

Perinatal outcomes in pregnant women presenting with preterm premature rupture of membranes at a regional hospital in KwaZulu-Natal Province, South Africa

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Background. Worldwide, the incidence of preterm premature rupture of membranes (PPROM) is between 1% and 4% of all pregnancies.

Objectives. The primary objectives of this study were to describe and compare the perinatal outcomes of HIV-positive and HIV-negative women presenting with PPRM to a regional hospital in KwaZulu-Natal.

Methods. This was a retrospective analytical cross-sectional study which reviewed files of pregnant women presenting with premature rupture of membranes at gestation between 28 and 36 completed weeks. These were identified from the labour ward birth register and from the neonatal ward admission book. Categorical and numerical variables pertaining to the method of confirmation of diagnoses, clinical profiles, modes of delivery, maternal outcomes and neonatal outcomes were considered.

Results. A total of 87 files were analysed. Forty-six women (53%) were HIV-negative and 41 (47%) were HIV-positive. Fifty-two percent were in the gestational age <34 weeks. Fifty-nine percent ($n=51$) of women delivered vaginally and 31% ($n=27$) delivered by caesarean delivery (CD). There was also no statistical significance between the Apgar scores of the HIV-exposed and HIV-unexposed neonates, birth weights and modes of delivery. There was no statistical significance in sepsis rates, the need for ventilation and the duration of hospital stay between the two groups. The odds of developing neonatal jaundice (NNJ) in the HIV-positive group was 0.14 (95% confidence interval (CI) 0 - 0.93), which was statistically significant. There was no reported maternal or neonatal mortality and no maternal morbidity associated with PPRM in either groups.

Conclusion. This study suggests that there are no immediate significant differences in neonatal and maternal outcomes in pregnancies complicated by PPRM between HIV-negative and HIV-positive women on ART except that of NNJ.

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Preterm delivery and prematurity are significant contributors to perinatal morbidity and mortality, and their inclusion in the list of sustainable development goal epitomises this. Worldwide, the incidence of preterm delivery is between 1% and 4% of all pregnancies, with higher incidence notably in low-income countries.^[1] This figure rises significantly if a patient has a history of premature rupture of membranes (PROM). It is estimated that 30 - 40% of cases of preterm delivery are preceded by PROM.^[2-6] As a complication of pregnancy, PROM has potentially devastating perinatal and maternal outcomes, not to mention the management dilemma it poses to the obstetrician. It is therefore no surprise that much international research has been done on this subject, with varying and sometimes conflicting findings.

The role of HIV as a confounding factor to preterm PROM (PPROM) has, however, not yet been adequately described. There are no clear distinctions in the management of PPRM in HIV-positive and HIV-negative groups. Studies have found an increased incidence of preterm deliveries, low birth weights and perinatal deaths as the main associated complications in the HIV-positive group.^[7-11] Other disputed complications in this group include increased risk of intrapartum hypoxia and neonatal encephalopathy.^[12-15]

HIV and chorioamnionitis have mutually deleterious effects on PPRM, as HIV is implicated in the pathogenesis of

chorioamnionitis, and HIV-positive patients who develop PPRM are much more likely to develop chorioamnionitis.^[16] The presence of chorioamnionitis, with or without rupture of membranes, can in turn increase the risk of vertical transmission of the virus from mother to the fetus.^[16,17]

Vertical transmission of the virus from mother to child has been researched in great depth, with encouraging results regarding the use of antiretroviral treatment (ART) in reducing transmission. The risk of vertical transmission varies based on the stages of pregnancy, with the highest risk occurring during parturition.^[18] Increases in the duration of the rupture of membranes, prematurity and prolonged labour after rupture of membranes increase the risk of perinatal HIV transmission.^[3,18] Some studies have reported an increased risk of preterm deliveries with the use of antiretroviral drugs (ARVs).^[20,21]

It is against this background that this study investigated the perinatal outcomes of HIV-positive, compared with HIV-negative women presenting with PPRM at the regional hospital in KwaZulu-Natal Province (KZN), South Africa.

Methods

We retrospectively analysed the files of pregnant women who presented with PPRM to a regional hospital in KZN from 1 January 2013 to 31 of December 2013. This hospital offers a regional level of

care to the surrounding suburban population. It also serves as a referral point for a nearby district hospital, rural and urban primary healthcare clinics, and serves a population of ~400 000 people. Due to the limitations of our neonatal facilities, viability is restricted to gestation of 28 weeks or a birth weight of 1 000 g.

Inclusion criteria were clinical files of women who presented or were referred with a history of having ruptured membranes, without exhibiting any signs of labour, and were between the 28th and 37th week of gestation. In the management of a fully developed fetus with PROM decision-making is generally less complicated. Conversely, the management of pregnancies of gestation less than 28 weeks is far more complex and inconsistent, thereby making it difficult to study retrospectively. Women with existing medical conditions such as hypertensive diseases that could influence perinatal outcomes were excluded. Further exclusion criteria were unknown gestational age, unknown HIV-status, congenital abnormalities and cases where corresponding neonatal files were missing.

When reviewing the clinical files, rupture of membranes was confirmed by either visualisation of amniotic fluid in the vagina on speculum examination, a convincing history of drainage of amniotic fluid, plus reduced amniotic fluid index on ultrasound scan or by observing persistent amniotic fluid staining of sanitary pads. The corresponding neonatal charts were also reviewed. It is important to note that, regardless of the gestational age, this institution does not offer expectant management for women with PPRM.

A data collection sheet was used to extract the required information from the medical files. Maternal and obstetric characteristics included demographic data, gestation, number of previous pregnancies and relevant obstetric history, HIV-status, rhesus factor and syphilis serology. Clinical data were assessed in respect of relevant clinical findings: laboratory investigations (haematology and microbiology), ultrasound scans, administration of antibiotics and corticosteroids, induction of labour and the eventual mode of delivery.

The primary outcomes of this study were the perinatal and maternal morbidity and mortality occurring before discharge. Collated perinatal data included Apgar scores at 1 and 5 minutes, admission to the neonatal ward or intensive care unit, need for ventilation, development of any of the following conditions: hyaline membrane disease, hypoxic ischaemic encephalopathy, intraventricular haemorrhage, congenital or nosocomial infections, necrotising enterocolitis and death. Maternal morbidity included increased length of hospital stay (more than 12 hours following vaginal delivery and more than 72 hours following caesarean section (CS)).

The variables on the data sheet were captured on a Microsoft Excel spreadsheet and imported into Stata version 13 (StataCorp LP, USA) for analysis. The HIV-positive and HIV-negative subgroups were then compared. The statistical analysis was performed using Pearson χ^2 test with $p < 0.05$ considered significant. We determined the mean and odds ratios (OR) for various outcomes between the two cohorts and their 95% confidence intervals (CI) were calculated. The study was approved by the Biomedical Ethics Committee at the University of KwaZulu-Natal (ref. no. BE 275/14), the provincial Department of Health and the facility manager.

Results

There was a total of 7 694 deliveries in 2013. Out of a total of 130 (0.2%) files of patients who potentially met the inclusion criteria

only 87 files were included in this study. Forty-three files were either missing or lacked the crucial information required for the study. Most women ($n=64$; 74%) fell in the age bracket of 18 - 34 years, with 13 (15%) women <18 years, and ($n=10$; 11%) >34 years of age.

Forty-six women (53%) were HIV-negative and 41 (47%) were HIV-positive. In the HIV-positive cohort 5 (12%) patients had CD4 counts <200 cells/ μL , 13 (32%) between 200 and 350 cells/ μL , 20 (49%) >500 cells/ μL , and 3 (7%) patients had unknown CD4 counts. All HIV-positive women were on a triple ART regimen. The clinical information of all reviewed patients is presented in Table 1.

Regarding the patients' gestational age, 24% ($n=21$) were between 28 and 32 weeks, 28% ($n=24$) were between 32 and 34 weeks, while 48% ($n=42$) were between 34 and 36 weeks. There were no statistical

Table 1. Comparison of clinical information of HIV-positive ($n=41$) and HIV-negative ($n=46$) participants

	HIV-negative, n (%)	HIV-positive, n (%)	p -value
Gestation (weeks)			
28 - 32	9 (20)	12 (29)	0.21
33 - 34	13 (28)	11 (27)	0.53
35 - 36	24 (52)	18 (44)	0.29
Time from PPRM to delivery (hours)			
<12	0	3 (7)	0.10
>12 and <24	10 (22)	8 (19)	0.51
>24	30 (65)	24 (59)	0.54
Unknown	6 (13)	6 (15)	
Confirmation of SROM			
Speculum	20 (43)	18 (44)	0.57
Pad inspection	5 (11)	9 (22)	0.13
History and low AFI	4 (9)	3 (7)	0.57
Digital exam	6 (13)	9 (22)	0.21
Unknown	11 (24)	2 (5)	0.01
Tocolysis			
Yes	5 (11)	9 (22)	0.13
No	35 (76)	29 (71)	0.37
Unknown	6 (13)	3 (7)	0.30
Steroid administration			
Yes	14 (30)	21 (51)	0.38
No	27 (59)	18 (44)	0.12
Unknown	5 (11)	2 (5)	0.27
Mode of delivery			
NVD	30 (65)	28 (68)	0.47
CD	16 (35)	13 (32)	0.47
Induction of labour			
Yes	11 (24)	11 (27)	0.54
No	14 (30)	13 (32)	0.43
Unknown	21 (46)	17 (41)	

SROM = spontaneous rupture of membranes; NVD = normal vaginal delivery; CD = caesarean delivery; AFI = amniotic fluid index; PPRM = preterm premature rupture of membranes.

differences pertaining to the clinical profile and management of the HIV-positive and HIV-negative women, except that women who were HIV-positive had steroids administered significantly more often.

The mean number of antenatal visits in the HIV-negative group was 4.17 (95% CI 3.43 - 4.91) whereas in the HIV-positive group it was 4.31 (95% CI 3.79 - 4.84) and there was no statistically significant difference between the 2 groups. Only 2 patients had no antenatal visits and both were HIV-negative. The number of patients who booked before 20 weeks of gestation in the HIV-negative and HIV-positive groups were 15 (33%) and 16 (39%), respectively, and this was not statistically significant. All the booked patients in this study were rhesus-positive. Only one patient was HIV-positive and had a positive screening test for syphilis.

In 38 (44%) women, the drainage of amniotic fluid was confirmed with the recommended use of a speculum. Ultrasound amniotic fluid index and regular pad inspection confirmed rupture of membranes in 7 (8%) and 14 (16%) women, respectively. Notably, 15 (17%) had the rupture of membranes confirmed by the observation of leakage of amniotic fluid during digital *per vaginam* examination. The common bacteriological risk factors for premature rupture of membranes could not be determined in both groups, as very few patients had specimens sent for analysis. One HIV-negative patient had a Bartholin's abscess and one HIV-positive patient had a urinary tract infection. None of the women exhibited any other pregnancy-related infections.

A total of 21 women (24%) had a latency period from rupture of membranes to delivery of <24 hours; 10 (22%) were in the HIV-negative

group and 11 (27%) were in the HIV-positive group. The difference was not statistically significant. Three women delivered within 12 hours and all were in the HIV-positive group. The majority of women (62%) had a latency of >24 hours, 30 (65%) and 24 (56%) in the HIV-negative and HIV-positive groups, respectively.

Women who had ruptured membranes for >12 hours and those who warranted suppression of labour to facilitate steroid lung maturity were routinely given prophylactic antibiotics. Fifty-seven (66%) women were given oral erythromycin and metronidazole in accordance with the hospital management protocol. Four women who were eligible for antibiotics were not prescribed any and 5 had antibiotics mentioned in the management plan, but no prescriptions were found in the files. Eight women were already in labour when the 12-hour period had elapsed. Antibiotic treatment was not prescribed in 9 patients.

Fifteen women (16%) had their labour suppressed using nifedipine to allow for fetal lung maturity. Betamethasone was given to 35 of the 45 women eligible to receive steroids for fetal lung maturity. There were no statistically significant differences between the 2 groups with respect to tocolysis and the use of steroids.

Twenty-two (25%) women had induced labour; 51 (59%) delivered vaginally and 27 (31%) delivered by caesarean delivery (CD). Indications for CD included fetal distress ($n=7$), breech presentation ($n=5$), anhydramnios ($n=3$), failed induction of labour ($n=3$), previous CD $\times 1$ ($n=4$), previous CD $\times 2$ ($n=2$), poor progress of labour ($n=2$), cord prolapse ($n=1$), high parity ($n=1$) and very low fetal weight ($n=1$). There were no statistically significant differences in the induction of labour and mode of delivery between the HIV-negative and HIV-positive groups.

Maternal outcomes

None of the mothers suffered any intrapartum or postpartum complications until discharge. Mothers who stayed in hospital for >3 days were kept as boarders awaiting completion of the intravenous antibiotic course for their babies and/or for adequate neonatal weight gain.

Neonatal outcomes

In the baby-weight category, 43 (49%) babies weighed 2 000 - 2 500 g, 21 (24%) weighed 1 500 - 1 999 g, 12 (14%) weighed >2 500 g and 11 (13%) weighed 1 000 - 1 500 g. There were significantly more males in the HIV-positive group and more females in the HIV-negative group ($p=0.03$). Clinical information on neonatal outcomes is presented in Table 2.

Overall, 54 babies were admitted to the nursery, 24 were HIV-negative and 30 were HIV-positive. Invasive ventilation was administered to 2 babies in each group. Twenty-six (30%) were discharged from the nursery within 24 hours, 9 (10%) were discharged between 24 and 48 hours and 19 (23%) were in the nursery for >48 hours.

The odds of being admitted to the nursery for >48 hours in the HIV-positive group was 1.74 (95% CI 0.64 - 4.76) and the odds of staying in hospital for more than 7 days in the HIV-positive infants was 1.68 (95% CI 0.51 - 5.51). Both odds ratios were not statistically significant. There were no correlations between CD4 cell counts of the mothers and the length of their stays in either the nursery or the hospital.

Twenty-three (26%) babies received intravenous antibiotics for suspected congenital sepsis on the basis of a raised white cell count. Twelve (26%) were in the HIV-negative group and 7 (17%) were HIV-positive. This finding was not statistically significant

Table 2. Comparison of neonatal outcomes of HIV-negative (N=46) and HIV-positive (N=41) women

	HIV-negative, n (%) [*]	HIV-positive, n (%) [*]	p-value
Birth weight (grams)			
1 000 - 1 499	4 (9)	7 (17)	0.20
1 500 - 1 999	9 (20)	12 (29)	0.21
2 000 - 2 499	27 (59)	16 (39)	0.05
>2 500	6 (13)	6 (15)	0.30
Sex			
Male	18 (39)	25 (61)	0.03
Female	28 (61)	16 (39)	0.03
Apgar at 5 min			
8 - 10	45 (98)	39 (95)	0.64
<8	1 (2)	2 (5)	0.64
Time spent in nursery (hours)			
<24	14 (30)	12 (15)	0.55
24 - 48	2 (4)	7 (8)	0.06
>48	8 (17)	11 (14)	0.21
Number needing invasive ventilation	2 (4)	2 (5)	0.64
Length of hospital stay post delivery (days)			
<3	22 (48)	21 (51)	0.46
3 - 7	19 (41)	13 (32)	0.40
>7	5 (11)	7 (17)	0.30

^{*}Percentages are of births within each group.

($p=0.44$). Routine neonatal septic screening by means of C reactive protein (CRP) and blood culture investigations were not helpful in confirming infection, except in 2 babies, where contamination was suspected.

A total of 8 babies (9%) developed neonatal jaundice (NNJ). Of these, only 1 was HIV-negative; 3 were male and 5 were female. The odds of developing NNJ in the HIV-positive group was 0.14 (95% CI 0 - 0.93), which was statistically significant. The mean birth weight was 2 450 g, with a range of 1 200 - 2 900 g. Six women delivered vaginally, while 2 delivered by CD. No babies suffered neurological or gastrointestinal complications associated with PPRM before discharge. There was also no perinatal mortality in the analysed files.

Discussion

This retrospective study found no significant differences in the perinatal and maternal outcomes of HIV-positive and HIV-negative women with pregnancies complicated by PPRM. There were no differences in respect of respiratory complications, neonatal intensive care unit admission, neonatal infections and length of hospital stay post delivery. None of the babies developed any neurological or gastrointestinal complications until they were discharged and there was surprisingly no perinatal mortality. This study also concurs with previous studies performed in other African countries, comparing HIV-positive and HIV-negative cohorts, which found little or no differences between HIV-positive and HIV-negative women with respect to gestational age, birth weight, and Apgar scores.^[22,23]

We could find no explanation for the skewed distribution of the sexes among the 2 groups. The differences were statistically significant. This could be a statistical error due to the higher number of missing or disqualified files.

Eight babies in this study developed NNJ and of these, only 1 was HIV-positive – this was a statistically significant finding. The higher incidence of NNJ among the babies of HIV-negative women is in keeping with the findings by Nakanga *et al.*^[24] in a study undertaken in Malawi in 2015. They hypothesised that the efavirenz (EFV) in the prevention of mother-to-child transmission (PMTCT) of HIV acted as a fetal liver enzyme inducer that would aid the conjugation of bilirubin. All women in this study were on a triple ART regimen that included EFV. However, in contrast to this and other studies, the male sex was not a risk factor for neonatal jaundice in this study.^[25,26]

The seropositivity rate in this study was 47%, which was higher than the KZN provincial seropositivity rate of 40.1%, but this may be due to the fact that HIV-positive women are more prone to sepsis and hence PPRM.^[27] Half of the women had CD4 counts of >350 cells/ μ L, while 12% had CD4 counts of <200 cells/ μ L. It is important to note that all the women were either on long-term or prophylactic ART, which consists of the fixed-dose combination of tenofovir (TDF), emtricitabine (FTC) and EFV as per national protocol. There was no association between low CD4 count and adverse outcomes, possibly because of the effect of the ART on suppressing the viral load.^[28]

The mean number of antenatal visits and mean gestational age at booking were similar between the HIV-positive and HIV-negative groups. There was no obvious association between PPRM and maternal age, poor antenatal clinic attendance or parity in this study. High-risk maternal age groups, teenagers and women >34 years of age accounted for 26% of the women in this study. Nulliparous women constituted 33% of women with PPRM, which was lower than in previous similar studies.^[29,30]

Seventeen percent of the women had the rupture of membranes confirmed by digital *per vaginam* examination despite the leakage of fluid having been noted in the patient history. Standard protocol recommends the use of a speculum to prevent ascending infection.^[31] We found no obvious explanation for this, however, disregard for protocol and the shortage of speculums were considered among the reasons for diagnosing PPRM by doing digital *per vaginam* examinations. In his study of 97 women with PROM in Chris Hani Baragwanath General Hospital (CHBGH), Iloanusi^[30] found that 35% of the women had a digital examination prior to the onset of labour, which was double the percentage compared with our study.

The most common microorganisms causing PPRM in this setting could not be determined due to the consistent omission of urogenital septic screening in nearly all of the women in this study. Iloanusi^[30] also found the same transgression at CHBGH. The lack of microbiological investigations did not seem to have any negative impact on the outcomes, as sepsis was not a significant finding in this study. In accordance with hospital protocol based on scientific evidence nearly all women were given prophylactic antibiotics (erythromycin and metronidazole).^[32-34] Babies delivered after prolonged rupture of membranes also received a course of intravenous antibiotics as standard neonatal protocol.

In resource-constrained areas, it could be argued that routine urogenital septic screening of patients with PPRM is not essential, particularly if immediate delivery is anticipated and if antibiotics are used routinely. Even if clinical chorioamnionitis is present, Osmanagaoglu and Unal^[35] found that neonatal outcomes in such patients were similar to those without clinical chorioamnionitis.

Following completion of steroids, a choice between expectant management and delivery is made.^[36] The protocol in our hospital setting recommends delivery of the neonate regardless of gestation because of concerns about the risk of infection and other complications associated with prolonged rupture of membranes. The fewer adverse outcomes in this study compared with others elsewhere seem to validate this school of thought.

The rate of CD in this study was 33%, which was slightly higher than in similar studies by Iloanusi^[30] at CHBGH and by Patil and Patil^[29] in India, who reported CD rates of 25% and 27%, respectively. The rate of CD for failed induction of labour was 11.1% compared with 7.6% in the Indian study and 16% in the CHBGH study.

Study limitations

Despite the limitations inherent to a retrospective study and the small sample size, this study provides a more objective comparison between HIV-positive and HIV-negative women with PPRM, given the homogeneity of the 2 groups in our study and the similarity in their management. Perhaps, more significantly, this study also reports some encouraging data on the benefit of the use of ART in all HIV-positive pregnant women regardless of their CD4 counts.

A major limitation of this study was that a significant number of files were either missing or were excluded due to a deficiency of crucial information required for the study, but this may not have had a negative impact on the overall findings because files from HIV-positive and HIV-negative women stood equal chances of being excluded. Deviation from the standard protocol of screening for infections in a form of midstream urine and vaginal swabs was noted. The extent to which sepsis is a risk factor for the PPRM and

the most common pathogenic organism could not be established. The above two points are concerning in view of the rising litigation claims being made against the public and private sectors and the cost of settling such claims.^[37] If the effect of medical litigation in obstetrics is to be minimised, it is absolutely imperative that clinicians and nurses ensure that evidence-based practice guidelines are followed, that medical records are comprehensively completed and that administrative staff ensure that records are safely stored.^[35]

Conclusion

This study suggests that there are no immediate significant differences in neonatal and maternal outcomes in pregnancies complicated by PPROM between HIV-negative and HIV-positive women who are on prophylactic or long-term ART, except in the development of NNJ, where ART was protective.

PPROM did not seem to significantly compound adverse perinatal outcomes associated with preterm delivery when the management strategy of immediate delivery after steroid fetal lung maturation, regardless of gestation, was employed.

A larger and more powered study is recommended to confirm the findings of this study. Furthermore, intermediate and long-term follow up is suggested to determine the development of late neonatal and maternal complications in this setting.

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