

was receiving ANC at the O&G department of UUTH, Uyo, for her fourth pregnancy, being Gravida 4 Para zero, with three miscarriages/terminations of pregnancy, zero alive {G4P0+3(0A)}. Her last menstrual period (L.M.P) was the 2nd of March 2015 and her expected date of delivery (E.D.D) was the 9th of December 2015. Her HIV diagnosis is of 10 years duration with nine years of highly active antiretroviral therapy [HAART] and she was compliant with her treatment regimen. Her HAART comprises Tenofovir, Lamivudine, and Efavirenz combination. She booked for antenatal care during the second trimester of pregnancy and her booking height, weight, and body mass index (BMI) were 1.74 meters (m), 67 kilograms (Kg), and 22.13 kg/m² respectively. She had past obstetrics history of previous antenatal admissions because of anemia in pregnancy and three previous first-trimester miscarriages/terminations of pregnancy. Her serial pack cell volume (PCV) in this pregnancy were 21% (on the 10th of November), 24% (on the 24th of November), 31% (on the 30th of November), and 30% (on the 8th of December) few days before her delivery. She was in clinical stage 2 of HIV/AIDS (as of December 2015): note that HIV/AIDS stage 2 patients are usually asymptomatic (i.e., in clinical latency or chronic HIV infection stage)³³ (Figure 1). Notably, the CD4 count was not done during this pregnancy. Notably, her VDRL tests, at booking, were reactive, both in the initial screening and confirmatory tests; consequently, she received syphilotherapy with parenteral benzathine penicillin. All other routine investigations, such as urinalysis, random blood glucose, liver function test, and abdominopelvic ultrasound scan, carried out did not show any abnormality. She had an uneventful pregnancy and eventually presented at the ante-natal ward for induction of labor at term due to the absence of initiation of spontaneous labor at term. Her 2.4 kilograms male baby was delivered through emergency cesarean section (secondary to failed induction

in a retroviral disease patient) at an estimated gestational age (EGA) of 40 weeks plus one day, with an APGAR score of 4 at the first minute, 5 at five minutes and 5 at 10 minutes. Her baby had a head circumference (HC) of 31 cm (normal range of 33 to 35cm at term)³⁴, a chest circumference of 32 cm (normal range of 30 to 33cm at term)[34], and crown-heel length of 48 cm(normal range of 47.53 to 552.61cm at term)[34]. He was immediately placed on nevirapine syrup. However, the mother's case note did not indicate whether he was screened with the VDRL test, whether the diagnosis of CS was made, and/or if treatment was given.

Furthermore, her placental delivery was spontaneous and complete, with clear amniotic fluid (liquor). Subsequently, a histopathological evaluation of her placenta (fetal membrane, umbilical cord, and disk) was done. Grossly, her placental weight was 400 grams before fixation in 10% neutral buffered formalin (and 400 grams after 48 hours of fixation), giving a PBWR of 16.67% (with an assessment of large placenta with small for gestational age infant). The fetal membrane was complete, transparent, and greyish, with its point of rupture being 20 cm from its marginal insertion to the placental disk. The umbilical cord measured 11 cm in length, and 1.2 cm in diameter, having 3 patent blood vessels (visualized in the transverse section), focal hematoma, excess torsion, and eccentric insertion to the disk. The placental disk was discoid shaped, measuring 20.0 x 10.5 x 1.0 cm in its widest dimensions, having a transparent greyish white fetal surface, patent connecting vessels, and complete soft to firm reddish-brown maternal surface with about 50 ml of clotted blood diffusely adherent to it, and a cut surface that is spongy, reddish-brown, and interspersed by several septa-like whitish foci (Figure 2). Microscopically: the fetal membrane showed squamous metaplasia of amnion as well as subamniotic hematoma of the fetal membrane; the umbilical cord showed focal edema and

hematoma; the placental disk showed avascular villi, large hypercellular villi, villous vasculopathy (obliterative vasculopathy with onion-skinning pattern) and calcification of the disk (Figure 3, 4 and 5).

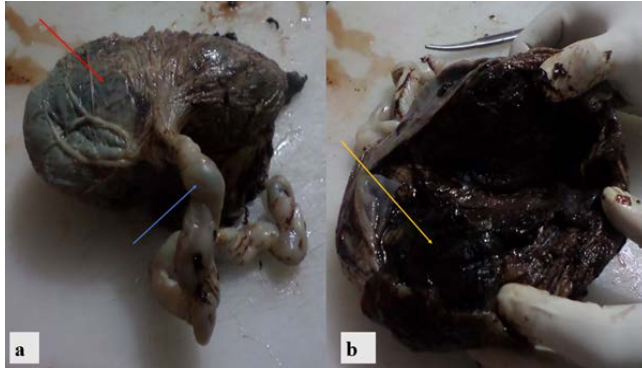


Figure 2: (a–b) Gross photographs of the placenta of the 36-year-old HIV-positive multigravida who had a reactive VDRL Test result. (a) This is the placenta, after 48 hours of fixation, displaying the fetal surface of the placental disk [red arrow] and the tortuous umbilical cord with focal hematomas [blue arrow]. (b) This is the maternal surface of the placenta with diffusely adherent blood clots [yellow arrow].

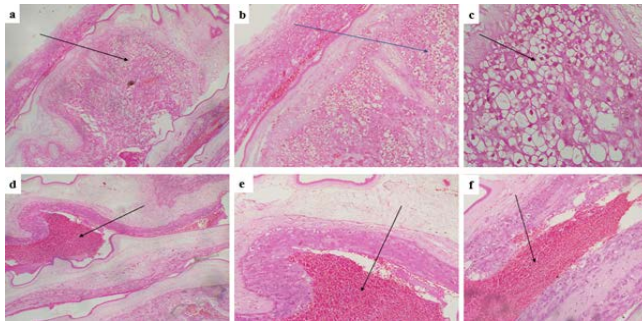


Figure 3: (a–f) Photomicrographs of the fetal membrane of the placenta of the 36-year-old HIV-positive multigravida who had a reactive VDRL Test result; with (a) to (c) displaying Squamous metaplasia of amnion and (d) to (f) displaying Subamniotic hematoma of fetal membrane. (a) Shows a focal area composed of sheets of squamous cells with clear cell changes [black arrow] within the amniotic layer of the fetal membrane [H&E stain, x 40]. (b) It also shows these sheets of squamous cells with clear cell changes [blue arrow] within the amniotic layer of the fetal membrane [H&E stain, x 100]. (c) It also shows these sheets of squamous cells with clear cell changes [black arrow] within the amniotic layer of the fetal membrane [H&E stain, x 400]. (d) Shows a focal accumulation of blood [black arrow] just beneath the amniotic layer of the fetal membrane [H&E stain, x 40]. (e) Also, shows a focal accumulation of blood [black arrow]

just beneath the amniotic layer of the fetal membrane [H&E stain, x 100]. (f) Shows another area of focal accumulation of blood [black arrow] just beneath the amniotic layer of the fetal membrane [H&E stain, x 100].

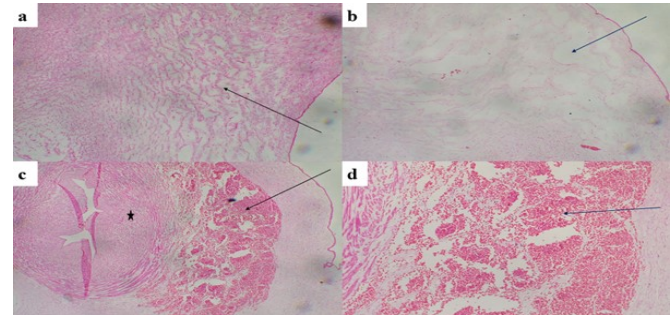


Figure 4: (a–d) Photomicrographs of the umbilical cord of the placenta of the 36-year-old HIV-positive multigravida who had a reactive VDRL Test result; (a) to (b) shows Umbilical edema and (c) to (d) shows Umbilical hematoma. (a) Shows a focal accumulation of fluid within the Wharton’s jelly [black arrow] [H&E stain, x 40]. (b) Shows another area with a focal accumulation of fluid within the Wharton’s jelly [blue arrow] [H&E stain, x 40]. (c) Shows a focal accumulation of blood within the Wharton’s jelly [black arrow] just adjacent to a thick-walled umbilical artery [black star] [H&E stain, x 40]. (d) Shows a focal accumulation of blood within the Wharton’s jelly [blue arrow] just adjacent to a thick-walled umbilical artery [H&E stain, x 100].

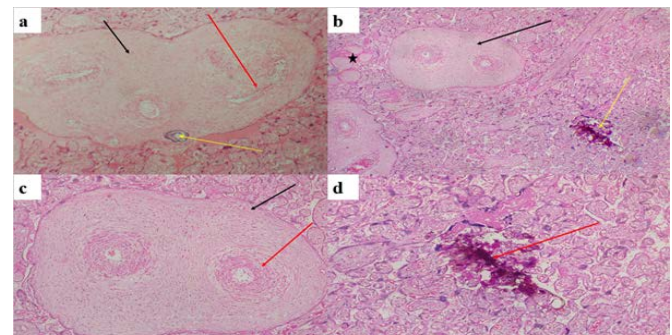


Figure 5: (a–d) Photomicrographs of the placental disk of the placenta of the 36-year-old HIV-positive multigravida who had a reactive VDRL Test result, showing some features of Syphilitic placentitis, namely: avascular villi, large hypercellular villi, villous vasculopathy (obliterative vasculopathy with onion-skinning pattern) and calcification of the disk. (a) Shows a large villous [black arrow] with three blood vessels with markedly diminished lumen due to villous vasculopathy [red arrow] as well as a focus of calcification [yellow arrow] [H&E stain, x 40]. (b) Shows another large villous [black arrow] with two blood vessels with markedly diminished lumen due to villous vasculopathy, a focus with three avascular villi [black star] as well as an adjacent focus of calcification [yellow arrow]

[H&E stain, x 40].(c) Shows the same large villous [black arrow] with two blood vessels with markedly diminished lumen due to villous vasculopathy [red arrow] [H&E stain, x 100].(d) Shows the same focus of calcification [red arrow] surrounded by numerous small-sized villi [H&E stain, x 100].

DISCUSSION

In this study, we aimed to compare the VDRL test results from the HIV-positive and HIV-negative pregnant women given their age, booking status, and gravidity, as well as to associate VDRL test reactivity to HIV/AIDS stage and to evaluate the perinatal/placental histopathological findings in the reactive VDRL test cases. In summary, we found that majority of the tests and controls were aged less than 35 years, booked for ANC, and multigravida. Also, the VDRL test results, for both the tests and controls, were not strongly associated with maternal age, booking for ANC, gravidity, and HIV/AIDS stage (in the tests only). Furthermore, we found that only one subject from the tests had a reactive VDRL test result, and historical data were extracted from her case note in addition to a histopathological examination of her placenta; these showed features consistent with CS and syphilitic placentitis.

We found that majority of the tests and controls were aged less than 35 years, accounting for 79.17% and 84.21% of the cases respectively. Similarly, the VDRL test results, for both the tests and controls, were not strongly associated with maternal age, with a p-value of 0.097. Notably, the study by Padovani C et al shows that most cases of maternal syphilis are aged less than 35 years¹⁸.

Also, we found that majority of the tests and controls were booked for ANC, accounting for 87.76% and 94.79% of the cases respectively. This was not statistically significant, with a p-value of 0.77. Likewise, the VDRL test results, for both the tests and controls, were not strongly associated with booking for ANC, with a p-value of 0.770. Notably, studies showed that most

cases of maternal syphilis are booked for ANC^{11,18}.

Furthermore, the VDRL test results, for both the tests and controls, were not strongly associated with gravidity, with a p-value of 0.331. However, the study by Padovani C et al has shown that maternal syphilis has been found more in multigravida women¹⁸.

Interestingly, the VDRL test results for the tests were not strongly associated with HIV/AIDS stages, given that the only reactive case was in HIV/AIDS stage 2. However, this finding was not reported in the studies reviewed for this study.

Importantly, we found that the VDRL test results of the tests and controls were 2.08% (1/48) and 0% (0/93) of the cases respectively. This was not statistically significant, with a p-value of 0.162. This finding showed a low reactivity rate in our environment. This is consistent with the prevalence rate in Akwalbom reported by Opone CA et. al¹². Indeed, this finding is consistent with several studies on HIV-syphilis co-infection in pregnancy which found low prevalence rates¹³⁻¹⁵.

Interestingly, historical data from the reactive VDRL subject's case note showed several vital obstetrical data.

She was 36-year-old at booking for ANC. This finding was not consistent with Duby J et. al., and Wahab AA et. al.'s case reports, with their patient's ages being 28, 29, and 21 years respectively^{23,35}. Also, studies by Biadgo B et. al., and Padovani C et. al., found maternal syphilis more in those aged less than 35 years^{15,18}. The reason for these differences is unknown.

She was in asymptomatic HIV/AIDS clinical stage 2. This finding was not reported in any of the studies reviewed.

She was booked for ANC. This is consistent with Duby J et. al., and Wahab AA et. al.'s case reports, whose patients booked for ANC^{23,35}. Also, Yitbarek and Ayele, and Padovani C et. al., in their

studies found that most maternal syphilis cases were booked for ANC^{11,18}.

She is a multigravida. This is consistent with the study by Padovani C et al, which found that most maternal syphilis cases were multigravida¹⁸. Also, DUBY J et. al, and Wahab AA et. al.'s case reports, had multigravida women^{23,35}.

She had a previous history of miscarriages {G4P0+3(0A)}. This finding is consistent with two studies that found a history of miscarriages in cases of maternal syphilis^{18,35}. This reflects persistent maternal syphilis, given that miscarriage is a strongly associated adverse pregnancy outcome⁷.

She had a normal BMI of 22.13 kg/m² (normal range of 18.6 to 25.0)³⁶ at the booking. Notably, none of the studies reviewed for this study surveyed BMI in HIV-syphilis co-infection. This normal BMI is consistent with her being compliant with HAART.

She had an average anemic range third trimester PCV (normal range of 29.16 to 36.92)³⁷, this finding is consistent with the second case in Wahab AA et. al.'s study, which had mild anemia³⁵.

She received syphilotherapy once a maternal syphilis diagnosis was made. This finding is consistent with several studies^{7,17,21,35}.

She had an emergency cesarean section secondary to failed induction of labor at term. This finding is consistent with the study by Padovani C et. al, where 57.04% of 306 cases of maternal syphilis were delivered through cesarean section¹⁸.

Notably, historical data, from the case note of the reactive VDRL subject, showed that the fetus had LBW, being 2.4 kilograms (normal range of ≥ 2.5 to 3.9)[34] at 40 weeks plus one day EGA. This finding is not consistent with other studies by DUBY J et. al, with a birth weight of 1,710 grams at 31 weeks GA; Padovani C et. al, with $\geq 2,500$ grams birthweight (86.30%) at ≥ 37 weeks GA

(82.96%) in 306 cases of maternal syphilis; and Wahab AA et. al., case series with birthweights of 4 kilograms at 38 weeks GA and 1.48 kilograms at 31 weeks GA respectively^{18,23,35}. These differences show the non-specific presentation of CS in terms of birth weight and GA, though most of these cases were preterm. However, De Santis M. et. al., in their study noted that though CS commonly presents asymptotically, LBW may be the only notable feature most of the time⁷.

Furthermore, the baby had intermediate APGAR scores of 4 at the first minute, 5 at five minutes, and 5 at 10 minutes (with APGAR scores at five minutes being categorized as normal {7-10}, intermediate {4-6}, and low {0-3} respectively), given its use in monitoring the baby's adjustments to extra-uterine life by measuring Appearance, Pulse, Grimace, Activity, and Respiration. Thus, implying intermediate adjustment of the index fetus to extrauterine life. This finding partially agrees with the finding in the case report by DUBY J et al, who found a change in APGAR scores from low {1} to intermediate {5} to normal {7} at first, five, and 10 minutes respectively²³. In contrast, Padovani C et al, in their survey of 306 maternal syphilis cases found that 98.88% of the babies have normal APGAR scores at five minutes $\{\geq 7\}$ ¹⁸. This difference could be explained by their larger sample size.

Notably, the fetal anthropometric measurement of 31cm HC (normal range of 33 to 35cm at term)³⁴ shows that there is microcephaly. This finding was not reported by notable studies reviewed^{4,20,35}. This could be either because anthropometric parameters in these studies were within normal ranges, hence considered non-essential, or they were not measured. Indeed, these fetal findings of LBW, intermediate APGAR scores, and microcephaly, though largely consistent with the asymptomatic presentation of CS, agree with the studies which found that majority of CS have asymptomatic presentation

while the symptomatic ones have subtle/non-specific presentation^{7,26,35}.

Notably, histopathological examination of the placenta from the reactive VDRL subject showed a net placental weight of 400 grams (average range of 385.36 to 765.66 grams) with PBWR of 16.67% (normal range of 20.59±3.92), however, an assessment of large placenta with small for gestational age infant was made because of the relatively big size of the placenta compared to the LBW. This assessment is consistent with some studies which report the occurrence of placentomegaly with LBW in CS^{4,20}.

Also, the fetal membrane displayed squamous metaplasia of amnion as well as subamniotic hematoma of the fetal membrane microscopically. Notably, studies reviewed did not report fetal membrane features in syphilis. Thus, this calls for further research to explore the range of placental fetal membrane lesions found in syphilis in pregnancy. However, it is of note that squamous metaplasia generally occurs as a sequela of chronic irritation/inflammation of an epithelial surface, in this case, syphilis may be the cause. Furthermore, the subamniotic hematoma could be because of complications (i.e., vascular rupture) of the vasculopathy caused by syphilis. Similarly, the amniotic fluid (liquor) of our study was clear, however, this is inconsistent with the finding of amniotic fluid infection by Kittipornpechdee N et al in their study²⁰. The reason for this difference is unknown, hence needs more research.

Likewise, the umbilical cord showed focal hematoma and excess torsion, with focal edema and hematoma microscopically. These findings contrasted the findings in the majority of the studies reviewed wherein no pathology was found in the umbilical cord^{23,25-27}. These focal hematomas and excess torsion could be a sign of excessive movement in-utero due to fetal distress secondary to the opportunistic infection inflammatory state fostered by the HIV-syphilis co-infection. Interestingly, most of these studies

found necrotizing funisitis of the umbilical cord (secondary to *T. pallidum* infection of the umbilical cord artery) to be pathognomonic of CS, but this was absent in our study²⁷⁻²⁹.

Importantly, our placental disk findings of avascular villi, large hypercellular villi, villous vasculopathy (obliterative vasculopathy with onion-skinning pattern), and calcification of the disk microscopically, are in agreement with most of the studies reviewed^{20,23,25,26,28}. However, we did not find acute or chronic villitis, erythroblastosis, intervillitis, and mural thrombus in the chorionic plate vessel as variably reported in these studies^{23,25,26,28}. The reason for this pattern could be that syphilis shows variable combinations of placental lesions per case. Notably, none of these studies reported calcification of disk, this could be because our case was an HIV-syphilis co-infection, in contradistinction to the studies reviewed, which have only syphilis infection. Thus, generally, the placental weight and disk features in our study are consistent with syphilitic placentitis, hence supporting a diagnosis of CS in our study^{20,25,26,28}.

The major limitation of this study is its small sample size; hence, we were unable to generate robust data that can be well extrapolated to the general population. Secondly, for histopathological evaluation of the placental tissue, we could not carry out histochemical (with silver stains) and immunohistochemical staining to identify *T. pallidum*. Thirdly, we could not carry out PCR studies on the placental tissue to identify *T. pallidum*. Fourthly, the trimester of ANC booking at which VDRL was done was not accessible. Fifthly, the VDRL test status, as well as the syphilotherapy history of the VDRL reactive case's baby and male partner (husband), was not accessible.

Finally, the next step for further research is to conduct a more robust multi-center HIV-syphilis co-infection in pregnancy screening survey (with NTTs and TTs) with fetoplacental association (using histopathological, histochemical,

immunohistochemical, and molecular biological studies) to generate more robust data that avail better extrapolation because of better control of HIV-syphilis co-infection in pregnancy (and its adverse outcomes).

CONCLUSIONS

In conclusion, the VDRL test (syphilis screening) done for HIV-positive and HIV-negative pregnant women during their ANC was found not to be strongly associated with their age, booking status, gravidity, and HIV/AIDS clinical stage. However, the only reactive VDRL case showed obstetrical, fetal, and placental histopathological features consistent with congenital syphilis and syphilitic placentitis. Thus, showing the critical role placental histopathological evaluation may play in the diagnosis of cases of maternal/congenital syphilis.

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Ethics Committee Approval: Ethical approval for this study was obtained from UUTH Health Research Ethics Committee (UUTH/AD/S/96/VOL.XII/115) as a part of a larger study on placental pathology in HIV-positive pregnant women. Patient confidentiality was protected, and informed consent was obtained.

Conflict of Interest: The authors declared no conflicts of interest.

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