Histomorphometric Survey of Placentas of HIV-positive Mothers in Relation to their Clinical Stage in a Teaching Hospital in Uyo, South-South Nigeria

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Abstract

Objectives: HIV infection in pregnancy affects the mother, her placenta and foetus resulting in perinatal/maternal morbidity and mortality. Studies show that HIV-positive mothers have several placental morphological changes. This study aimed to describe the histomorphometric parameters/lesions of placentas of HIV-positive mothers in Uyo, Akwa Ibom State, Nigeria.

Methods: We studied 144 pregnant mothers (48 HIV-positive as tests vs 96 HIV-negative as controls) in this study. Their placentas (foetal membrane, umbilical cord, and placental disk) were collected post-delivery and systematically evaluated (grossly/microscopically) to determine their range of histomorphometric placental parameters/lesions. Relevant obstetric data were gotten from their case notes.

Results: The tests delivered more through C-section than the controls (52.1% vs 31.3%), having respective mean birth weights of 2.84 ± 0.75 vs 3.16 ± 0.69 kilograms (p value = 0.004). Their respective mean placental weights were 575 ± 190.15 vs 664.69 ± 167.42 grams (p value = 0.003), with mean placenta-birth weight ratio of 20.17 ± 4.87 vs 20.54 ± 4.57% (p value = 0.33). The tests' placental foetal membranes, umbilical cords and disks mainly displayed acute chorioamnionitis (47.9%), acute umbilical phlebitis (14.6%) and villous vasculopathy (33.3%) respectively. The tests had higher stage/grade of placental inflammation than the controls. The tests had two Stage 4 HIV disease state cases presenting with most severe form of placental inflammatory lesions.

Conclusions: The commonest placental histomorphometric parameters/lesions were acute chorioamnionitis, acute umbilical phlebitis and acute intervillositis. There was no significant association of HIV/AIDS disease stage with the most severe forms of placental inflammatory lesions.

Keywords: Placenta, HIV/AIDS, pregnancy, funisitis, chorioamnionitis, intervillositis

Introduction

HIV infection in pregnancy affects the mother, her placenta and foetus, with progressive viral disease, altering the course of the pregnancy and resulting in perinatal or maternal morbidity and mortality.[1–8] Notably, based on its natural history, HIV infection can be categorised into four stages, where stage 1 is asymptomatic disease while stage 4 is Acquired Immunodeficiency Disease Syndrome (AIDS).[7,9,10] Studies have shown that HIV-positive mothers have several placental morphological changes such as greenish

yellow discolouration of foetal membrane, reduced placental weight, chorioamnionitis, villitis, choriodeciduitis, funisitis, decidual cell necrosis, villous vasculopathy, etc.[3,6,11–18] Studies have also shown that these mothers are at increased risk of adverse perinatal outcomes, including stillbirth, low birth weight (LBW), preterm birth (PTB), infant mortality from pneumonia or neonatal sepsis, and mother-to-child transmission of HIV (MTCT).[3,19–27] Importantly, Akwa Ibom State (our study location) had the second highest HIV prevalence in Nigeria, particularly among pregnant women. The prevalence of HIV in Akwa Ibom State has ranged from 10.9% to 4.8% in contrast to Nigerian prevalence of 4.1% since 2010 till date.[28–36]

However, although numerous studies have shown profound adverse histomorphometric parameters and lesions in the placenta of HIV-positive mothers with associated adverse perinatal outcomes, to the best of our knowledge, these placental histomorphometric parameters and lesions have not been surveyed or reported in Uyo, Akwa Ibom State and Nigeria, in general. This obvious gap in knowledge underscores the medical importance of our study and provides an immediate rationale for it.

Therefore, in this study we aimed to survey the range of histomorphometric parameters and lesions in the placenta of HIV-positive mothers and to relate these parameters/lesions with their stage of HIV disease in Uyo, Akwa Ibom State, Nigeria. Also, we aimed to compare our findings with those of other similar studies conducted elsewhere. As a deliverable, we hope that our findings will inform clinical evaluation and management of foeto-maternal complications of HIV infection in affected women in Akwa Ibom State and Nigeria and thus help in the attainment of the third goal of the United Nations' Sustainable Development Goals (SDGs).[37,38]

Methods

This study was a prospective cross-sectional hospital-based analytical study, involving two study groups: the test (cases) and control groups. This study was conducted at the University of Uyo Teaching Hospital (UUTH), Uyo, Akwa Ibom State, in the departments of Obstetrics and Gynaecology, and Histopathology.

UUTH, Uyo is a 500-bed tertiary healthcare facility in the South-South region of Nigeria.

The sampling method was a convenient sampling technique; samples (relevant historical data from subjects' case notes and their placentas) were collected for six consecutive months, from December 2015 to May 2016.

Inclusion Criteria: All consenting HIV-positive (test group) and HIV-negative (control group) pregnant women, any time from 28 weeks of gestation before disposal of their placenta, who came to the hospital for obstetrics/delivery care, within the six months duration of this study.

Exclusion Criteria: All non-consenting HIV-positive and HIV-negative pregnant women within the study period. Furthermore, all HIV-negative pregnant women with grossly abnormal placenta, such as placental tumours as well as those who delivered before 28 weeks of gestation.

General Assessment of Subjects: The case notes of all consenting pregnant women (HIV-positive or HIV-negative status) were accessed by the investigator during the delivery period of each index subject. Important data regarding relevant historical and physical examination findings were extracted from these case notes. All collected data were recorded in the "data collection pro forma for extracting data from the mother's case note", for each subject.

Histomorphometrical Assessment of the placenta (for both groups):

a. ***Sample collection***: At the third (3rd) stage of labour, the labour ward staff takes delivery of the placenta, which is then collected by the principal investigator for labelling and placement in a wide-mouth bucket containing 10% neutral buffered formalin.

b. ***Grossing (Macroscopy)***: The three main placental components: the foetal membranes, umbilical cord and placental disk, were examined systematically after 48 hours of fixation (consistent with handling of an infectious specimen).[2,39–44] Weighed after examining and removing clots, membranes and cords.[2,43,45–47]

c. ***Sample Section Procedure***:

i. Umbilical cord: two cassettes

ii. Foetal membrane roll: two cassettes

iii. Placental disk/parenchyma: six cassettes. More cassettes were submitted in cases with numerous lesions to sample all lesion types.[2,39,41,42,44]

d. ***Fixation, tissue processing, embedding, microtomy and staining*** were performed in accordance with standard histological techniques, and Haematoxylin and Eosin (H&E) staining was used.

e. ***Microscopy***: A CX22 Olympus light microscope was used to carry out systematic Histopathologic evaluations of the three components of the placenta (umbilical cord, foetal membrane, and placental disk). The terminology/criteria used for placental diagnosis in this study was according to the schemata in the studies by Huettner PC, Schwartz DA et al and Redline RW et al.[2,12,48–50]

Cost and Ethical Considerations: Ethical approval for this study was obtained from UUTH Health Research Ethics Committee (UUTH/AD/S/96/VOL.XII/115). Patient confidentiality was protected, and informed consent was obtained.

Data Analysis: Data generated/collected in this study were written in a "Patient Case Report" form and transferred into Microsoft Office Excel 2013 and SPSS version 20.0 statistical software for statistical analysis. Additionally, we calculated the placental-birth weight ratio (PBWR), according to Perry IJ et al and Panti AA et al formulae, for both groups as a ratio of placental weight to birth weight multiplied by 100.[51,52] We used cross tabulation, Pearson's chi-square test, likelihood ratio, Fisher's exact test and linear-by-linear association to test for statistical differences between the variables of both groups. Statistical significance was set at a ***P*** value of ≤ 0.05. The results were reported as text, tables, charts, graphs, and photomicrographs.

Results

A total of 144 mothers were admitted to this study (48 HIV-positive mothers as tests and 96 HIV-negative mothers as controls). The tests' age range, mean, median and mode age were 21 - 38 years, 30.23 ± 4.32, 30 and 29 years respectively. The controls' age range, mean, median and mode age were 19 - 41 years, 29 ± 4.36, 28.5 and 28 years respectively (**Table 1**). The tests delivered 52.1% of their babies through caesarean section while the controls delivered 66.6% of their babies through spontaneous vaginal delivery (**Table 1**). The tests delivered 95.8% babies alive, with 4.2% macerated still births, while the controls delivered 94.8% babies alive, with 4.2% fresh still births (**Figure 1**). The mean, median and mode of birth weight of tests' babies were 2.84 ± 0.75, 2.95 and 3.3 kg, with 26.5% of their babies having low birth weight, while the controls' mean, median and mode of birth weight were 3.16 ± 0.69, 3.2 and 3.2 kg, with 9.4% of their babies having low birth weight; giving a statistically significant p-value (0.004) (**Table 1**).

Table 1: Frequency distribution of mothers' age, mode of delivery, birth weight, placental weight and placental-birth weight ratio between the test and control populations

	Test group (n = 49)		**Control group (n = 96)**		**Statistical significance**	
Status	Frequency	Percentage (%)	Frequency	Percentage (%)	P-value	Chi-squared value
Age group						

< 16	0	0	0	0		
16 - 23	3	6.25	7	7.37		
24 - 31	25	52.08	61	64.21		
32 - 34	10	20.83	12	12.63		
35 - 40	10	20.83	14	14.74		
41 - 45	0	0	1	1.05		
> 45	0	0	0	0		
Total	48	100	95	100		
Mode of delivery						
Caesarean section	25	52.1	30	31.3	0.47	4.8
Instrumental	0	0	2	2.1		
Vaginal	23	47.9	64	66.6		
Total	48	100	96	100		
Birth weight (kg)						
< 2.5	13	26.5	9	9.4	0.004	8.45
2.5 - 4.5	36	73.5	87	90.6		
> 4.5	0	0	0	0		
Total	49	100	96	100		
Placental weight (grams)						
250 - 399	6	12.5	0	0	0.003	17.96
400 - 549	11	22.9	12	12.7		
550 - 699	17	35.4	36	38.3		
700 - 849	12	25	34	36.2		
850 - 999	1	2.1	9	9.6		
> 999	1	2.1	3	3.2		
Total	48	100	94	100		
Placental-birth weight ratio (PBWR)						
< 15.8	3	6.1	6	6.5	0.33	2.23
15.8 - 20.6	28	57.2	42	45.2		
> 20.6	18	36.7	45	48.3		
Total	49	100	93	100		

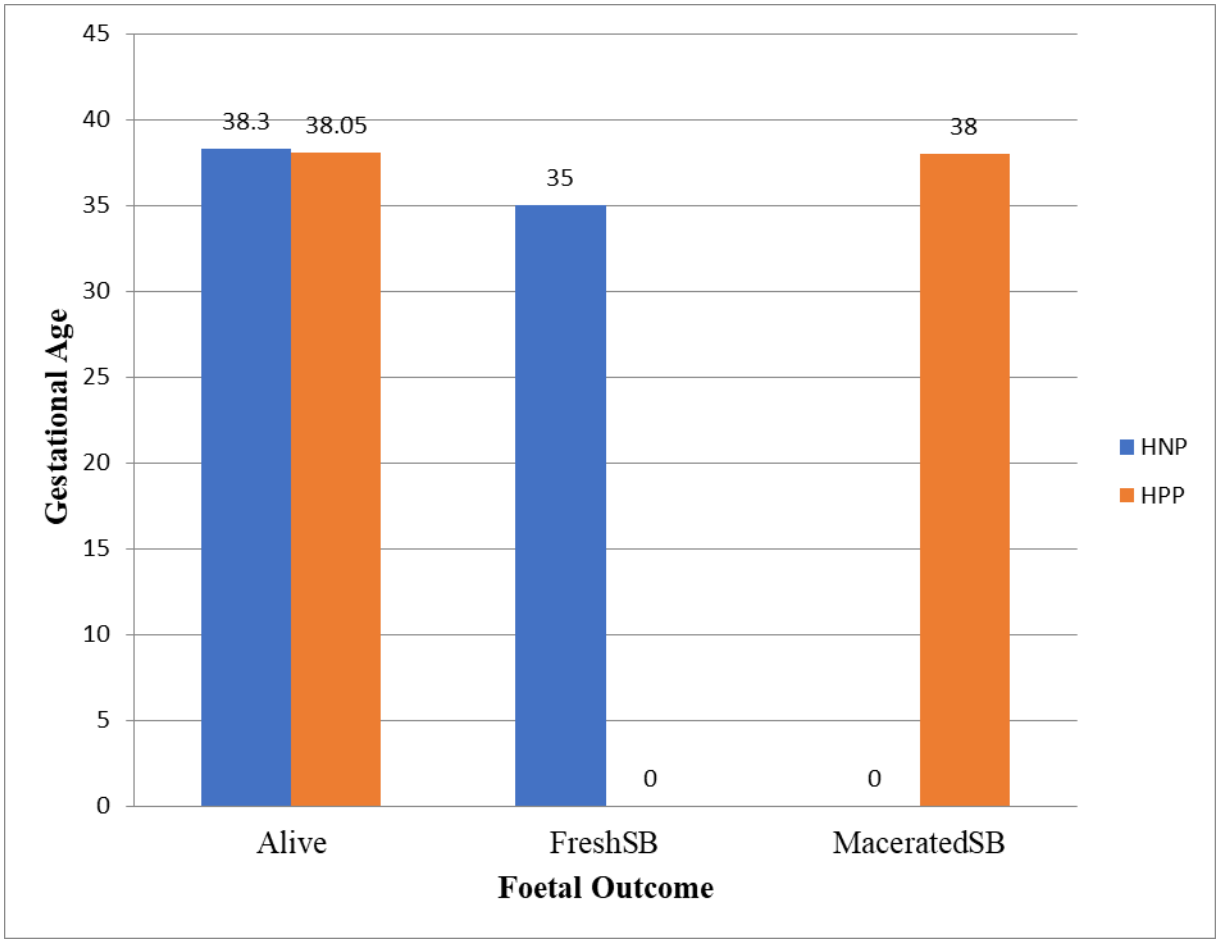

Figure 1: Frequency distribution of foetal outcome in relation to gestational age in both the test and control groups. FreshSB: Fresh Stillbirth; MaceratedSB: Macerated Stillbirth; HNP: HIV-negative (control) group; HPP: HIV-positive (test) group.

The tests' mean, median and mode of placental weight were 575.51 ± 190.15, 550 and 600 grams, while the controls' mean, median and mode of placental weight were 664.69 ± 167.42, 650 and 700 grams; giving a statistically significant p-value (0.003) (**Table 1**). The tests' mean, median and mode of placenta-birth weight ratio were 20.17 ± 4.87, 19.7 and 20, while the controls' mean, median and mode of placenta-birth weight ratio were 20.54 ± 4.57, 20.36 and 20; giving a statistically non-significant p-value (0.33) (**Table 1**).

Grossly, the tests' foetal membrane displayed greenish yellow to brown discolouration in 60.4% cases, whereas the controls displayed this discolouration in 45.2% cases (**Table 2, Figure 3a**). The tests' commonest foetal membrane histopathologic lesion was acute chorioamnionitis (47.9%) while the controls' commonest foetal membrane histopathologic lesion was chronic choriodeciduitis [chronic inflammatory lesion involving the chorion and decidua] (72.6%); giving statistically significant p-values for acute choriodeciduitis, chronic choriodeciduitis, decidual cell necrosis [zones of accidental cell death in the decidua], and acute chorioamnionitis (**Table 2, Figure 4a**).

Table 2: Placental Histopathological Changes and Lesions in the Foetal Membrane using Huettner PC, Schwartz DA et al and Redline RW et als schemata in the test and control groups

	Test group ***(n = 48)***		**Control group** ***(n = 96)***		**p-value**
Histopathological changes and lesions	Number present	Number absent	Number present	Number absent	

Greenish yellow to brown discolouration of membranes	29 (60.4%)	19 (39.6%)	43 (45.2%)	52 (54.7%)	0.08
Acute choriodeciduitis	20 (41.7%)	28 (58.3%)	8 (8.4%)	87 (91.6%)	0.00[a]
Chronic choriodeciduitis	13 (27.1%)	35 (72.9%)	69 (72.6%)	26 (27.4%)	0.00[b]
Acute on chronic choriodeciduitis	3 (6.3%)	45 (93.8%)	10 (10.5%)	85 (89.5%)	0.40
Decidual cell necrosis	13 (27.1%)	35 (72.9%)	6 (6.3%)	89 (93.7%)	0.001[c]
Chronic chorioamnionitis	4 (8.3%)	44 (91.7%)	5 (5.3%)	90 (94.7%)	0.47
Acute chorioamnionitis	23 (47.9%)	25 (52.1%)	20 (21.1%)	75 (78.9%)	0.001[d]
Acute on chronic chorioamnionitis	0 (0%)	48 (100%)	1 (1.1%)	94 (98.9%)	0.70

➢*Note: "a, b, c and d" showed statistically significant difference ($p \leq 0.05$) between the test and control groups. These differences reveal strong association with HIV infection in "a, c and d", but strong dissociation with HIV infection in "b".*

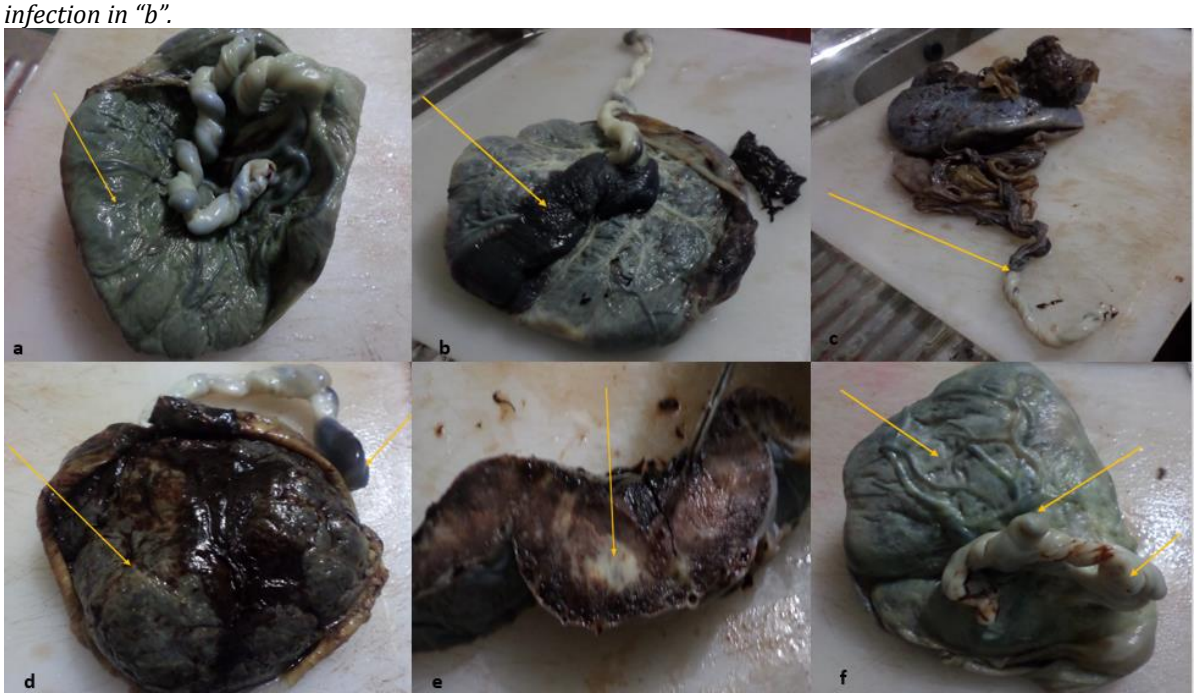

Figure 3: Gross morphology photographs of the placentas of (a) 36-year-old HIV-positive mother showing meconium (greenish brown) staining of the foetal surface, (b) 30-year-old HIV-negative mother showing massive chorionic plate haematoma of the foetal surface of the placental disk, (c) 24-year-old HIV-positive mother showing velamentous insertion of the umbilical cord to the foetal membrane instead of the foetal surface of the placental disk, (d) 37-year-old HIV-positive mother showing massive umbilical cord haematoma as well as maternal surface of the placental disk, (e) 19-year-old HIV-negative mother showing an area of massive infarction of the cut surface of the placental disk, and (f) 24-year-old HIV-positive mother showing two false knots of the umbilical cord as well as opaque greenish grey maternal surface of the placental disk..

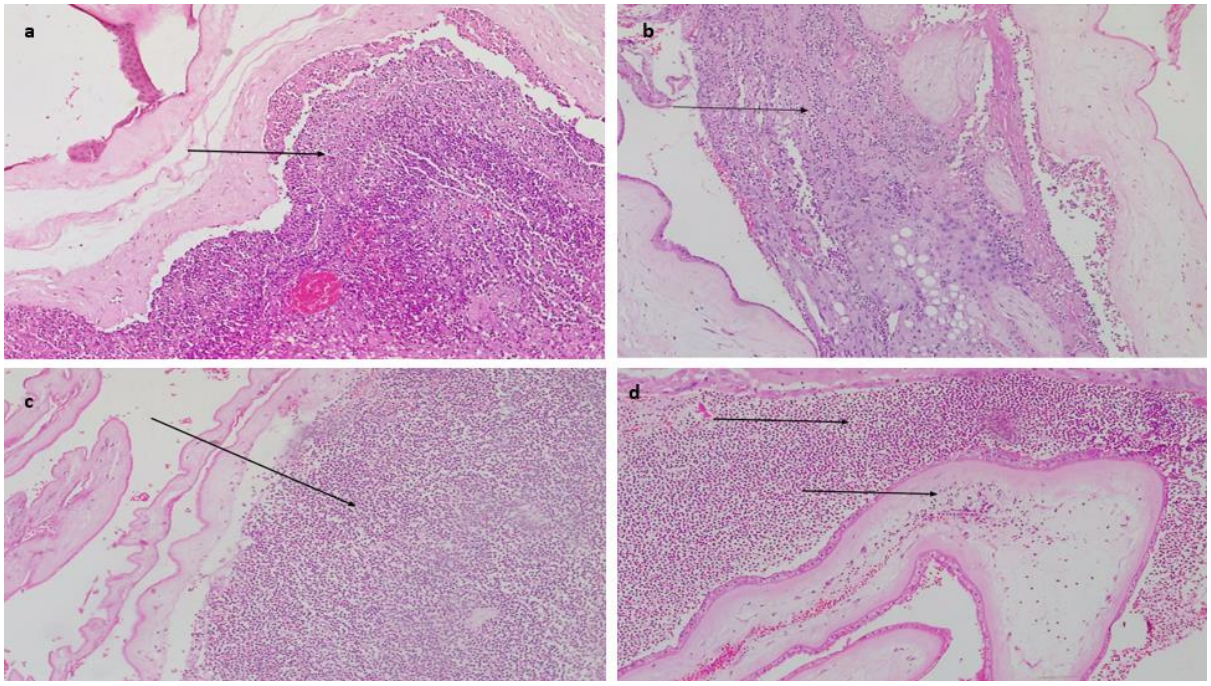

Figure 4: Photomicrographs of the Foetal Membrane of (a) 34-year-old HIV-Positive mother showing Acute Suppurative Necrotizing Chorioamnionitis (Stage 3 Grade 2) with Acute Choriodeciduitis [H&E x 100], (b) 29-year-old HIV-positive mother showing acute choriodeciduitis, [H&E x 100], (c) 24-year-old HIV-positive mother showing acute suppurative chorioamnionitis, [H&E x 100], and (d) 22-year-old HIV-positive mother showing severe acute suppurative deciduitis with mild acute chorionitis, [H&E x 100].

The tests' commonest umbilical cord histopathologic lesion was acute umbilical phlebitis (14.6%) while the controls' commonest umbilical cord histopathologic lesion was acute funisitis (5.3%); giving statistically non-significant p-values (**Table 3**).

Table 3: Placental Histopathological Lesions in the Umbilical Cord using Huettner PC, Schwartz DA et al and Redline RW et als schemata in test and control groups

	Test group ***(n = 48)***		**Control group** ***(n = 96)***		**p-value**
Histopathological lesions	Number present	Number absent	Number present	Number absent	
Chronic umbilical vasculitis	1 (2.1%)	47 (97.9%)	1 (1.1%)	94 (98.9%)	0.62
Acute umbilical phlebitis	7 (14.6%)	41 (85.4%)	4 (4.2%)	91 (95.8%)	0.06
Acute umbilical panvasculitis	2 (4.2%)	46 (95.8%)	0 (0%)	95 (100%)	0.11
Acute funisitis	5 (10.4%)	43 (89.6%)	5 (5.3%)	90 (94.7%)	0.30

➢*Note: there was no statistically significant difference ($p \leq 0.05$) between the test and control groups. These differences reveal weak association with HIV infection.*

The tests' commonest placental disk histopathological lesion was villous vasculopathy (33.3%) while the controls' commonest placental disk histopathological lesion was massive perivillous fibrin deposition (38.9%); giving statistically significant p-values for chronic villitis, chronic intervillositis, acute intervillositis, maternal floor infarct and intervillous thrombohaematoma (**Table 4, Figures 6a and 6b**).

Table 4: Placental Histopathological Lesions in the Placental Disk using Huettner PC, Schwartz DA et al and Redline RW et als schemata to compare the test and the control groups

	Test group ***(n = 48)***	**Control group** ***(n = 96)***	**p-value**

Histopathological lesions	Number present	Number absent	Number present	Number absent	
Chronic villitis	0 (0%)	48 (100%)	17 (17.9%)	78 (82.1%)	0.002[a]
Chronic intervillositis	0 (0%)	48 (100%)	14 (14.7%)	81 (85.3%)	0.005[b]
Acute villitis	3 (6.3%)	45 (93.8%)	2 (2.2%)	93 (97.8%)	0.20
Acute intervillositis	15 (31.3%)	33 (68.8%)	6 (6.3%)	89 (93.7%)	0.00[c]
Villous vasculopathy	16 (33.3%)	32 (66.7%)	20 (21.1%)	75 (78.9%)	0.10
Haemorrhagic endovasculitis	0 (0%)	48 (100%)	0 (0%)	95 (100%)	
Villous stromal fibrosis	0 (0%)	48 (100%)	1 (1.1%)	94 (98.9%)	1.00
Infarction	14 (29.2%)	34 (70.8%)	35 (36.8%)	60 (63.2%)	0.46
Cytotrophoblastic hyperplasia	0 (0%)	48 (100%)	0 (0%)	95 (100%)	
Massive perivillous fibrin deposition	13 (27.1%)	35 (72.9%)	37 (38.9%)	58 (61.1%)	0.16
Maternal floor infarct	2 (4.2%)	46 (95.8%)	17 (17.9%)	78 (82.1%)	0.02[d]
Retroplacental haematoma	2 (4.2%)	46 (95.8%)	8 (8.4%)	87 (91.6%)	0.55
Acute chorionitis of chorionic plate	4 (8.3%)	44 (91.7%)	5 (5.3%)	90 (94.7%)	0.48
Acute chorionic plate vasculitis	5 (10.4%)	43 (89.6%)	4 (4.2%)	91 (95.8%)	0.28
Intervillous thrombohaematoma	5 (10.4%)	43 (89.6%)	0 (0%)	95 (100%)	0.001[e]

➢*Note: "a, b, c, d and e" showed statistically significant difference ($p \leq 0.05$) between the test and control groups. These differences reveal strong association with HIV infection in "c and e", but strong dissociation with HIV infection in "a, b and d".*

On further evaluation of these inflammatory lesions involving the foetal membrane, umbilical cord, and chorionic plate of the placenta disk, we found that the tests had the most severe forms (stage/grade) of acute chorioamnionitis and acute funisitis (20.83%), while the controls had none (0%) of the most severe forms of acute chorioamnionitis or acute funisitis; giving statistically significant p-values for acute chorionitis (stage 1, grade 1), acute suppurative chorioamnionitis (stage 2, grade 1), acute suppurative necrotizing chorioamnionitis (stage 3, grade 2), acute choriodeciduitis, chronic choriodeciduitis, acute panvasculitis (stage 2, grade 1) and placental membrane inflammation (PMI) (**Table 5, Figure 4a, Figure 5a**).

Table 5: Grading and Staging of Placental Inflammatory Lesions of the Foetal Membrane, Umbilical Cord and Chorionic Plate using Huettner PC, Schwartz DA et al and Redline RW et als schemata in the test group in comparison with the control group

	Test group *(n =48)*		**Control group *(n = 96)***		
Histopathological lesions	Present (%)	Absent (%)	Present (%)	Absent (%)	P-value
Acute chorionitis (stage 1, grade 1)	7 (14.58)	41 (85.42)	2 (2.08)	94 (97.92)	0.003[a]
Acute chorioamnionitis (stage 2, grade 1)	4 (8.33)	44 (91.67)	3 (3.13)	93 (96.87)	0.171
Acute suppurative chorioamnionitis (stage 2, grade 2)	0	48 (100)	12 (12.5)	84 (87.5)	0.011[b]
Acute suppurative necrotizing chorioamnionitis (stage 3, grade 2)	10 (20.83)	38 (79.17)	0	96 (100)	0.000[c]
Chronic chorioamnionitis	0	48 (100)	5 (5.21)	91 (94.79)	0.108
Acute choriodeciduitis	23 (47.92)	25 (52.08)	3 (3.13)	93 (96.87)	0.000[d]
Acute on chronic choriodeciduitis	3 (6.25)	45 (93.75)	8 (8.33)	88 (91.67)	0.657
Chronic choriodeciduitis	17 (35.42)	31 (64.58)	69 (71.88)	27 (28.12)	0.000[e]
Acute chorionitis of chorionic plate	6 (12.5)	42 (87.5)	6 (6.25)	90 (93.75)	0.201
Acute chorionic plate vasculitis	5 (10.42)	43 (89.58)	4 (4.17)	92 (95.83)	0.144

Acute phlebitis (stage 1, grade 1)	4 (8.33)	44 (91.67)	3 (3.13)	93 (96.87)	0.171
Chronic phlebitis	0	48 (100)	1 (1.04)	95 (98.96)	0.478
Acute panvasculitis (stage 2, grade 1)	2 (4.17)	46 (95.83)	0	96 (100)	0.044[f]
Acute funisitis (stage 3, grade 1)	7 (14.58)	41 (85.42)	6 (6.25)	90 (93.75)	0.099
Acute necrotizing funisitis (stage 3, grade 2)	1 (2.08)	47 (97.92)	0	96 (100)	0.156
Placental membrane inflammation	13 (27.08)	35 (72.92)	7 (7.29)	89 (92.71)	0.001[g]

Note: "a, b, c, d, e, f and g" showed statistically significant difference ($p < 0.05$) between the test and control groups. These differences reveal strong association with HIV infection in "a, c, d, f and g", but strong dissociation with HIV infection in "b and e".

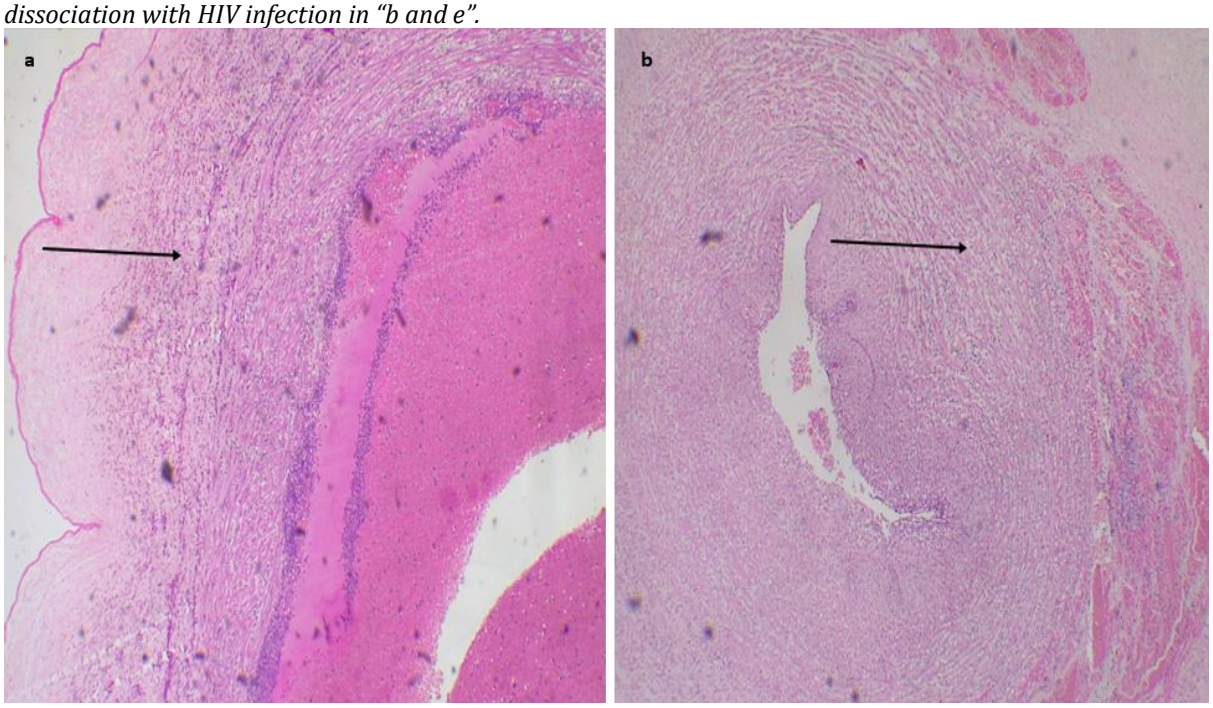

Figure 5: Photomicrographs of the Umbilical cord of the placenta from (a) 32-year-old HIV-positive mother showing Acute Funisitis (Stage 3 Grade 2), [H&E x 100], and (b) 24-year-old HIV-positive mother showing acute phlebitis, [H&E x 40].

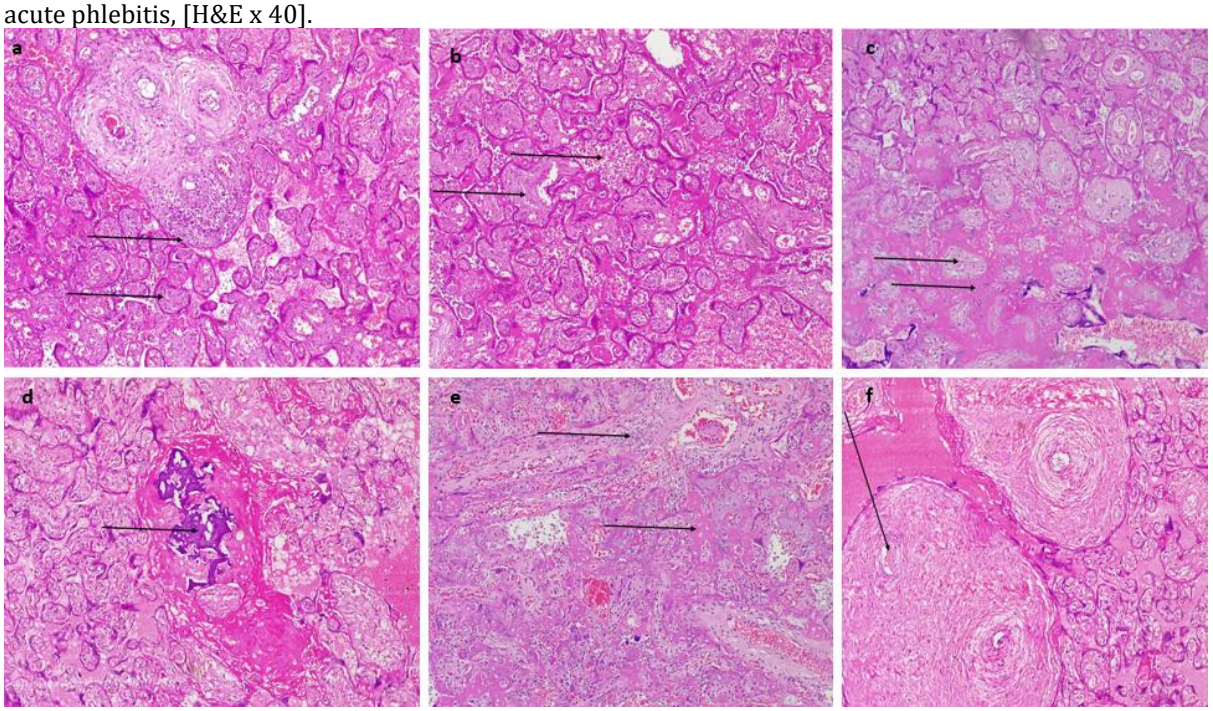

Figure 6: Photomicrographs of the placental disk of (a) 32-year-old HIV-positive mother showing Acute Villitis as well as Acute Vasculitis of Stem Villous [H&E x 100], (b) 32-year-old HIV-positive mother showing Infarction as well as Acute Intervillositis [H&E x 100], (c) 35-year-old HIV-positive mother showing infarcted villi and massive perivillous fibrin deposition, [H&E x 100], (d) 29-year-old HIV-positive mother showing calcification and massive perivillous fibrin deposition, [H&E x 100], (e) 30-year-old HIV-positive mother showing acute villitis and fibrin deposition, [H&E x 100], and (f) 29-year-old HIV-positive mother showing chronic vasculitis with obliterative features, [H&E x 100].

Importantly, majority of the tests' subjects (66.67%) were in stage 1 of HIV disease, and only two patients were in stage 4 (4.17%) disease (**Table 6**). Both tests' subjects with stage 4 HIV disease were found to have greenish yellow to brown discolouration of the foetal membrane, acute chorioamnionitis, acute choriodeciduitis and decidual cell necrosis (**Table 6**). The cross tabulation (exploring relationships) between the stages of HIV/AIDS with mean placental-birth weight ratio was not statistically significant between the stages [p-value = 0.71] (**Figure 2**). The tests' umbilical cord lesions had acute umbilical panvasculitis strongly related with advanced HIV/AIDS disease state (**Table 7**). Placental disk lesions like acute intervillositis, acute deciduitis, villous vasculopathy and massive perivillous fibrin deposition were found commonly with advanced HIV/AIDS disease state (**Table 8**).

Table 6: Exploratory relationship between Stages of HIV/AIDS and Histopathological Changes and Lesions in the Foetal Membrane of placenta of the test group

	Stage of HIV	***(n = 48)***			**p value**
Histopathological changes and lesions	1 *(n = 32)*	2 *(n = 13)*	3 *(n = 1)*	4 *(n = 2)*	
Greenish yellow to brown discolouration of membranes	Present (20; 62.5%)	Present (7; 53.8%)	Absent	Present (2; 100%)	0.372
Acute choriodeciduitis	Present (14; 43.8%)	Present (4; 30.8%)	Absent	Present (2; 100%)	0.240
Chronic choriodeciduitis	Present (6; 18.8%)	Present (6; 46.2%)	Present (1; 100%)	Absent	0.073
Acute on chronic choriodeciduitis	Present (3; 9.4%)	Absent	Absent	Absent	0.659
Decidual cell necrosis	Present (8; 25%)	Present (3; 23.1%)	Absent	Present (2; 100%)	0.115
Chronic chorioamnionitis	Present (3; 9.4%)	Present (1; 7.7%)	Absent	Absent	0.955
Acute chorioamnionitis	Present (16; 50%)	Present (4; 30.8%)	Present (1; 100%)	Present (2; 100%)	0.183
Acute on chronic chorioamnionitis	Absent	Absent	Absent	Absent	

➢*Note: there was no statistically significant difference between the stages, indicating a weak association between the lesions and the stages of disease. However, the in-stage association was most significant for stage 4 disease subjects, using percentage proportionality.*

Table 7: Exploratory relationship between Stages of HIV/AIDS and Histopathological Lesions in the Umbilical Cord of placenta of the test group

	Stage of HIV	***(n = 48)***			**p value**
Histopathological lesions	1 *(n = 32)*	2 *(n = 13)*	3 *(n=1)*	4 *(n = 2)*	
Chronic umbilical vasculitis	Absent	Present (1; 7.7%)	Absent	Absent	0.432
Acute umbilical phlebitis	Present (5; 15.6%)	Present (2; 15.4%)	Absent	Absent	0.909
Acute umbilical panvasculitis	Present (1; 3.1%)	Absent	Absent	Present (1; 50%)	0.011[a]
Acute funisitis	Present (3; 9.4%)	Present (1; 7.7%)	Absent	Present (1; 50%)	0.306

➢*Note: "a" showed statistically significant difference between the stages, indicating a strong association between acute umbilical panvasculitis and the stages of disease. The in-stage association for acute umbilical panvasculitis was most significant for stage 4 disease subjects, using percentage proportionality.*

Table 8: Exploratory relationship between Stages of HIV/AIDS and Histopathological Lesions in the Placental Disk of placenta of the test group

	Stage of HIV	***(n = 48)***			**p value**
Histopathological lesions	1 *(n = 32)*	2 *(n = 13)*	3 *(n=1)*	4 *(n=2)*	
Chronic villitis	Absent	Absent	Absent	Absent	
Chronic intervillositis	Absent	Absent	Absent	Absent	
Acute villitis	Present (2; 6.2%)	Present (1; 7.7%)	Absent	Absent	0.970
Acute intervillositis	Present (10; 31.3%)	Present (4; 30.8%)	Absent	Present (1; 50%)	0.853
Villous vasculopathy	Present (11; 34.4%)	Present (4; 30.8%)	Absent	Present (1; 50%)	0.848
Villous stromal fibrosis	Absent	Absent	Absent	Absent	
Infarction	Present (9; 28.1%)	Present (5; 38.5%)	Absent	Absent	0.616
Massive perivillous fibrin deposition	Present (9; 28.1%)	Present (2; 15.4%)	Present (1; 100%)	Present (1; 50%)	0.246
Maternal floor infarct	Present (2; 6.3%)	Absent	Absent	Absent	0.791
Retroplacental haematoma	Present (1; 3.1%)	Present (1; 7.7%)	Absent	Absent	0.891
Acute chorionitis of chorionic plate	Present (3; 9.4%)	Present (1; 7.7%)	Absent	Absent	0.955
Acute chorionic plate vasculitis	Present (2; 6.2%)	Present (2; 15.4%)	Absent	Present (1; 50%)	0.220
Chorionic plate haematoma	Absent	Absent	Absent	Absent	
Intervillous thrombohaematoma	Present (4; 12.5%)	Present (1; 7.7%)	Absent	Absent	0.896

➢*Note: There was no statistically significant difference between the stages, indicating a weak association between the lesions and the stages of disease. However, in-stage association was most significant for stage 4 disease subjects, using percentage proportionality.*

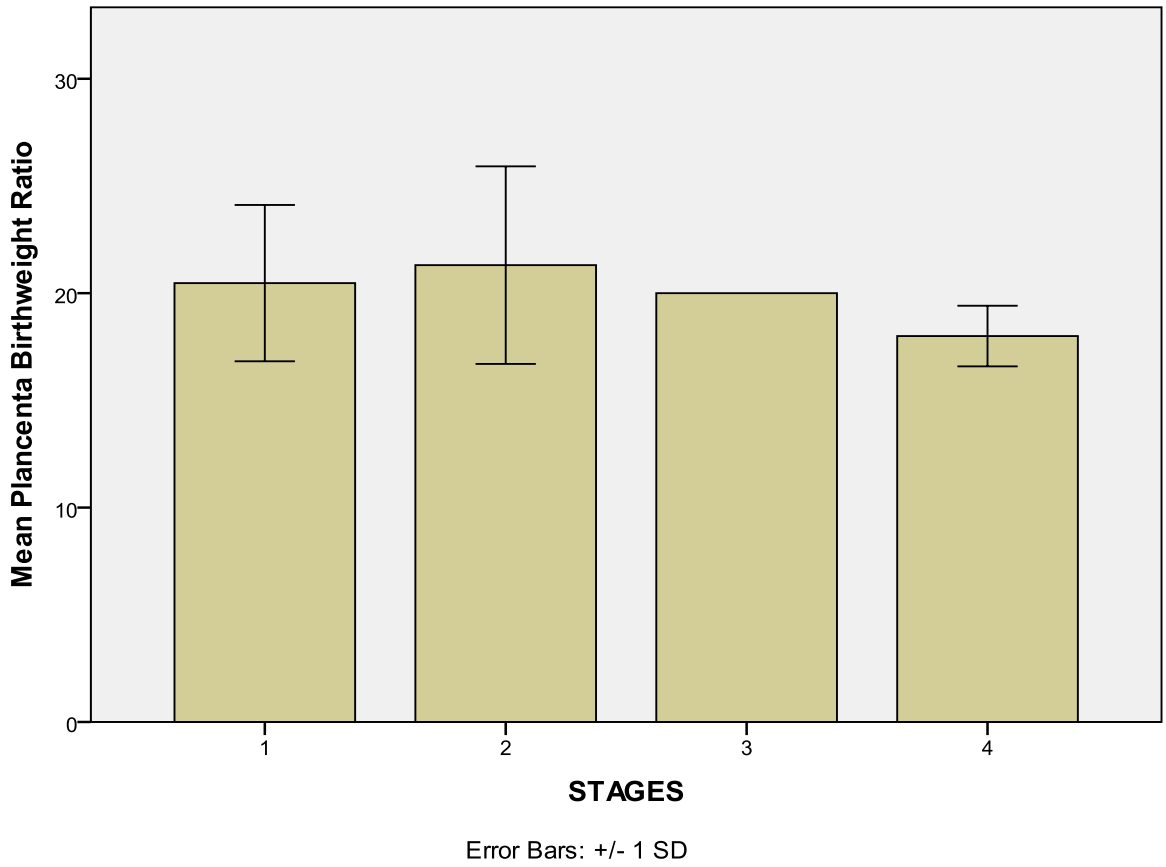

Figure 2: Exploratory relationship between Stages of HIV/AIDS and mean placental-birth weight ratio in the test group. Note: F value = 0.46 and p value = 0.71; there was a weak association between the stages of HIV/AIDS and the mean placental-birth weight ratios of the test group.

Discussion

The mean, median and modal ages of this study were near each other. Studies reviewed for this survey found similar age statistics.[4,11,12,53] This makes our study comparable to these studies.

The test group had their babies mainly through caesarean section (52.1%) while the control group had more of spontaneous vaginal delivery (66.6%). This finding agrees with Lopez et al, Schuetz et al and Schwartz et al.[11,12,53]

The test and control groups' babies birth weights were within the normal birth weight range (2.5 to 4.5 kg), however none of their babies were macrosomic (with birth weight > 4.5 kg). The reason for this is unknown. Importantly, 26.5% of test group babies had low-birthweight (< 2.5kg) while 9.4% of the control group babies had low-birthweight. This low-birthweight was strongly associated with HIV infection (p-value = 0.004). This may reflect compromised in-utero placental function from HIV infection. This agrees with various studies both within Nigeria and abroad.[3,19–27]

The test group placental weights were mainly within the lowest placental weight bracket of 250 – 399 grams (12.5%) while none of the control group's placentas were within this weight category. This finding was strongly associated with HIV infection (p-value = 0.003). This strong association may reflect compromised in-utero perfusion state from HIV infection. Notably, the test and control groups' mean placental weights (575.51 ± 190.15 and 664.99 ± 167.42 grams) were higher than the weights found in relevant studies: Schwartz et al, Lopez et al, Schuetz et al and Vermaak et al.[5,11,12,53] The reason for this finding is unknown, hence requires further investigation.

The test and control groups' placenta-birth weight ratios were similarly reduced (6.1% and 6.5% respectively). This finding was weakly associated with HIV infection (p-value = 0.33). These contrasted with other studies by D'Costa et al and Jauniaux et al.[14,54] The reason for this unknown, hence requires further research.

The test group's foetal membrane showed discolouration and acute inflammatory lesions predominantly. Notably, 60.4% of test group's foetal membrane had greenish yellow to brown discolouration while 45.2% of control group's foetal membrane were discoloured. This discolouration indicates meconium staining of foetal membrane due to probable occurrence of foetal distress in-utero. Foetal distress may be caused by in-utero inflammation from HIV infection. This further illuminates the test group's higher rate of caesarean section. This finding was weakly associated with HIV infection (p-value = 0.08). This contrasted with the findings of Schuetz et al and Lopez et al.[11,53] This may reflect better obstetrics/perinatal care.

The test group showed more acute foetal membrane inflammatory lesions than the control group, namely: acute chorioamnionitis (47.9% versus 21.1%) and acute choriodeciduitis (41.7% versus 8.4%). These findings were strongly associated with HIV infection (p-values of 0.001 and 0.000 respectively). These were consistent with works/studies by Huettner PC, and Salafia and Popek.[2,13] The major aetiology of acute inflammatory lesions (particularly suppurative forms) of the foetal membrane is ascending bacterial infection, resulting in maternal inflammatory response.[2,13,50] HIV infection lowers the immunity of its host to create a conducive environment for opportunistic infections. Hence the strong association of acute foetal membrane inflammatory lesions with HIV infection in this study. HIV-positive mothers will benefit from ascending bacterial infection evaluation. Further research to isolate the possible aetiologic agents is needful.

Notably, acute chorioamnionitis is the commonest lesion in the test group's foetal membrane. This was consistent with similar studies: Schwartz et al, D'Costa et al, Schuetz et al, Ferrero et al, Jauniaux et al, Mwanyumba et al, Anderson, Zevallos and Gu.[4,11,12,14,18,54,55] However, it was inconsistent with the studies by Lopez et al and Vermaak et al, who found foetoplacental vasculopathy, marginal infarct and villitis of unknown aetiology (VUE) as their test group's commonest placental lesions.[5,53] This may reflect lower proportions of opportunistic infections in their test group because of better preventive/prophylactic and interventional modalities.

Furthermore, acute chorioamnionitis of higher stage and grade occurred more in the foetal membrane of the test group than the control group. Acute suppurative necrotizing chorioamnionitis (stage 3, grade 2) was strongly associated with HIV infection (p-value = 0.000). Thus, HIV infection engendered a suitable in-utero environment for virulent opportunistic microbial agents. In support of this, none of the control group's placenta had this stage and grade of chorioamnionitis. This was consistent with studies by Schuetz et al and Schwartz et al.[11,12] Furthermore, the test group's placenta (27.08%) showed more placental membrane inflammation (PMI) than the control group's placenta (7.29%). PMI is the combined presence of chorioamnionitis and funisitis. This was strongly associated with HIV infection (p-value = 0.001). This was consistent with the PMI of Schwartz et al.[12]

The findings of test group's acute chorioamnionitis (47.9%) and acute choriodeciduitis (41.7%) suggest that these lesions may occur in one of every two HIV-positive mothers. These lesions may also be of higher stage and grade, having found 20.83% of test group's acute suppurative necrotizing chorioamnionitis being stage 3, grade 2.

Importantly, the test groups' umbilical cord displayed more of acute inflammatory lesions. These acute inflammatory lesions include acute umbilical phlebitis, acute umbilical panvasculitis and acute funisitis. This finding tallies with the high proportion of acute inflammatory lesions in the foetal membrane. Notably, whereas acute inflammatory lesions of the foetal membrane signify maternal inflammatory response, acute inflammatory lesions of the umbilical cord signify foetal inflammatory response. These findings were loosely associated with HIV infection (p-values > 0.05). The reason is unknown. These findings were consistent with studies by Schuetz et al and Schwartz et al.[11,12]

Furthermore, the test group's umbilical cord had higher stage and grade of acute inflammatory lesions than the control group's umbilical cord. Notably, acute panvasculitis (stage 2, grade 1) was strongly

associated with HIV infection (p-value = 0.044). Thus, a strong association is revealed with staging and grading. This staging and grading agree with the concept of ascending opportunistic infection. This is consistent with the study by Anderson, Zevallos and Gu.[4] The immediate clinical implication of this finding is in ascending opportunistic infection evaluation of HIV-positive mothers' babies.

The test group's placental disk commonest lesion was acute intervillositis (31.3%). The other lesions of the test group's placental disk were acute chorionic plate vasculitis (10.4%), acute chorionitis of chorionic plate (8.3%), acute villitis (6.3%). Notably, acute intervillositis, acute chorionitis of the chorionic plate, and acute villitis signify maternal inflammatory response, while acute chorionic plate vasculitis signifies foetal inflammatory response. This shows thriving opportunistic infections environment from HIV infection. Amongst all these inflammatory lesions, only acute intervillositis was strongly associated with HIV infection (p-value = 0.000). This is consistent with the concept of ascending opportunistic infection. The reason for the loose association with HIV infection found for the other lesions is unknown. These findings are consistent with the study by Lopez et al.[53] The immediate clinical implication is in the obstetrics care given to HIV-positive mothers.

Furthermore, the test group's placental disk also had villous vasculopathy [characterised by concentric vascular endothelial and fibroblastic proliferative thickening secondary to inflammation, leading to its obstruction] (33.3%), infarction (29.2%) and massive perivillous fibrin deposition (27.1%). Interestingly, these three lesions denote maternal circulatory disorders as categorized by United States and Canadian Academy of Pathology (USCAP).[2] This is consistent with the findings of low-birth-weight as well as foetal membrane discolouration (indicative of foetal distress). Notably, villous vasculopathy constituted the most common lesion found in the test groups' placental disk. This may be due to a hostile in-utero inflammatory environment. The high intravascular inflammatory cell traffic occurring in inflammatory response usually led to oxidant collateral vascular damage (i.e., vasculopathy). This finding is consistent with studies by Lopez et al, and Bittencourt and Garcia who found foetoplacental vasculopathy as the commonest lesion in the placenta of HIV-positive mothers.[17,53] The immediate clinical implication is in the biophysical evaluation of HIV-positive mothers to monitor their placental vascular activity; knowing that a good placental vascular network/supply directly relates to good foetal nutrient/oxygen supply as well as waste products excretion. Thus, villous vasculopathy directly affects foetal growth and metabolic functions. These maternal circulatory disorders were loosely associated with HIV infection (p-values > 0.05). These were consistent with study by Schwartz et al.[12] Furthermore, the reason for the high proportions of massive perivillous fibrin deposition in both groups is not known, hence an opportunity for more research.

Notably, majority of the test group were in stage 1 HIV/AIDS disease. This may reflect the success of the use of highly active anti-retroviral therapy (HAART) in their management according to the recommendations of prevention of mother to child transmission (PMTCT) programme.[26,31,34] However, on exploring relationships across all the aspects of the placenta with stages of HIV/AIDS, we found that all the severe inflammatory lesions involved the test group subjects having stage 4 disease. This shows a direct relationship between stage of HIV/AIDS and the occurrence of severe inflammatory lesion or the sequelae thereof, especially for foetal membrane lesions. This reflects the direct/linear relationship between immune competence/inflammatory response and opportunistic infection. This finding, indeed, casts a dark shadow on the wellbeing of test group's foetuses/neonates because of higher probability of adverse perinatal outcomes. Indeed, studies by Ferrero et al, Mwanyumba et al, and Bhoopat et al, implicated this inflammatory state, especially histologic chorioamnionitis, in the occurrence of vertical transmission of HIV from mother to child in utero through the placenta.[16,18,55] Furthermore, studies (particularly Nigerian studies) show that these adverse foetal/perinatal outcomes include spontaneous abortion, stillbirth, intrauterine growth restriction (IUGR), low birth weight (LBW), small for gestational age (SGA), preterm birth, neonatal sepsis, and neonatal encephalopathy.[25–27] The immediate clinical implication is need for closer monitoring of HIV-positive mothers' clinical states, placental functions and their foetuses (particularly in stage 4 disease) to ensure good pregnancy outcomes.

This study has indeed shown that HIV infection can cause alterations/lesions (directly or indirectly) in placental anatomy; thus, affirming that altered histomorphometric parameters and lesions in the placenta of HIV-positive mothers and the associated adverse perinatal outcome are present in Uyo, Akwa Ibom State. This has provided the needed data to commence the filling of the identified knowledge gap. This study has also provided data to use in attainment of goal three of the United Nation's Sustainable Development Goals (SDGs) in our environment.

The limitations of this study were derived basically from the structure of its study design. Being a prospective hospital-based study, the findings cannot be accurately extrapolated to the general population. The maternal obstetrical as well as perinatal data were extracted from the subjects' case notes; the difficulties encountered ranged from inadequate documentation to missing case notes. Also, the accuracy of the case notes' data largely depended on the competence of the clinicians and midwives in documenting it. Additionally, though yellow-brown fetal membrane discoloration was found, we were not able to histopathologically evaluate for meconium. Furthermore, autopsies were not performed on the macerated and fresh stillbirths to evaluate effects of HIV.

Conclusions

The test group had 26.5% of their babies in Low-Birth-Weight category and 12.5% of their placentas weighing < 400 grams. Their placental foetal membrane, umbilical cord and disk showed acute chorioamnionitis, acute panvasculitis (stage 2, grade 1), and acute intervillositis as strongly associated lesions with HIV infection. Though there is a linear relationship between severity of placental histopathological lesions and stage of HIV/AIDS, no significant association was found.

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