CLINICAL ARTICLE

Impact of maternal HIV on umbilical cord lactate measurement at delivery in a South African labor ward

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Abstract

Objectives: To assess umbilical artery actate levels and perinatal outcomes among women with and without HIV infection.

Methods: The present prospective cohort study recruited women planning to undergo vaginal delivery at Kalafong Hospital, South Africa, between March 3 and November 12, 2014. Umbilical artery lactate levels were measured and perinatal outcome data were recorded. Outcome analyses were stratified by maternal HIV status, and a subgroup analysis was performed where women with a CD4 count below 350×10^6 cells/L were compared with women without HIV.

Results: In total, 936 women with singleton fetuses were enrolled. Maternal HIV status was available for 897 (95.8%) participants, of whom 202 (21.6%) had HIV infections. Overall, 186 (92.1%) women with HIV infections received prophylaxis or treatment. There was no difference between participants with and without HIV infections in the preterm delivery rate (*P*=0.770), mode of delivery (*P*=0.354), neonatal resuscitation rate (*P*=0.717), 1- or 5-minute Apgar scores below 7 (*P*=0.353), or the rate of having an umbilical artery lactate level above 5.45 mmol/L (*P*=0.301). Similarly, there were no differences in outcomes in the subgroup analysis of women with a CD4 count below 350×10^6 cells/L.

Conclusion: Umbilical artery lactate levels and perinatal outcomes were found to be comparable between patients with and without HIV infections in a South African setting

Keywords: HIV; Lactate; Maternal; Middle income; Perinatal; South Africa; Delivery

Synopsis: Acidosis, assessed by umbilical artery lactate, and perinatal outcomes were found to be comparable between patients with and without HIV in a South African setting

1 INTRODUCTION

The burden of HIV among pregnant women in South Africa is estimated to be approximately 30% [1]. Prenatal testing for HIV in South Africa is routine, occurring at a rate of at least 95% [2], and prevention of mother-to-child transmission (PMTCT) programs are almost ubiquitous in prenatal care [3]. In 2014, South Africa followed the 2010 WHO Guidelines for managing maternal HIV in pregnancy with highly

active antiretroviral treatment (HAART) administered to women with a CD4 count lower than 350×10^6 cells/L [4]. Women with a CD4 count higher than 350×10^6 cells/L received antiretroviral (ARV) prophylaxis for PMTCT, including azidothymidine during pregnancy and nevirapine during delivery.

Alongside maternal HIV infection, South Africa has a high perinatal mortality rate of 33.4 per 1000 deliveries [1]. A significant contributor to this perinatal mortality rate is intrapartum and neonatal death, which often results from intrapartum hypoxia and acidosis [6]. Furthermore, there is an increase in intrapartum asphyxia-related neonatal death among women infected with HIV in South Africa [7]. Because one-third of pregnant women in South Africa have HIV, it is important that clinicians have an understanding the adverse maternal and perinatal outcomes that can occur.

It was considered that maternal HIV status might play a role in intrapartum acidosis in settings where the burden of HIV is large and adverse perinatal outcomes are common [9]. In addition, the use of antiretroviral therapy (ART) in pregnancy might affect the measurement of acidosis. A previous study [8] found that umbilical artery lactate is an inexpensive and effective way to measure acidosis in the clinic and can be used in the assessment of neonatal outcome. Consequently, the aim of the present prospective cohort study was to assess umbilical artery lactate results (as a measure of acidosis) and intrapartum and neonatal outcomes among women with and without HIV who were delivering in a large tertiary unit in South Africa.

2 MATERIALS AND METHODS

The present prospective cohort study was conducted among women planning on undergoing a vaginal delivery between March 3 and November 12, 2014, at Kalafong Hospital, Pretoria, South Africa, a tertiary hospital with an annual delivery rate of more than 6000 deliveries. All women who intended to have a vaginal delivery were eligible for enrollment, regardless of the ultimate delivery mode. The study was approved by the University of Western Australia Human Research Ethics Committee (ref. no. RA/4/1/6581) and the University of Pretoria, Pretoria, South Africa (ref. no. 7/2014). All participants provided written or verbal informed consent.

The present study cohort was part of a larger uncontrolled, before-and-after study, the details of which have been presented elsewhere [10]. A protocol was developed and is available on request.

For all patients, the umbilical artery was sampled immediately after delivery from a double-clamped segment of cord. Umbilical artery lactate was measured using a handheld meter (Roche Accutrend Plus; Roche, Rotkreuz, Switzerland) with a demonstrated coefficient of variation of 1.8%–3.0% [1].

For the present study, data were collected from the birth registry and patient case files. The maternal data collected were HIV status, CD4 count, demographic and clinical characteristics, mode of delivery, and labor adverse events; the neonatal data collected were umbilical artery lactate, need for resuscitation, Apgar score, delivery weight, and gestational age at delivery.

SPSS version 22.0 (IBM, Armonk, NY, USA) was used for data analysis. Variables were stratified by HIV status and were expressed as mean±SD or median (interquartile range; range) for continuous data, and absolute numbers and percentages for categoric data. Continuous lactate data underwent natural logarithm transformation to produce a normal distribution and were summarized as the geometric mean (95% confidence interval). Umbilical artery lactate levels were dichotomized on the basis of the previous cohort study [10] with values above a cutoff level of 5.45 mmol/L considered abnormally high.

To consider the potential confounding impact of HAART, outcomes were also compared between patients with HIV who had a CD4 count less than 350×10^6 cells/L or an unknown CD4 count and women who did not have HIV **;** this was performed under the assumption that women with an unknown CD4 count were more likely to have a low count or adverse outcomes. The CD4 count of 350×10^6 cells/L was established in a study in South Africa [12] as the cutoff for women to be considered at high risk and to receive HAART. Viral loads were not measured; consequently, there were no data on patient response to treatment.

Univariate comparisons were tested using the independent *t* test for continuous variables and the χ^2 or Fisher exact test for categoric variables. All tests were two-sided and $P<0.05$ was considered statistically significant.

3 RESULTS

During the study period, there were 4668 deliveries at Kalafong Hospital. Nine hundred and ninety four women consented to be enrolled in the study and data were collected as planned. Of the 994 deliveries, 936 were singleton deliveries. Of these, HIV-infection status was unknown for 39 (4.2%) women, resulting in 897 (95.8%) patients being included in the present analysis. There were 202 patients with HIV infections and 186 (92.1%) were receiving ARV prophylaxis or HAART. CD4 status was known for 177 (87.6%) of the patients with HIV, and 98 (55.4%) of the patients with known CD4 status had a count higher of 350×10^6 cells/L or higher. These women were treated with a dual therapy regimen of azidothymidine during pregnancy and intrapartum nevirapine for PMTCT. The study included 695 patients who did not have HIV.

The maternal characteristics of the study cohort by HIV status are presented in Table 1. Women with HIV infections were older, and correspondingly had greater gravidity and parity (all $P<0.001$). There were no differences in delivery characteristics between the patients with and without HIV infections, including the frequency of different delivery modes (spontaneous and assisted, 124/202 [61.4%] versus 453/695 [65.2%]) or cesarean delivery (76/202 [38.0%] versus 238/695 [34.2%] between infected and non-infected women ($P=0.354$) (Table 2). In addition, there was no difference in the frequency of suspected fetal distress, as determined by cardiotocography ($P=0.752$) (Table 2).

Table 1 Maternal characteristics. [a]

Variable	Patients with HIV infection (n=202)	Patients without HIV infection (n=695)	*P* value
Maternal age, y	29.5±5.6	26.8±6.5	<0.001
Pregnancy duration at delivery, wk	38.6±3.01	38.9±3.19	0.3212
Gravidity	3 (2–3; 1–6)	2 (1–3; 1–8)	<0.001
Parity	1 (0–3; 0–7)	1 (1–2; 0–5)	<0.001
Nulliparous	41 (20.3)	286 (41.2)	<0.001
ARV prophylaxis or HAART	186 (92.1)	NA	

Abbreviations: ARV, antiretroviral; HAART, highly active antiretroviral treatment; NA, not applicable.
[a] Values are given as mean±SD, median (interquartile range; range), or number (percentage), unless indicated otherwise.

Table 2 Delivery characteristics. [a]

Variable	HIV positive (n=202)	HIV negative (n=695)	*P* value
Delivery mode			
Spontaneous vaginal delivery	103 (50.9)	387 (55.7)	0.529
Assisted vaginal delivery	21 (10.4)	66 (9.5)	
Cesarean	76 (37.6)	238 (34.2)	
Unknown	2 (1)	4 (0.6)	
Indication for cesarean			
Abruption	3 (1.5)	7 (1.0)	0.702
Prepartum hemorrhage	3 (1.5)	3 (0.4)	0.132
Pre-eclampsia	5 (2.5)	9 (1.3)	0.329
Breech	1 (0.5)	18 (2.6)	0.093
Malpresentation	2 (1.0)	4 (0.6)	0.622
Failed induction of labor	3 (1.5)	7 (1.0)	0.702
Delayed progress 1st stage	15 (7.4)	60 (8.6)	0.585
Delayed progress 2nd stage	5 (2.5)	8 (1.2)	0.182
Intrauterine growth restriction	2 (1.0)	0 (0)	0.051
Other	2 (1.0)	7 (1.0)	>0.99
Suspected fetal distress	38 (18.8)	124 (17.8)	0.752
VBAC in labor	11 (5.4)	32 (4.6)	0.622
VBAC not in labor	4 (2.0)	9 (1.3)	0.504
Decision to delivery time, min [b]	82 (39–125; 2–858)	64 (34–112; 3–1440)	0.065

Abbreviations: VBAC, vaginal delivery after cesarean.
[a] Values are given as number (percentage) or median (interquartile range; range) unless stated otherwise.
[b] Assisted vaginal delivery (n=92) and cesarean delivery (n=280) only.

Umbilical artery lactate data were available for 196 (97.0%) of the patients with HIV infections and 660 (95.0%) of the patients without HIV. The mean umbilical artery lactate level was 4.8 mmol/L (95% confidence interval 4.6–5.0) among patients with HIV and 4.5 mmol/L (95% confidence interval 4.2–4.9) among patients without HIV (*P*=0.121). There was no difference in the rate of neonates having a lactate level

above 5.45 mmol/L between the patients with (66/196 [33.7%]) and without (249/660 [37.7%]) HIV infections (*P*=0.301).

The mean delivery weight did not differ between the patients who did (2977±636 g) and did not (3029±632 g) have HIV (*P*=0.312). Pregnancy duration at delivery data were available for 846 (94.3%) of the study cohort (Table 1), with no difference in the mean pregnancy duration at delivery between the groups (*P*=0.322). The preterm delivery rate (<37 weeks) was similar among patients with HIV infections (37/186 [19.9%]) and those without (125/660 [18.9%]) (*P*=0.770).

There was no difference between the groups with and without HIV in the need for neonatal resuscitation (46/195 [23.6%] vs 150/671 [22.4%], respectively; *P*=0.717), 1-minute Apgar scores below 7 (28/195 [14.4% vs 98/682 [14.4%], respectively; *P*=0.997), or 5-minute Apgar scores below 7 (15/195 [7.7%] vs 40/682 [5.9%], respectively; *P*=0.353). There was no difference in the rate of admission to the neonatal special care unit (27/199 deliveries of HIV positive women where admission data were known and 96/688 deliveries of HIV negative women where admission data were known; all levels of special care including intensive care (ICU), high dependency and ward nursery), but there a trend toward a higher proportion of admissions to the high dependency unit was observed among patients with HIV (10/199 [5.0%]) compared with those without (19/688 [2.8%]) (*P*=0.058).

Overall, 103 patients had a low or unknown CD4 count. When compared with patients without HIV, no differences were observed in the rate of spontaneous vaginal delivery (46/103 [44.7%] vs 387/691 [56.0%]), assisted vaginal delivery

(15/103 [14.6%] vs 66/691 [9.6%]), or cesarean delivery (42/103 [40.8% vs 238/691 [34.4%]) (*P*=0.069).

The preterm delivery rate was similar between the low or unknown CD4 count group and the patients without HIV (18/90 [20.0%] vs 125/660 [18.9%], *P*=0.810). The mean delivery weight among patients with low or unknown CD4 (2933±663 g) did not differ from that among patients without HIV (3029±632 g) (*P*=0.157). Similarly, there was no difference in the need for neonatal resuscitation (30/100 [30.0%] vs 150/671 [22.4%], *P*=0.092) or the incidence of umbilical artery lactate levels above 5.45 mmol/L (41/101 [40.6%] vs 249/663 [37.7%]; *P*=0.558) between patients with HIV and those without .

4 DISCUSSION

To the best of our knowledge, the present study is the largest to compare umbilical artery lactate after delivery between patients with and without HIV infections. Among the 897 women and neonates included in the analysis, there were no differences in umbilical artery lactate levels, mode of delivery, or neonatal outcomes between the two groups. This objective measurement of acidosis, coupled with the lack of difference between the two study groups, supports the current protocol whereby intrapartum management of women with HIV in a setting such as South Africa does not differ from that of women without HIV in terms of intrapartum fetal monitoring.

In the study setting, lactate was used as a measure of acidosis; this differs from the widely accepted gold standard of umbilical cord pH [13]. However, lactate has been shown to be an accurate measure of acidosis [8] that can easily be determined with

a handheld point-of-care device. The mean lactate levels in both groups in the present study were similar to those reported in another large cohort study [14]; however, nearly one-third of participants in the present study delivered a neonate with a umbilical artery lactate level higher than 5.45 mmol/L. This varies from the findings of White et al. [1], who found that only 13% of neonates had an umbilical artery lactate level above the 95% centile when they introduced universal sampling. This discrepancy is likely to be reflective of perinatal outcomes in the present study unit as a whole (for both women with and without HIV); by way of example, the frequency of early neonatal death for all neonates with delivery weight greater than 500 g was 0.2% in the study of White et al. [1], whereas it is 16.7% in provincial tertiary units (including the present study unit) in South Africa [16].

Several studies on obstetric and perinatal outcomes of women and neonates as a consequence of HIV and its associated treatment have been conducted. A South African study [7] of women with HIV conducted in 2006–2008 in the same region as the present study found an increase in intrapartum asphyxia-associated neonatal deaths. By contrast, there was no difference in the rate of suspected fetal distress or high umbilical artery lactate levels in the present study. Moreover, women with HIV in the present study were older and had greater parity—two factors that have often been associated with adverse perinatal outcomes [17]. This difference between the current study and others could be due to the number of women enrolled or the fact that the study unit is a tertiary obstetric unit with the resources to respond to clinically acute situations. Although the present study was not powered to predict mortality, the lack of objective evidence for a higher incidence of hypoxia among patients with HIV is reassuring. Notably, no differences in delivery weight or preterm delivery rate

were observed among women with HIV, both of which have frequently been cited as concerns of prophylaxis and HAART use in early pregnancy [18]; however, it should be noted that there was no information on when the study participants commenced treatment regimens.

Evidence regarding whether ART in pregnancy is associated with hyperlactemia in neonates is conflicting [17], although it seems that ART is unlikely to be associated with pathologic hyperlactemia [18]. Consistent with this, El-Beitune et al. [19] did not find any impact of treatment on umbilical cord gas pH or base excess. This finding was replicated in the present study, where the vast majority of patients with known HIV infections were receiving ARV prophylaxis or HAART, and the lactate outcomes for their neonates were comparable to those of women without HIV. Here, it is suggested that umbilical artery lactate sampling in a unit with a high prevalence of HIV can be introduced without concern of ART impacting on the results.

CD4 counts were available for almost 90% of the study cohort. All women with a CD4 count of less than 350×10^6 cells/L should have been receiving HAART; however, from the present study data it is not possible to comment on the relationship between the time of CD4 count measurement and the initiation of HAART. By contrast, most women with a CD4 count above 350×10^6 cells/L would have been receiving ARV prophylaxis, although it is possible that some could have been started on HAART and the higher count was a repeat investigation with adequate response. Owing to viral load data being unavailable, the recorded CD4 count was used as a surrogate for viral response and this is acknowledged as a limitation. That said, a CD4 count below 350×10^6 cells/L is more likely to be

associated with lack of suppression of viral load and with perinatal transmission of HIV [20]. A lack of viral load suppression could increase poor obstetric outcomes as a function of immune suppression, the socioeconomic factors that led to the lack of treatment, and the potential limited prenatal care that resulted in no or late initiation of treatment. Other than an increase in puerperal sepsis, there is limited robust evidence that intrapartum outcomes are worse among women infected with HIV [21]; this is supported by the findings of the present study and strengthened by the subgroup analysis of women with a low CD4 count.

Kalafong hospital is a tertiary unit in a middle-income country; consequently, the findings are not applicable to all settings with a high HIV burden. Nevertheless, there are many units within South Africa where the use of umbilical artery lactate measurements could be considered as a tool for assessing intrapartum care and neonatal outcomes [22], and the present study data indicate that the inclusion of patients with HIV infections in this process would be acceptable. The vast majority of individuals infected with HIV live in low- and middle-income countries; consequently, there will be other settings where the distribution of HIV and perinatal outcomes will be similar and where the present evidence can be applied to the assessment of intrapartum care.

The present study had strengths; the large prospective cohort had an HIV rate reflective of the South African population, and, because all women were eligible for inclusion in the study, the perinatal outcomes are likely to reflect those of an unselected population. Additionally, the lactate cutoff used to indicate adverse

outcomes was robust, being similar to that found in other large high-income country cohorts[15].

The study had some limitations. First, some HIV status data were missing; however, given the large sample numbers and that fact that the missing HIV status corresponded to less than 5% of women, it is unlikely that these data would markedly changes the findings. Second, although the cohort was large, it did not capture all deliveries within the study period. Third, there were no paired samples to confirm that the umbilical artery lactate samples were arterial, as previously discussed [10]; however, the lactate cutoff values have been replicated in other large cohort studies [10, 23] and there is a well-documented positive association between venous lactate and the prediction of arterial lactic acidemia.

In conclusion, umbilical artery lactate—as an objective measure of intrapartum acidosis—and delivery and perinatal outcomes were found to be comparable between women who were and were not infected with HIV in a South African setting.

Author contributions

ERA contributed to the design of the study, data collection, and writing the manuscript. RCP and JED contributed to the design of the study, supporting its conduct and revising the manuscript. EAN contributed to the design of the study, data analysis, and revising the manuscript.

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Conflicts of interest

The authors have no conflicts of interest.

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