The effect of maternal HIV status on perinatal outcome at Mowbray Maternity Hospital and referring midwife obstetric units, Cape Town

Deon Kennedy, MMed (O&G), FCOG (SA)
Sue Fawcus, MA (Oxon), MB BCh, FRCOG
Department of Obstetrics and Gynaecology, University of Cape Town

Max Kroon, FCPaed (SA)
Neonatal Service, Mowbray Maternity Hospital, and School of Child and Adolescent Health, University of Cape Town

Objectives. To study the effect of maternal HIV status on perinatal outcome at Mowbray Maternity Hospital (a secondary-level hospital in Cape Town) and its satellite community midwife obstetric units.

Design. A retrospective descriptive and comparative study.

Setting. Public sector maternity facilities serving historically disadvantaged populations.

Subjects. All deliveries at Mowbray Maternity Hospital and its referral midwife obstetric units from January to December 2008.

Outcome measures. Stillbirth, early neonatal death, perinatal mortality and neonatal encephalopathy rates in HIV-positive and HIV-negative subjects.

Results. There was a total of 18 870 deliveries at the units studied, 3 259 (17.2%) of them to HIV-positive mothers. The stillbirth rate in the HIV-positive population was 17.1/1 000 births, compared with 8.3/1 000 in the HIV-negative population (odds ratio (OR), 2.07, 95% confidence interval (CI) 1.5 - 2.8). The early neonatal death rate in the HIV-positive population was 4.6/1 000 live births, compared with 3.1/1 000 in the HIV-negative population (OR 1.46, 95% CI 0.8 - 2.6). The perinatal mortality rate in the HIV-positive population was 21.7/1 000 births, compared with 11.7 in the HIV-negative population (OR 1.91, 95% CI 1.4 - 2.5). A comparison of the pattern of primary obstetric causes of perinatal mortality showed that infection, intra-uterine growth restriction (IUGR) and antepartum haemorrhage (APH) were significantly more common as causes for perinatal death in the HIV-positive population. The risk of neonatal encephalopathy in the HIV-exposed population was 4.9/1 000 live births compared with 2.07 in the HIV-negative group (OR 2.36, 95% CI 1.28 - 4.35). The 1 643 women (8.7% of total deliveries) who were not tested for HIV were at particularly high risk of adverse perinatal outcome. This group included women who had either declined testing or not attended for antenatal care.

Conclusion. The perinatal mortality rate in the group of HIV-exposed mothers was significantly higher than that in the HIV-negative group due to a higher stillbirth rate. Infection, IUGR and APH were significantly more common obstetric causes for mortality in the HIV-infected population. The risk of neonatal encephalopathy was also significantly higher in the HIV-positive population.

By the end of 2009 there were 33.4 million people living with the human immunodeficiency virus (HIV), with sub-Saharan Africa being the regions worst affected.[1] Anonymous seroprevalence studies of antenatal clinic attendees in South Africa reports an average national infection rate of 29 - 30% in this group.[2]

Maternal HIV infection is a leading underlying cause of maternal and child morbidity and mortality in South Africa.[3,4] In the Metro West (former Peninsula Maternal and Neonatal Service) of Cape Town, maternal HIV infection is known to have contributed to a recent increase in maternal mortality rates.[5]

A review of the world literature suggests a clear association between HIV infection and stillbirth. A meta-analysis of 31 trials reported a fourfold increase in stillbirths if a group of mothers infected with HIV is compared with a similar group of mothers testing negative for HIV.[6]

In spite of a steady decline in perinatal mortality in First-World countries, it is feared that the HIV epidemic will negate any progress made in this regard in developing countries. This point is illustrated by a registry-based study done in Tanzania analysing 14 444 singleton deliveries. The association between maternal HIV status and pregnancy outcome was studied, and the HIV-infected mothers were found to have a 75% higher risk of preterm delivery compared with the HIV-negative mothers. The risk of perinatal death in the HIV-infected group was found to be 89% higher than that in the non-infected group.[7]

A smaller prospective study performed in Kenya, comparing perinatal outcome in a seropositive group of mothers with that in a matched seronegative group, found a significant increase in preterm birth in the seropositive group (21% v. 9.1%). In addition, a small increase in perinatal mortality was found in the seropositive group.[8]

In India, Kumar *et al*., studying the impact of HIV-1 on pregnancy outcome in a cohort of tribal women in Manipur district, confirmed a significantly higher incidence of placental membrane inflammation (histological evidence of funisitis or chorio-amnionitis) in the HIV-positive group.[9] They concluded that HIV infection was associated with adverse fetal outcome.

In Tshwane, South Africa, an audit in 2006 showed that both stillbirth and neonatal mortality rates were significantly higher for HIV-positive than HIV-negative mothers, with intrapartum asphyxia, preterm labour and infections contributing to the difference.[10]

The association between HIV status and perinatal mortality at Mowbray Maternity Hospital (MMH) and in its referring midwife obstetric units (MOUs) is the subject of this study. At MMH during 2006 the perinatal mortality rate was recorded as 29.4/1 000 deliveries. At the MOUs the perinatal mortality rate was 15.8/1 000 deliveries. Annual routine statistics show that the prevalence of HIV infection among women delivering at MMH during 2006 was 19%.

Aims and objectives

The aim of this study was to study the impact of maternal HIV status on perinatal outcome at MMH, a secondary-level hospital in Cape Town, South Africa, and its catchment MOUs.

Specific objectives were: (*i*) to compare the perinatal mortality rate in HIV-exposed group with that in the HIV-negative group; (*ii*) to determine, where possible, the primary obstetric cause of adverse outcome and compare this in HIV-exposed and HIV-negative women; and (*iii*) to compare the incidence of neonatal encephalopathy in the HIV-exposed group and the HIV-negative group.

Methods

The study was a retrospective descriptive and comparative audit conducted during 2008. MMH is a level two obstetric hospital serving a low- to middle-income urban population. Three community MOUs refer to MMH: Khayelitsha, Guguletu and Mitchells Plain.

During the year of the study MMH and referral MOUs followed the Western Cape Department of Health prevention of mother-to-child transmission (PMTCT) policy. This included voluntary counselling and testing of all pregnant women for HIV. For seropositive women, CD4 estimation was performed and those with levels <250 cells/µl were referred for triple antiretroviral therapy. For HIV-positive women with CD4 counts above 250 cells/µl, routine PMTCT measures included treatment of the mother with zidovudine from 28 weeks' gestation as well as nevirapine as a single dose during labour. The newborn was treated with single-dose nevirapine and zidovudine for 1 or 4 weeks; infant feeding options included exclusive formula feeding or exclusive breastfeeding.

All data pertaining to HIV testing, results and treatment were entered into the PMTCT registers for the facility. All deliveries at MMH and its referral MOUs from January 2008 to December 2008 could therefore be audited with respect to HIV status.

All deliveries in which the outcome was a perinatal death (stillbirth or early neonatal death of an infant weighing 500 g or more) or a newborn infant with neonatal encephalopathy were identified, analysed in detail and discussed at the perinatal audit meetings held on a monthly basis at MMH and its satellite MOUs. For each adverse outcome a purpose-designed form is completed which includes demographic data, pregnancy and labour details, and the cause of adverse perinatal outcome. Cause of death is determined by clinical features as well as histological examination of the placenta.

The forms, completed prospectively at the monthly meetings, were used to derive data for this study. In addition, data were entered into the South Africa Perinatal Problem Identification Program (PPIP) electronic database, and this was used to check for completeness of the data set. Cross-checking with registers was done, and for any missing data the folders were retrieved and missing data extracted.

Although not part of the PPIP, MMH has routinely collected data on infants with neonatal encephalopathy and discussed such cases at the monthly perinatal audit meetings since 2002. The diagnosis of neonatal encephalopathy was made by the neonatologists based on the Fenichel and Sarnat criteria and divided into mild, moderate and severe according to the Thompson (Groote Schuur) scoring system.[11-13]

Approval for the study was granted by the UCT Faculty of Health Sciences Human Research Ethics Committee (HREC REF: 282/2010). Since this was a register and folder review, no consent was required and confidentiality of data was ensured.

Results

There was a total of 18 870 deliveries at the units studied, 3 259 (17.2%) of them to HIV-positive mothers (Table I).

At the time of the study CD4 testing was not universal, being done in 67% of the HIV-positive population. Of those with known CD4 counts, 48.3% had a count less than 350 cells/µl. The data on

Table I. Numbers of deliveries according to HIV status at MMH and referral MOUs

Institution	Total HIV-positive deliveries	Total HIV-negative deliveries	Total untested deliveries	Total No. of deliveries
MMH	1 747 (18.7%)	7 044 (75.4%)	547 (5.8%)	9 338
Mitchells Plain MOU	368 (8.7%)	3 235 (77.1%)	589 (14%)	4 192
Khayelitsha MOU	659 (25.8%)	1 678 (65.7%)	216 (8.4%)	2 553
Guguletu MOU	485 (17.4%)	2 011 (72.1%)	291 (10.4%)	2 787
Total	3 259 (17.2%)	13 968 (74%)	643 (8.7%)	18 870

perinatal outcome in the HIV-positive group were not stratified by CD4 count.

Table II shows the stillbirth, early neonatal death and perinatal mortality rates in HIV-positive and negative women for the combined population of MMH and the three MOUs.

There were 300 stillbirths in 2008, 56 in HIV-positive, 117 in HIV-negative and 127 in HIV-untested women. The stillbirth rate (number of stillbirths per 1 000 total births) in the HIV-positive population for the units studied was 17.1/1 000 births. In the HIV-negative population the rate was 8.3/1 000 births. The odds ratio (OR) was 2.07 (95% confidence interval (CI) 1.5 - 2.8), with a *p*-value of <0.0001.

There were 79 early neonatal deaths in 2008, 15 in HIV-positive, 44 in HIV-negative and 20 in HIV-untested women. The early neonatal death rate in the HIV-positive population was 4.6/1 000 live births, compared with a rate of 3.1/1 000 in the HIV-negative population. The OR was 1.46 (95% CI 0.8 - 2.6), with a *p*-value of 0.26.

The perinatal mortality rate in the HIV-positive population was 21.7/1 000 births and that in the HIV-negative population 11.7/1 000 births. The OR was 1.91 (95% CI 1.4 - 2.5), with a *p*-value of <0.0001.

A comparison of the pattern of primary obstetric causes of perinatal mortality showed that infection, intra-uterine growth restriction (IUGR) and antepartum haemorrhage (APH) were significantly more common causes of perinatal death in the HIV-positive population (Table III). In 75.3% of cases the findings of histological examination of the placenta were available and aided in the diagnosis of the primary cause of mortality; the rest of the diagnoses were made on clinical grounds.

For perinatal deaths caused by infection, chorio-amnionitis was the pathological diagnosis. This diagnosis was made either clinically or by histological examination of the placenta for both HIV-positive and HIV-negative patients. Additional serological tests for infection, such as the TORCH screen, were rarely done, so these less common causes of perinatal infection were not identified.

In 2008, there were 54 babies diagnosed with neonatal encephalopathy (predominantly hypoxic ischaemic encephalopathy), 16 in HIV-positive, 31 in HIV-negative and 7 in HIV-untested women. The rate of neonatal encephalopathy in the HIV-exposed population was 4.9/1 000 deliveries, compared with 2.07/1 000 deliveries in the HIV-negative group. This statistic included all babies born with neonatal encephalopathy, some of whom had early neonatal deaths. Comparing the two groups, the OR was 2.36 (95% CI 1.28 - 4.35), with the *p*-value 0.008.

This study showed the untested group of patients to be at a particularly high risk of adverse perinatal outcome. This group included both mothers who declined HIV testing and those who had no antenatal care in the index pregnancy.

There was no significant difference in age and parity between the HIV-positive and negative groups with regard to stillbirths or neonatal deaths (Tables IV and V).

Table IV compares the results and statistical analysis of demographic data in the group of mothers with a stillbirth. The *p*-value was calculated comparing the HIV-exposed with the HIV-negative group.

Table V compares demographic data in HIV-positive and negative women with early neonatal deaths.

Table II. Comparison of perinatal mortality rates according to HIV status for the combined study population

	HIV-positive	HIV-negative	Untested	OR* (CI)	*p*-value
Stillbirth rate	17.1/1 000	8.3/1 000	77.2/1 000	2.07 (1.5 - 2.8)	<0.0001
Neonatal death rate	4.6/1 000	3.1/1 000	10.3/1 000	1.4 (0.81 - 2.6)	0.26
Perinatal mortality rate	21.7/1 000	11.5/1 000	87.6/1 000	1.91 (1.4 - 2.5)	<0.0001

*Comparing HIV-positive with HIV-negative group.

Table III. Comparison of perinatal mortality rate per primary obstetric cause

Primary obstetric cause	HIV-positive	HIV-negative	Untested	OR* (CI)	*p*-value
Preterm labour	4.2/1 000	3.0/1 000	34.0/1 000	1.3 (0.76 - 2.5)	0.35
Infection	**5.2/1 000**	**1.2/1 000**	**5.4/1 000**	**4.3 (2.19 - 8.4)**	**<0.0001**
Asphyxia	3.3/1 000	1.8/1 000	4.8/1 000	1.8 (0.89 - 3.6)	0.14
IUGR	**3.0/1 000**	**0.6/1 000**	**2.4/1 000**	**4.7 (1.93 - 11.7)**	**0.0005**
APH	**3.6/1 000**	**1.2/1 000**	**12.1/1 000**	**2.8 (1.37 - 5.93)**	**0.006**
Unexplained	2.7/1 000	1.8/1 000	13.9/1 000	1.48 (0.69 - 3.17)	0.41
Hypertension	0.3/1 000	0.5/1 000	4.8/1 000	0.5 (0.06 - 4.2)	0.86
Congenital abnormality	0.6/1 000	0.5/1 000	3.6/1 000	1.2 (0.2 - 5.9)	0.86
Other	0.0	0.4/1 000	4.2/1 000		

*Comparing HIV-positive with HIV-negative group.
Bold type indicates primary causes with statistically significant difference between the two study groups.

Table IV. Comparison of demographics by HIV status in the group of mothers with stillbirth

	HIV-positive	HIV-negative	Untested	*p*-value*
Maternal age (yrs)(mean (SD))	27.9 (5.9)	25.9 (5.4)	24.9 (6.1)	0.076 (NS)
Birth weight (g) (median)	1 400	2 010	1 040	0.678 (NS)
Gestation (wks) (median)	32	32	27.5	0.525 (NS)
Gravidity (median)	2	2	1	
Parity (median)	1	1	0	

*Comparing HIV-positive and HIV-negative groups.
SD = standard deviation; NS = non-significant.

Table V. Comparison of demographic data by HIV status in group of mothers with early neonatal death

	HIV-positive	HIV-negative	Untested	*p*-value*
Maternal age (yrs) (mean (SD))	27.2 (2.8)	26.2 (5.9)	25.2 (6.7)	0.362 (NS)
Birth weight (g) (median)	900	1 020	920	0.208 (NS)
Gravidity (median)	2	2	3	
Parity (median)	1	1	3	

*Comparing HIV-positive and HIV-negative groups.
NS = non-significant.

Discussion

The study findings that stillbirth and perinatal mortality rates were significantly higher in HIV-positive mothers compared with HIV-negative mothers corresponds with other studies, including the Tshwane study.[10] There was no significant difference in neonatal death rates; this could possibly be explained by the high quality of neonatal care at MMH. Our study showed that infection, IUGR and APH were significantly more common as a cause of perinatal death in HIV-positive than HIV-negative mothers. This differs from the Tshwane study,[10] where preterm labour and asphyxia were more common. However the neonatal encephalopathy rate was significantly higher in the HIV-exposed group and it is therefore possible that intrapartum hypoxia resulted in morbidity rather than mortality.

Other researchers have shown an association between maternal HIV status and preterm labour,[7] IUGR[14-16] and APH.[17] The mechanism by which maternal HIV infection could cause these adverse outcomes and the differences between different geographical areas are not currently understood, and require more research. It is possible that subclinical chorio-amnionitis may be more common in HIV-infected mothers and that this could explain the association with preterm labour and perinatal hypoxia.[9,18]

Our data also indicate no significant differences in demographic factors and birth weight between HIV-exposed and negative groups, therefore excluding these as possible confounding factors for the study findings. This study did not collect information on socio-economic status; this is known to independently influence perinatal outcome and could also be associated with a higher prevalence of HIV infection. The effect of low socio-economic status as a potential confounding factor for the observed association between maternal HIV infection and perinatal mortality needs to be further explored.

The current study also did not stratify HIV-positive mothers by CD4 count or HIV clinical staging. This needs to be investigated by future research, as does the impact of antiretroviral treatment on perinatal outcome.

Our study and others referred to in this paper were done in resource-limited countries but results in a study by Ellis *et al.* in a large inner city hospital in Atlanta, USA, were similar.[19] They comment in their conclusion that a seropositive mother was 'more likely to have a perinatal death'.[19]

The increased risk of neonatal encephalopathy in the HIV-exposed group could be due to the immune suppression caused by the virus resulting in higher rates of clinical and subclinical intra-uterine infection. The fetus exposed to this environment has a much reduced capacity to tolerate the stress of labour without becoming acidotic and suffering the consequences thereof.[20] Several studies have found chorio-amnionitis to be a risk factor for neonatal encephalopathy.[21,22]

Our results indicate that the group of patients who did not have an HIV test during the pregnancy was at much higher risk of perinatal mortality and morbidity than the other two groups. The untested group consists mainly of patients who were 'unbooked' at any medical institution for antenatal care, and a small number who declined a test. Lack of antenatal care is thought to be an independent risk factor for adverse pregnancy outcome.

Conclusion

Perinatal mortality and neonatal encephalopathy rates at MMH and referring MOUs were significantly higher in an HIV-exposed group compared with HIV-negative counterparts. Infection, IUGR and APH were more common as obstetric causes for mortality in the HIV-positive group.

More comprehensive testing is needed to reduce the number of HIV-untested mothers.

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