcher. Finally, an electron microscopy and immunohistopathology will be invaluable in identifying definite lesion which cannot be visualized under light microscope.

In conclusion, this study will remain a stepping stone for more studies on placenta changes in preeclampsia/eclampsia among Nigeria women which will enable us build our data based information for local references.

REFERENCES


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57. Management of severe pre-eclampsia and eclampsia, Royal College of Obstetricians and Gynaecologists (2006)


APPENDIX 1

CONSENT FORM

DR EMMANUEL HERO GBEJEGBE

DEPARTMENT OF OBSTETRICS & GYNAECOLOGY

IRRUA SPECIALIST TEACHING HOSPITAL, IRRUA

PROJECT TITLE: PLACENTAL CHANGES IN PATIENTS WITH

PREECLAMPSIA/ECLAMPSIA AS SEEN IN IRRUA SPECIALIST

TEACHING HOSPITAL, IRRUA EDO STATE.

RESEARCHER: DR EMMANUEL HERO GBEJEGBE, (MBBS BENIN)

I hereby confirm that:

1. I have been counselled and I understand the nature of the research.

2. I have had the opportunity to ask questions.

3. I understand that my participation is voluntary and the information from the study
   will be kept confidential.

4. I agree to take part in the above study.

---------------------------------------------
---------------------------------------------
Researcher Name of participant or patient’s relation
Date---------------- Date---------------------------

---------------------------------------------
---------------------------------------------
Signature Signature
APPENDIX 2

PLACENTAL EXAMINATION FORM

DATE:

HOSPITAL NO:

NAME:

AGE:

PARITY:

GESTATIONAL AGE AT DELIVERY:

MAXIMUM BLOOD PRESSURE:

DEGREE OF PROTEINURIA:

DIAGNOSIS:

BIRTH WEIGHT:

PLACENTAL WEIGHT:

DEGREE OF INFARCTS (as % of maternal surface area):

HAEMATOMA:

MOTHER’S STATE AT DISCHARGE: Alive       Dead

BABY’S STATE AT DISCHARGE: Alive       Dead