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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 fetus 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***: A prospective cross-sectional hospital-based analytical study was conducted at the departments of Obstetrics and Gynecology, and Histopathology, University of Uyo Teaching Hospital, Nigeria from December 2015 to May 2016. We studied 144 pregnant mothers (48 HIV-positive as the test group vs. 96 HIV-negative as controls). Their placentas (fetal membrane, umbilical cord, and placental disk) were collected post-delivery and evaluated (grossly/microscopically) to determine the range of histomorphometric placental parameters/lesions. Relevant obstetric data were obtained from their case notes. ***Results:*** The test group delivered more through cesarean section than the control group (52.1% vs. 31.3%), with mean birth weights of 2.8±0.7 and 3.1±0.6 kg (p = 0.004). The mean placental weights were 57±190.1 and 664.6±167.4 g (p = 0.003), with mean placenta-birth weight ratio of 20.1±4.8 and 20.5±4.57% (p = 0.33). The test groups placental fetal membranes, umbilical cords, and disks mainly displayed acute chorioamnionitis (47.9%), acute umbilical phlebitis (14.6%), and villous vasculopathy (33.3%). The test group had a higher stage/grade of placental inflammation than the control group. In the test group, two stage 4 HIV disease state cases presented with the 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 between HIV/AIDS disease stage with the most severe forms of placental inflammatory lesions.

HIV infection in pregnancy affects the mother, her placenta, and the fetus, 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 categorized into four stages: asymptomatic, mildly symptomatic, moderately symptomatic, and severely symptomatic (with AIDS).[7,9,10] Studies have shown that HIV-positive mothers have several placental morphological changes such as greenish yellow discoloration of fetal 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, infant mortality from pneumonia or neonatal sepsis, and mother-to-child transmission of HIV.[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 4.8% to 10.9%, in contrast to the Nigerian prevalence of 4.1% since 2010.[28–36]

Although numerous studies have shown profound adverse histomorphometric parameters

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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, in general. This 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. 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 feto-maternal complications of HIV infection in affected women in Akwa Ibom state and Nigeria and help attain the third goal of the United Nations' Sustainable Development Goals.[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 Gynecology, and Histopathology. UUTH is a 500-bed tertiary healthcare facility in the South-South region of Nigeria.

We used a convenient sampling technique. Samples (relevant historical data from case notes and their placentas) were collected from December 2015 to May 2016. 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 of this study were included.

The exclusion criteria consisted of all non-consenting HIV-positive and HIV-negative pregnant women, all HIV-negative pregnant women with grossly abnormal placenta, such as placental tumors, and those who delivered before 28 weeks of gestation. The investigator accessed the case notes of all consenting pregnant women (HIV-positive or HIV-negative status) 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 form for each subject.

Histomorphometric assessment of the placenta (for both groups):

1. Sample collection: at the third stage of labor, the labor ward staff takes delivery of the placenta, which is then collected by the principal investigator for labeling and placement in a wide-mouth bucket containing 10% neutral buffered formalin.
2. Gross (macroscopy): the three main placental components (fetal membranes, umbilical cord, and placental disk) were examined systematically after 48 hours of fixation (consistent with the handling of an infectious specimen).[2,39–44] They were weighed after examining and clots, membranes, and cords removed.[2,43,45–47]
3. Sample section procedure:
   - Umbilical cord: two cassettes.
   - Fetal membrane roll: two cassettes.
   - Placental disk parenchyma: six cassettes. More cassettes were submitted in cases with numerous lesions to sample all lesion types.[2,39,41,42,44]
4. Fixation, tissue processing, embedding, microtomy, and staining were performed using standard histological techniques and stained with hematoxylin and eosin.
5. Microscopy: an Olympus CX22 light microscope was used to carry out systematic histopathologic evaluations of the three components of the placenta (umbilical cord, fetal membrane, and placental disk). The terminology/criteria used for placental diagnosis in this study was according to the schemata in the studies by Huettner,[2] Schwartz et al,[12] and Redline et al.[48–50]

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 generated/collected in this study were written in a 'Patient Case Report' form and transferred into Microsoft Office Excel 2013 and SPSS Statistics (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Additionally, we calculated the placental/birth weight ratio 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.

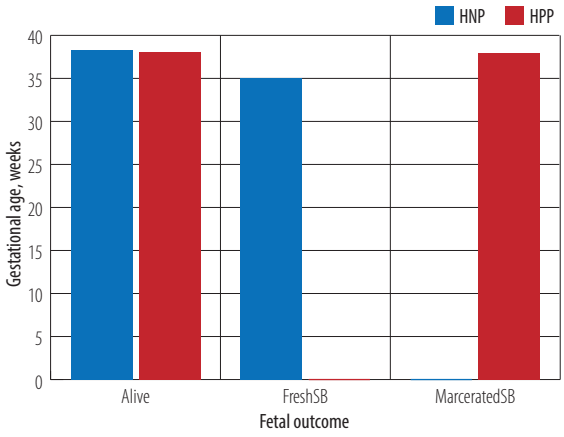
RESULTS

A total of 144 mothers were admitted to this study (48 HIV-positive mothers as tests and 96 HIV-negative mothers as controls). The test group age range, mean, median, and mode were 21–38 years, 30.2±4.3, 30, and 29 years, respectively. The control group age range, mean, median, and mode were 19–41 years, 29.0±4.3, 28.5, and 28 years, respectively [Table 1]. The tests delivered 52.1% of their babies through cesarean section, while the controls delivered 66.7% through spontaneous vaginal delivery [Table 1]. The test group delivered 95.8% live births with 4.2% macerated stillbirths, while the controls delivered 94.8% live births and 4.2% fresh stillbirths [Figure 1]. The mean, median, and mode of birth weight of tests' babies were 2.8±0.7 kg, 2.95 kg, and 3.3 kg, with 26.5% of infants having LBW, while the controls' mean, median, and mode of birth weight were 3.1±0.6 kg, 3.2 kg, and 3.2 kg, with 9.4% of infants having LBW, $p = 0.004$ [Table 1].

The tests' mean, median, and mode of placental weight were 575.5±190.1 g, 550 g, and 600 g,

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.

Status	Test group (n = 48)		Control group (n = 96)		Statistical significance	
	Frequency	Percentage, %	Frequency	Percentage, %	*p*-value	Chi-squared
Age group, years						
< 16	0	0.0	0	0.0	-	-
16–23	3	6.3	7	7.4	-	-
24–31	25	52.1	61	64.2	-	-
32–34	10	20.8	12	12.6	-	-
35–40	10	20.8	14	14.7	-	-
41–45	0	0.0	1	1.1	-	-
> 45	0	0.0	0	0.0	-	-
Total	48	100	95	100	-	-
Mode of delivery						
Cesarean section	25	52.1	30	31.3	0.47	4.8
Instrumental	0	0.0	2	2.1	-	-
Vaginal	23	47.9	64	66.7	-	-
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	0.0	-	-
Total	49	100	96	100	-	-
Placental weight, g						
250–399	6	12.5	0	0.0	0.003	17.96
400–549	11	22.9	12	12.8	-	-
550–699	17	35.4	36	38.3	-	-
700–849	12	25.0	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						
< 15.8	3	6.1	6	6.5	0.33	2.23
15.8–20.6	28	57.1	42	45.2	-	-
> 20.6	18	36.7	45	48.4	-	-
Total	49	100	93	100	-	-



FreshSB: fresh stillbirth; MaceratedSB: macerated stillbirth; HNP: HIV-negative (control) group; HPP: HIV-positive (test) group.

Figure 1: Frequency distribution of fetal outcome in relation to gestational age in both the test and control groups.

while in the control group these values were 664.6±167.4 g, 650 g, and 700 g, respectively ($p = 0.003$) [Table 1]. The tests' mean, median, and mode of placental birth weight ratio were 20.1±4.8, 19.7, and 20, and 20.54±4.57, 20.36, and 20 in the control group, respectively ($p = 0.003$) [Table 1].

The tests group fetal membrane displayed greenish yellow to brown discoloration in 60.4% of cases, whereas the controls displayed this discoloration in 45.3% of cases [Table 2, Figure 2]. The most common fetal membrane histopathologic lesion in the test group was acute chorioamnionitis (47.9%) and chronic choriodeciduitis (chronic inflammatory lesion involving the chorion and decidua) in the control group (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 and Figure 3].

The test group's commonest umbilical cord histopathologic lesion was acute umbilical phlebitis (14.6%) while the control group's commonest umbilical cord histopathologic lesion was acute funisitis (5.3%) [Table 3].

The test group's commonest placental disk histopathological lesion was villous vasculopathy (33.3%) and the most common in the control group was massive perivillous fibrin deposition (38.9%); giving statistically significant *p*-values for chronic villitis, chronic intervillositis, acute intervillositis, maternal floor infarct, and intervillous thrombohematoma [Table 4 and Figure 4].

On further evaluation of these inflammatory lesions involving the fetal 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 (20.8%), while the controls had none; 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 3 and Figure 5].

Importantly, the majority of the test group subjects (66.7%) were in stage 1 of HIV disease, and only two patients were in stage 4 (4.2%) [Table 6]. Both test group subjects with stage 4

Table 2: Placental histopathological changes and lesions in the fetal membrane in the test and control groups.

Histopathological changes and lesions	Test group, n = 48		Control group, n = 96		*p*-value
	Present n (%)	Absent n (%)	Present n (%)	Absent n (%)	
Greenish yellow to brown discoloration of membranes	29 (60.4)	19 (39.6)	43 (45.3)	52 (54.7)	0.08
Acute choriodeciduitis	20 (41.7)	28 (58.3)	8 (8.4)	87 (91.6)	< 0.001[a]
Chronic choriodeciduitis	13 (27.1)	35 (72.9)	69 (72.6)	26 (27.4)	< 0.001[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 (0.0)	48 (100)	1 (1.1)	94 (98.9)	0.70

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

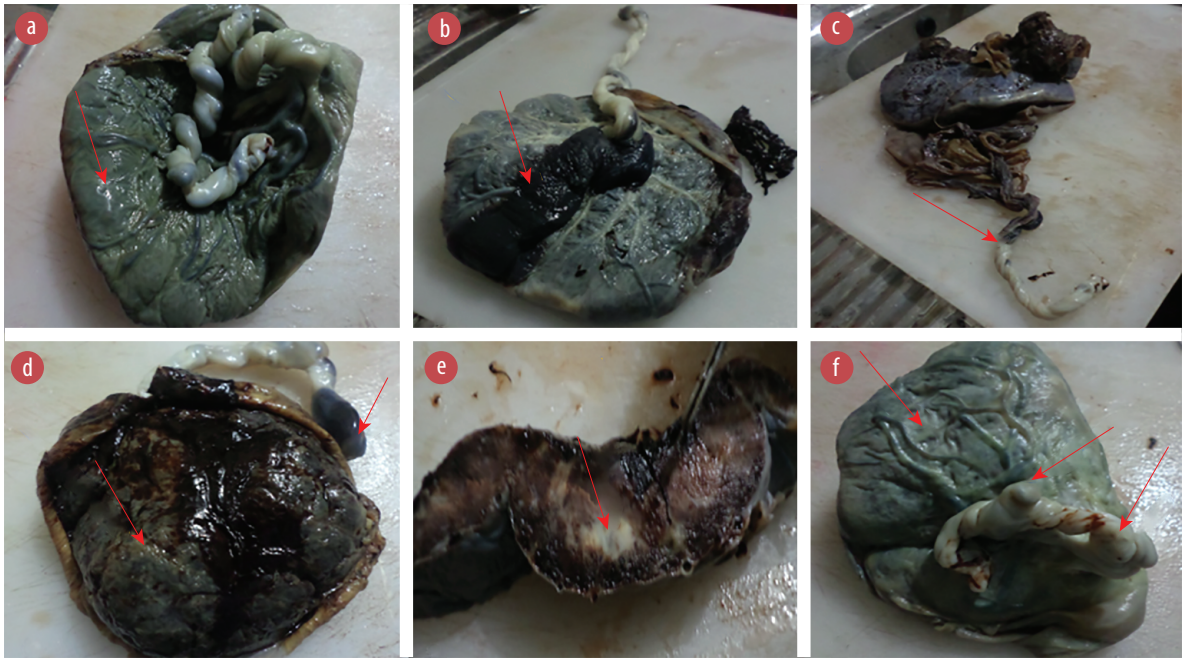


Figure 2: Gross morphology of the placentas of **(a)** a 36-year-old HIV-positive mother showing meconium (greenish brown) staining of the fetal surface; **(b)** a 30-year-old HIV-negative mother showing massive chorionic plate hematoma of the fetal surface of the placental disk; **(c)** a 24-year-old HIV-positive mother showing velamentous insertion of the umbilical cord to the fetal membrane instead of the fetal surface of the placental disk; **(d)** a 37-year-old HIV-positive mother showing massive umbilical cord hematoma as well as maternal surface of the placental disk; **(e)** a 19-year-old HIV-negative mother showing an area of massive infarction of the cut surface of the placental disk; and **(f)** a 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.

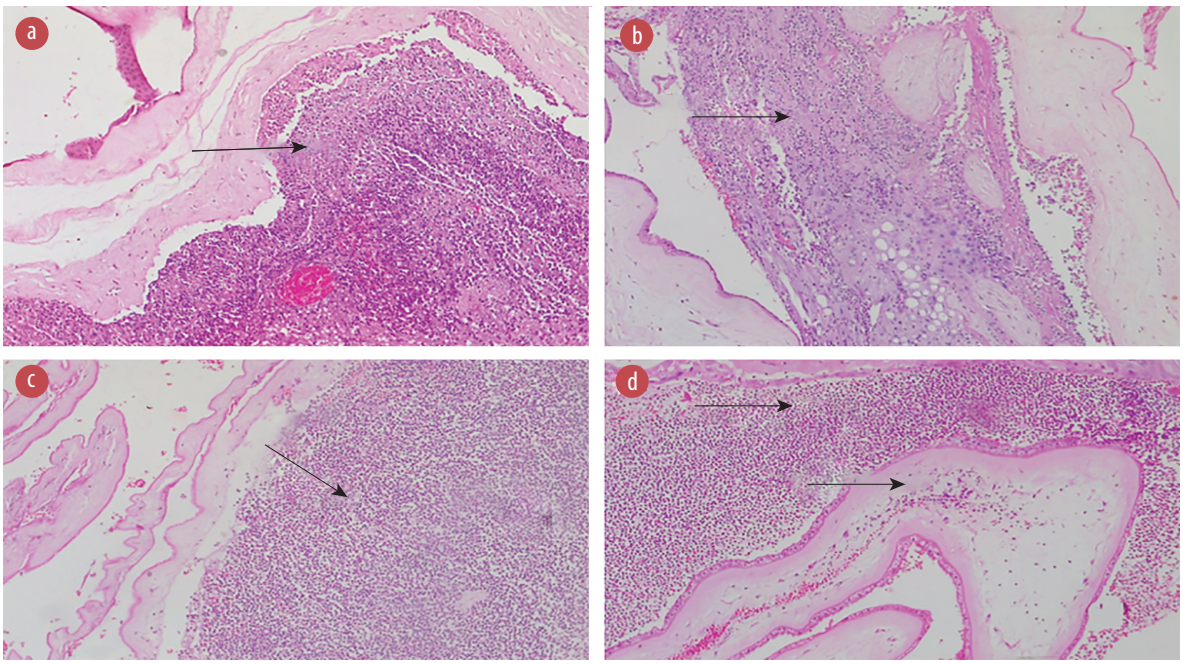


Figure 3: Photomicrographs of the fetal membrane of **(a)** a 34-year-old HIV-positive mother showing acute suppurative necrotizing chorioamnionitis (stage 3, grade 2) with acute choriodeciduitis; **(b)** a 29-year-old HIV-positive mother showing acute choriodeciduitis; **(c)** a 24-year-old HIV-positive mother showing acute suppurative chorioamnionitis; and **(d)** a 22-year-old HIV-positive mother showing severe acute suppurative deciduitis with mild acute chorionitis. All images stained with hematoxylin and eosin, magnification = 100 ×.

Table 3: Placental histopathological lesions in the umbilical cord in the test and control groups.

Histopathological lesions	Test group, n = 48		Control group, n = 96		*p*-value
	Present n (%)	Absent n (%)	Present n (%)	Absent n (%)	
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 (0.0)	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 a weak association with HIV infection.

Table 4: Placental histopathological lesions in the placental disk to compare the test and the control groups.

Histopathological lesions	Test group, n = 48		Control group, n = 96		*p*-value
	Present n (%)	Absent n (%)	Present n (%)	Absent n (%)	
Chronic villitis	0 (0.0)	48 (100)	17 (17.9)	78 (82.1)	0.002[a]
Chronic intervillositis	0 (0.0)	48 (100)	14 (14.7)	81 (85.3)	0.005[b]
Acute villitis	3 (6.3)	45 (93.8)	2 (2.1)	93 (97.8)	0.20
Acute intervillositis	15 (31.3)	33 (68.8)	6 (6.3)	89 (93.7)	< 0.001[c]
Villous vasculopathy	16 (33.3)	32 (66.7)	20 (21.1)	75 (78.9)	0.10
Hemorrhagic endovasculitis	0 (0.0)	48 (100)	0 (0.0)	95 (100)	-
Villous stromal fibrosis	0 (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 (0.0)	48 (100)	0 (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 hematoma	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 thrombohematoma	5 (10.4)	43 (89.6)	0 (0.0)	95 (100)	0.001[e]

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

HIV disease were found to have greenish yellow to brown discoloration of the fetal 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 [Figure 6]. The test group umbilical cord lesions had acute umbilical panvasculitis strongly related to 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].

DISCUSSION

Our study found that the mean, median, and modal ages were near each other. Studies reviewed for this survey found similar age statistics.[4,11,12,53] This makes our study comparable.

The test group had their infants mainly through cesarean section (52.1%), while the control group had more spontaneous vaginal deliveries (66.7%), in agreement with previous findings.[11,12,53]

In both groups the babies, birth weights were within the normal range (2.5–4.5 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 LBW (< 2.5 kg) while 9.4% of the control group had LBW infants. This was strongly associated with HIV infection ($p = 0.004$). This may reflect a compromised in utero placental function from HIV infection. This agrees with various studies within Nigeria and abroad.[3,19–27]

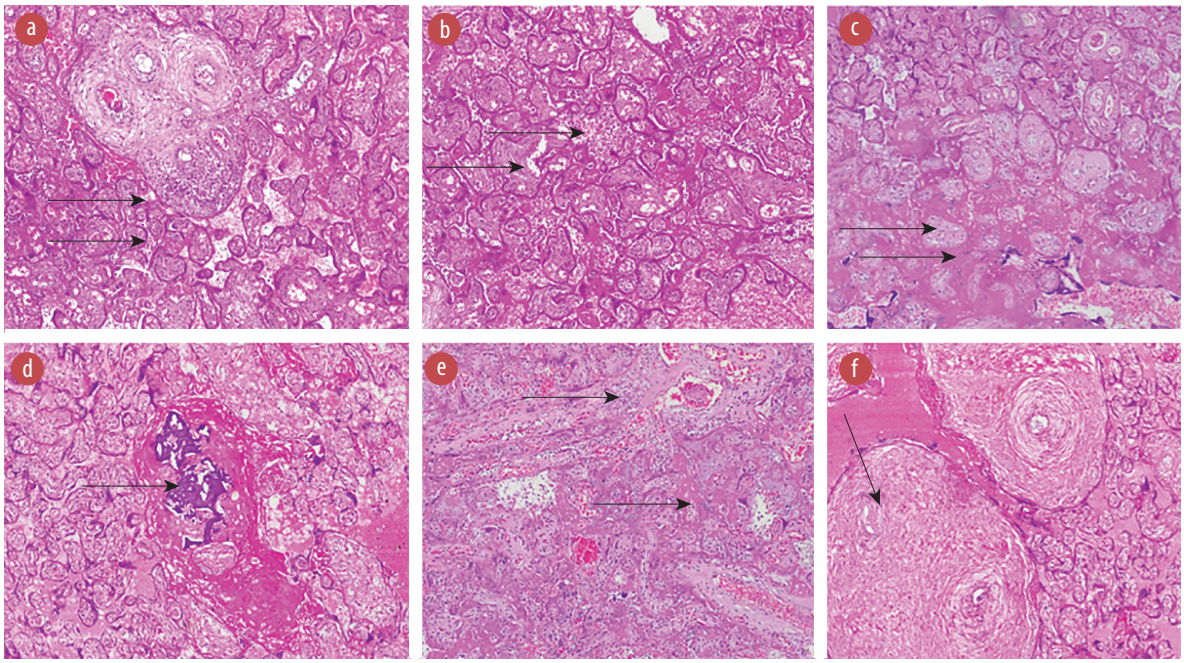


Figure 4: Photomicrographs of the placental disk of **(a)** a 32-year-old HIV-positive mother showing acute villitis and acute vasculitis of stem villous; **(b)** a 32-year-old HIV-positive mother showing infarction and acute intervillositis; **(c)** a 35-year-old HIV-positive mother showing infarcted villi and massive perivillous fibrin deposition;**(d)** a 29-year-old HIV-positive mother showing calcification and massive perivillous fibrin deposition; **(e)** a 30-year-old HIV-positive mother showing acute villitis and fibrin deposition; and **(f)** a 29-year-old HIV-positive mother showing chronic vasculitis with obliterative features.
All images hematoxylin and eosin staining, magnification = 100 ×.

Table 5: Grading and staging of placental inflammatory lesions of the fetal membrane, umbilical cord, and chorionic plate in the test and control groups.

Histopathological lesions	Test group, n = 48		Control group, n = 96		*p*-value
	Present n (%)	Absent n (%)	Present n (%)	Absent n (%)	
Acute chorionitis (stage 1, grade 1)	7 (14.6)	41 (85.4)	2 (2.1)	94 (97.9)	0.003[a]
Acute chorioamnionitis (stage 2, grade 1)	4 (8.3)	44 (91.7)	3 (3.1)	93 (96.9)	0.171
Acute suppurative chorioamnionitis (stage 2, grade 2)	0 (0.0)	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 (0.0)	96 (100)	0.000[c]
Chronic chorioamnionitis	0 (0.0)	48 (100)	5 (5.2)	91 (94.8)	0.108
Acute choriodeciduitis	23 (47.9)	25 (52.1)	3 (3.1)	93 (96.9)	0.000[d]
Acute on chronic choriodeciduitis	3 (6.3)	45 (93.8)	8 (8.3)	88 (91.7)	0.657
Chronic choriodeciduitis	17 (35.4)	31 (64.6)	69 (71.9)	27 (28.1)	0.000[e]
Acute chorionitis of chorionic plate	6 (12.5)	42 (87.5)	6 (6.3)	90 (93.8)	0.201
Acute chorionic plate vasculitis	5 (10.4)	43 (89.6)	4 (4.2)	92 (95.8)	0.144
Acute phlebitis (stage 1, grade 1)	4 (8.3)	44 (91.7)	3 (3.1)	93 (96.9)	0.171
Chronic phlebitis	0 (0.0)	48 (100)	1 (1.0)	95 (99.0)	0.478
Acute panvasculitis (stage 2, grade 1)	2 (4.2)	46 (95.8)	0 (0.0)	96 (100)	0.044[f]
Acute funisitis (stage 3, grade 1)	7 (14.6)	41 (85.4)	6 (6.3)	90 (93.8)	0.099
Acute necrotizing funisitis (stage 3, grade 2)	1 (2.1)	47 (97.9)	0 (0.0)	96 (100)	0.156
Placental membrane inflammation	13 (27.1)	35 (72.9)	7 (7.3)	89 (92.7)	0.001[g]

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

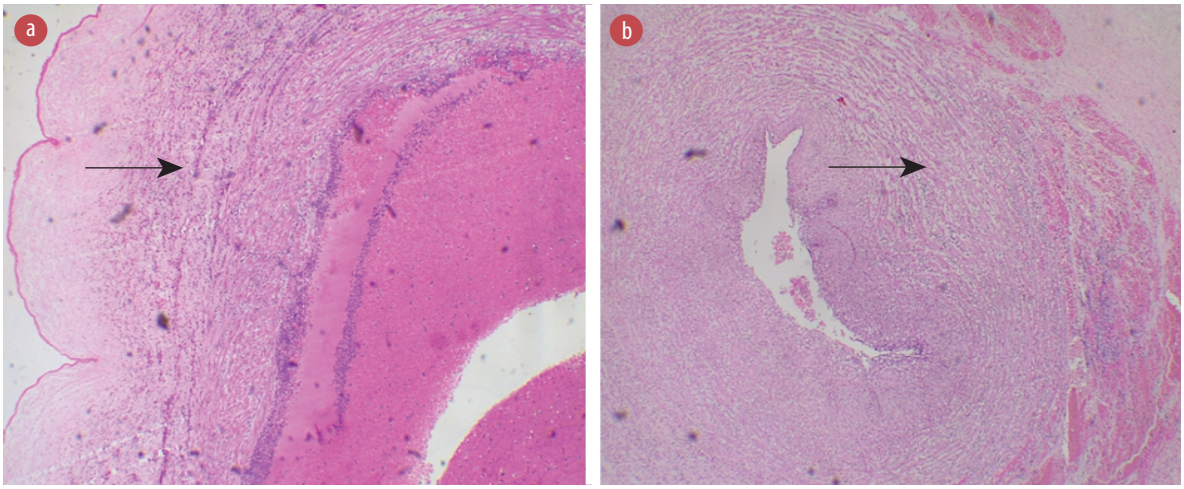


Figure 5: Photomicrographs of the umbilical cord of the placenta from **(a)** a 32-year-old HIV-positive mother showing acute funisitis (stage 3, grade 2). **(b)** A 24-year-old HIV-positive mother showing acute phlebitis. Hematoxylin and eosin staining, magnification = 100 ×.

Table 6: Exploratory relationship between stages of HIV/AIDS and histopathological changes and lesions in the fetal membrane of placenta of the test group.

Histopathological changes and lesions	Stage of HIV (n = 48)				*p*-value
	1 (n = 32) (n; %)	2 (n = 13), (n; %)	3 (n = 1) (n; %)	4 (n = 2) (n; %)	
Greenish yellow to brown discoloration of membranes	Present (20; 62.5)	Present (7; 53.8)	Absent	Present (2; 100)	0.372
Acute chorio-deciduitis	Present (14; 43.8)	Present (4; 30.8)	Absent	Present (2; 100)	0.240
Chronic chorio-deciduitis	Present (6; 18.8)	Present (6; 46.2)	Present (1; 100)	Absent	0.073
Acute on chronic chorio-deciduitis	Present (3; 9.4)	Absent	Absent	Absent	0.659
Decidual cell necrosis	Present (8; 25.0)	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; 50.0)	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 disease stages. However, the in-stage association was most significant for stage 4 disease subjects, using percentage proportionality.

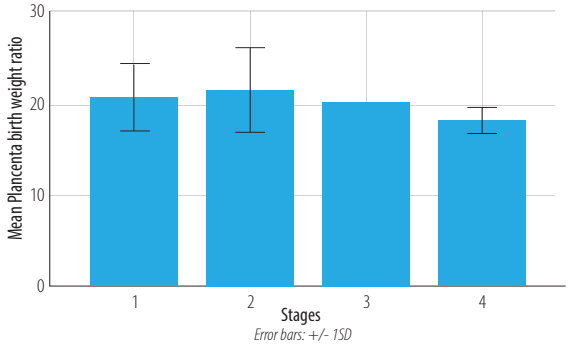


Figure 6: Exploratory relationship between stages of HIV/AIDS and mean placental/birth weight ratio in the test group. Note: F value = 0.46 and $p = 0.71$. There was a weak association between the stages of HIV/AIDS and the mean placental/birth weight ratios of the test group.

The test group's placental weights were mainly within the lowest placental weight bracket of 250–399 g (12.5%) while none of the control group's placentas were within this weight category. This finding was strongly associated with HIV infection ($p = 0.003$). This strong association may reflect a compromised in utero perfusion state from HIV infection. Notably, the test and control groups' mean placental weights (575.5±190.1 g and 664.9±167.4 g) were higher than those reported in similar studies.[5,11,12,53] The reason for this finding is unknown and requires further investigation.

The test and control groups' placental/birth weight ratios were similarly reduced (6.1% and 6.5%, respectively). This finding was weakly associated

Table 7: Exploratory relationship between stages of HIV/AIDS and histopathological lesions in the umbilical cord of placenta of the test group.

Histopathological lesions	Stage of HIV (n = 48)				*p*-value
	1 (n = 32) (n; %)	2 (n = 13) (n; %)	3 (n = 1)	4 (n = 2) (n; %)	
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)	0.011[a]
Acute funisitis	Present (3; 9.4)	Present (1; 7.7)	Absent	Present (1; 50.0)	0.306

Note: [a]showed a statistically significant difference between the stages, indicating a strong association between acute umbilical panvasculitis and the disease stages. 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.

Histopathological lesions	Stage of HIV (n = 48)				*p*-value
	1 (n = 32) (n; %)	2 (n = 13) (n; %)	3 (n = 1) (n; %)	4 (n = 2) (n; %)	
Chronic villitis	Absent	Absent	Absent	Absent	-
Chronic intervillositis	Absent	Absent	Absent	Absent	-
Acute villitis	Present (2; 6.3)	Present (1; 7.7)	Absent	Absent	0.970
Acute intervillositis	Present (10; 31.3)	Present (4; 30.8)	Absent	Present (1; 50.0%)	0.853
Villous vasculopathy	Present (11; 34.4)	Present (4; 30.8)	Absent	Present (1; 50.0)	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)	0.246
Maternal floor infarct	Present (2; 6.3)	Absent	Absent	Absent	0.791
Retroplacental hematoma	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; 6.3)	Present (2; 15.4)	Absent	Present (1; 50.0)	0.220
Chorionic plate hematoma	Absent	Absent	Absent	Absent	-
Intervillous thrombohematoma	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 disease stages. However, the in-stage association was most significant for stage 4 disease subjects, using percentage proportionality.

with HIV infection ($p = 0.33$), which is in contrast with other studies.[14,54] The reason for this unknown and requires further research.

In the test group, fetal membranes showed discoloration and acute inflammatory lesions. Notably, 60.4% of the test group's fetal membrane had greenish yellow to brown discoloration while 45.3% of the control group's fetal membranes were discolored. This discoloration indicates meconium staining of the fetal membrane most likely due to fetal distress in utero. Fetal distress may be caused by in utero inflammation from HIV infection. This further illuminates the test group's higher rate of cesarean section. This finding was weakly associated with HIV infection ($p = 0.08$), and in contrast with previous studies.[11,53] This may reflect better obstetrics/perinatal care.

The test group showed more acute fetal membrane inflammatory lesions than the control group, namely acute chorioamnionitis (47.9% vs. 21.1%) and acute choriodeciduitis (41.7% vs. 8.4%). These findings were strongly associated with HIV infection ($p = 0.001$ and $p < 0.001$, respectively). These were consistent with previous studies.[2,13] The major etiology of acute inflammatory lesions (particularly suppurative forms) of the fetal 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 fetal 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 etiologic agents is needed.

Notably, acute chorioamnionitis was the commonest lesion in the test group the fetal membranes. This was consistent with similar studies.[4,11,12,14,18,54,55] However, it was inconsistent with studies that found fetoplacental vasculopathy, marginal infarct, and villitis of unknown etiology as their test group's commonest placental lesions.[5,53] This may reflect lower proportions of opportunistic infections in the test groups because of better preventive/prophylactic and interventional modalities.

Furthermore, acute chorioamnionitis of higher stage and grade occurred more in the fetal membranes of the test group than the control group. Acute suppurative necrotizing chorioamnionitis (stage 3, grade 2) was strongly associated with HIV infection ($p < 0.001$). Thus, HIV infection engendered a suitable in utero environment for virulent opportunistic microbial agents. In support of this, none of the control group placentas had this stage and grade of chorioamnionitis. This was consistent with previous studies.[11,12] Furthermore, the test group placentas (27.1%) showed more PMI than the control group (7.3%). PMI is the combined presence of chorioamnionitis and funisitis and was strongly associated with HIV infection ($p = 0.001$). This was consistent with the PMI of Schwartz et al.[12]

Acute chorioamnionitis (47.9%) and acute choriodeciduitis (41.7%) found in the test group suggest that these lesions may occur in one in every two HIV-positive mothers. These lesions may also be of higher stage and grade, having found 20.8% acute suppurative necrotizing chorioamnionitis being stage 3, grade 2.

Importantly, the test group's umbilical cords displayed more 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 fetal membrane. Notably, whereas acute inflammatory lesions of the fetal membrane signify maternal inflammatory response, acute inflammatory lesions of the umbilical cord signify fetal inflammatory response. These findings were loosely associated with HIV infection ($p > 0.05$). The reason is unknown and the findings were consistent with previous studies.[11,12]

Furthermore, the test group's umbilical cords had a higher stage and grade of acute inflammatory lesions than the control group. Notably, acute panvasculitis (stage 2, grade 1) was strongly associated with HIV infection ($p = 0.044$). Thus, a strong association is revealed with staging and grading. This staging and grading agree with the concept of ascending opportunistic infection and are consistent with the findings of a previous study.[4] The immediate clinical implication of this finding is in ascending opportunistic infection evaluation of HIV-positive mothers' babies.

In the placental disks of the test group, the most common lesion was acute intervillositis (31.3%). Other lesions included acute chorionic plate vasculitis (10.4%), acute chorionitis of the chorionic plate (8.3%), and 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 fetal inflammatory response. This variety of inflammatory lesions on the placental disk shows how an HIV-infected environment is ideal for opportunistic infectious pathogens to trigger a wide range of inflammatory reactions. Amongst all these inflammatory lesions, only acute intervillositis was strongly associated with HIV infection ($p < 0.001$). 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 López 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 (33%), which is characterized by concentric vascular endothelial and fibroblastic proliferative thickening secondary to inflammation, leading to its obstruction, 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.[2] This is consistent with the findings of LBW as well as fetal membrane discoloration (indicative of fetal 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 previous studies in which the authors 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 fetal nutrient/oxygen supply as well as waste products excretion. Thus, villous vasculopathy directly affects fetal growth and metabolic functions. These maternal circulatory disorders were loosely associated with HIV infection ($p > 0.05$) consistent with the 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 in their management according to the recommendations of prevention of mother to child transmission program.[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 the stage of HIV/AIDS and the occurrence of severe inflammatory lesions or the sequelae thereof, especially for fetal 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 well-being of the test group's fetuses/neonates because of the higher probability of adverse perinatal outcomes. Indeed, previous studies 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 fetal/perinatal outcomes include spontaneous abortion, stillbirth, intrauterine growth restriction, LBW, small for gestational age, preterm birth, neonatal sepsis, and neonatal encephalopathy.[25–27] The immediate clinical implication is needed for closer monitoring of HIV-positive mothers' clinical states, placental functions, and their fetuses (particularly in stage 4 disease) to ensure good pregnancy outcomes.

This study has 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 the attainment of goal three of the United Nation's Sustainable Development Goals.

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 and 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.

CONCLUSION

One-quarter (26.5%) of babies in the test group were in the LBW category, and 12.5% of their placentas weighed > 400 g. Their placental fetal 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 the severity of placental histopathological lesions and stage of HIV/AIDS, no significant association was found.

Disclosure

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