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**THE EFFECT OF HIV STATUS ON PERINATAL
OUTCOME AT MOWBRAY MATERNITY HOSPITAL
AND REFERRING MOUS**

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DECLARATION.

I, Deon Kennedy, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being ,or is to be submitted for another degree in this or any other university.

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ABSTRACT.

Background: 33,4 Million people were living with the Human Immune Deficiency virus by the end of 2009 with sub-Saharan Africa the most affected region. Maternal HIV infection is the leading cause of maternal and child morbidity and mortality in South Africa. A meta-analysis of world literature suggests a clear association between HIV infection and perinatal mortality.

Aims and Objectives:

To study the effect of HIV status on perinatal outcome at Mowbray Maternity Hospital(a secondary level hospital in Cape Town, South Africa.) and its catchment MOUs.

Specific aims:

- 1) To compare the perinatal mortality rate in the group of HIV exposed with the HIV negative group and the untested group.
- 2) To determine where possible, the primary obstetric cause of adverse outcome and compare this in HIV exposed to the HIV negative and the untested group.
- 3) To compare the incidence of Neonatal Encephalopathy in the group of HIV exposed with the HIV negative group and the untested group.

Methods: The study was a retrospective descriptive and comparative audit. All deliveries at MMH and its referral midwife obstetric units from January 2008 to December 2008 were audited with respect to HIV status and other demographic data. All deliveries with perinatal mortality and or neonatal encephalopathy were identified and analyzed in detail.

Results: There was a total of 18 870 deliveries at the units being studied. The number of deliveries to HIV positive mothers were 3259 (17,2 %). The stillbirth rate in the HIV positive population for the units being studied was 17,1 per 1000 deliveries. In the HIV negative population this rate was 8,3 per 1000 deliveries. The odds ratio was **2,07** [CI, 1.5-2.8] with a p-value of **<0,0001**. The neonatal death rate in the HIV positive population was 4,6 per 1000 deliveries, this as opposed to a rate of 3,1 per 1000 in the HIV negative population. The odds ratio was calculated as 1,46 [CI, 0.8-2.6] with a p-value of 0,26. The perinatal mortality rate in the HIV population was 21,7 per 1000 deliveries. In the HIV negative population this rate was 11,7 per 1000 deliveries. The odds ratio was **1,91** [CI, 1.4-2.5] with a p-value of **<0,0001**. A comparison of the pattern of primary obstetric cause for perinatal mortality showed that infection, intra uterine growth restriction and ante partum haemorrhage were significantly more common as a cause for perinatal death in the HIV positive population. The risk of neonatal encephalopathy in the HIV exposed population was 4,9 per 1000 deliveries as opposed to 2,07 per 1000 deliveries in the HIV negative group. Comparing the two groups found an odds ratio of **2,36** [CI, 1.28-4.35] with the p-value **0,008**.

The untested group of patients is shown in this study to be at particularly high risk of adverse perinatal outcome. This consists mostly of mothers who have had no antenatal care in the index pregnancy.

Discussion: The perinatal mortality rate in the group of HIV exposed mothers was significantly higher than the HIV negative group due to a higher stillbirth rate. The lack of difference in neonatal death rate could be due to the high standard of neonatal care at the hospital. There was no significant difference in demographic data between the HIV positive and negative groups.

Conclusion: Parturients who were infected with HIV were at significantly increased risk of perinatal mortality. Infection, intra uterine growth restriction and antepartum haemorrhage 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.

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INTRODUCTION:

The Millennium Declaration by the United Nations general assembly was signed on 18 September 2000. This gathering took place in New York at the United Nations millennium summit and was the largest ever gathering of heads of state. There were 8 goals set out in this document with an undertaking by 198 heads of state to attempt achieving these goals by 2015. The 8 goals in the section on development and poverty eradication are known as the millennium development goals.

Goal 4 of the declaration reads as follows: "REDUCE CHILD MORTALITY". One of the targets specified in achieving this goal is to reduce by two thirds between 1990 and 2015 the younger than five year child mortality rate.

According to World Health Organisation figures an estimated 4 million pregnancies end with a stillbirth annually worldwide.¹ 98 % of these are from developing countries.² This figure is considered a gross underestimation as a large number of deliveries are performed outside of healthcare facilities and are thus either not reported or captured in official statistics.^{3,4} As a consequence studying epidemiology and causes of perinatal mortality in developing countries is complex. In sub-Saharan Africa it is estimated that stillbirths account for more than 3 % of all births.²

A multitude of factors lead to the high rate of perinatal mortality in developing countries. Several studies have suggested that exposure to the Human Immunodeficiency virus in utero poses an independent risk factor for adverse perinatal outcome.⁵

South Africa has the largest population of people living with HIV in the world, the UNAIDS report in 2008 states this to be 5,7 million people with a prevalence of 20.9%.⁶ The association between HIV status and perinatal mortality in the Peninsula Maternal and Neonatal Service (PMNS), Cape Town is the subject of this study. In Cape Town (South Africa), the Western Cape Department of Health has adequate infrastructure in place and record keeping in the PMNS for HIV status and perinatal mortality is of good standard. This situation in combination with the fact that the population being serviced by the public health facilities is one living in a developing country, thus faced by the same risks for adverse pregnancy outcome as parturients in other developing countries, makes it an ideal situation for study. At Mowbray Maternity Hospital during 2006 the perinatal mortality rate was recorded as 29,4 per 1000 deliveries. At the MOUs the perinatal mortality rate was 15,8 per 1000 deliveries.

LITERATURE REVIEW.

By the end of 2009 about 33,4 million people worldwide were living with the Human Immune Deficiency virus (HIV). Sub-Saharan Africa is the most affected area in the world in this regard with 67 % of the world's population living with HIV residing in this region.⁶ This is a staggering 22,4 million people. The number of newly infected children in sub-Saharan Africa in 2008 was estimated at 390 000. This 2009 UNAIDS update on the AIDS epidemic again comments on the disproportionate impact of HIV on women and girls. In Cote d'Ivoire HIV prevalence among females were twice as high as in their male counterparts. The reason for this is multi factorial. Due to physiological factors women are at increased risk of contracting the virus. In addition to this physiological susceptibility to heterosexual transmission of the virus, women in sub-Saharan Africa are also faced with social and economic disadvantages that increase their risk of contracting HIV even further.

Maternal Human Immune Deficiency virus infection is the leading underlying cause of maternal and infant death in South Africa.^{7,8}

HIV prevalence in pregnancy is especially high in Southern Africa, with the prevalence in pregnant women attending antenatal clinic in Uganda, South Africa and Botswana during 2003-2004 ranging from 6 to 39%.⁹

Annual routine statistics show that the prevalence of HIV infection among pregnant mothers delivering at Mowbray Maternity Hospital during 2008 was 19%.

A review of 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 the Human Immune Deficiency Virus is compared to a similar group of mothers testing negative for the Human Immune deficiency Virus.¹⁰

In spite of a steady decline in perinatal mortality in first world countries, it is feared that the Human Immune Deficiency Virus epidemic will negate any progress made with regards to this in developing countries. This point is illustrated by a registry based study done in Tanzania analysing 14 444 singleton deliveries. The association between maternal Human Immune deficiency virus status and pregnancy outcome was studied. The group of HIV infected mothers had a 75% higher risk of preterm delivery compared to HIV negative mothers. The risk of perinatal death in the HIV group was found to be 89% higher than the non infected-group.⁹

A smaller prospective study performed in Kenya comparing perinatal outcome in a sero-positive group of mothers to a matched sero-negative group, found a significant increase in preterm birth in the sero-positive group [21% vs. 9.1%]. In addition, a small increase in perinatal mortality was found in the sero-positive group. On histopathologic examination of the placenta, a trend towards more chorio-amnionitis was found in the preterm group versus the term deliveries, this however was the same for both HIV positive and negative mothers.⁴

An Indian group, Kumar et al, studying the impact of HIV-1 on pregnancy outcome in a cohort of tribal women in Manipur, India, confirmed a significantly higher

incidence of placental membrane inflammation (histological evidence of funicitis or chorio-amnionitis.)¹¹ in the HIV positive group. They concluded that HIV infection was associated with adverse maternal and foetal outcome.

A large randomised controlled trial by Chi et al (Human Immunodeficiency Prevention Trials Network 024) attempted to lower the incidence of chorio amnionitis in a predominantly HIV infected cohort by prophylactic antibiotics.¹² The findings were that antibiotic use did not have an effect on any of the outcome measures. There was no association found between stillbirth and HIV . Within the HIV positive group was found an inverse relationship between CD4 count and stillbirth rate. Univariate analysis of their data showed that the following factors were predictors of stillbirth:

- Previous stillbirth
- Antenatal haemorrhage
- Clinical chorioamnionitis
- Polymorphonuclear infiltration on placental histology.

Birth weight of infants born to mothers infected with the HIV virus has been the subject of study by many investigators. Bultereys et al found that maternal HIV-1 infection was significantly associated with intra uterine growth restriction.¹³ Birth weight was also found to be significantly lower compared to the HIV negative group. Lambert et al found a 6% incidence of intra uterine growth restriction in babies born to an HIV positive mother in 2000.¹⁴

Antenatal haemorrhage was found to be a risk factor for stillbirth in the cohort of mostly HIV positive mothers studied by Chi et al.¹²

A recent study conducted in Tshwane [South Africa] and published in the latest Perinatal Problem Identification Programme reports a similar trend in perinatal mortality rate as in the above literature (ref 10). The perinatal mortality rate in the group of mothers testing positive for HIV was found to be 40,5 per 1000 as opposed to 22,7 in the HIV negative group. There was also noted to be a difference in the

pattern of primary obstetric cause of mortality between the two groups.⁷ The perinatal mortality rate per obstetric cause showed in the HIV positive group a trend toward preterm labour, infection and intrapartum asphyxia being the main causes of adverse outcome. In the HIV negative group hypertension was the main cause of perinatal mortality.

In the Peninsula Maternal and Neonatal Service (PMNS) the impact of HIV on maternal mortality has been well documented; it would be of interest to investigate the impact of HIV infection on perinatal mortality in the PMNS.¹⁵

DEFINITIONS.

Stillbirth.

The World Health Organisation has defined stillbirth as a foetal death late in pregnancy.³ The gestational age when a miscarriage becomes a stillbirth is therefore left to the individual country policy as the gestation for foetal viability differs between developing and developed countries. For international comparison a stillbirth is defined as a loss after 22 weeks gestation or when gestation is unknown, death of a foetus weighing 500 grams or more without any signs of life at delivery.

Early neonatal death.

An early neonatal death is defined as the death of a live born infant weighing more than 500 grams at birth, within the first 7 days after birth. Moss et al report that more than two thirds of neonatal deaths occur within the first week of life.¹⁶

Neonatal Encephalopathy.

Neonatal encephalopathy is a clinical syndrome of disturbed neurologic function of the term and near term infant in the early neonatal period, manifested by respiratory difficulties, depression of tone and reflexes and frequently by seizures.¹⁷

The disorder includes the condition hypoxic ischemic encephalopathy and is only called by this name if there is evidence that intra partum asphyxia is the cause of the encephalopathy. There has been a consensus statement by three bodies addressing the diagnosis of intrapartum asphyxia (American College of Obstetrics and Gynecology; American Academy of Pediatrics; International Cerebral Palsy Task Force.) The essential criteria for diagnosis:¹⁸

-metabolic acidosis (pH <7,0) on umbilical artery blood gas

- Apgar score of <3 at 5 minutes.

-neonatal encephalopathy

-cerebral palsy

-exclusion of other causes of cerebral palsy.

The severity of encephalopathy following the asphyxia is graded as per Sarnat score¹⁹ into mild, moderate and severe depending on clinical assessment.

AIMS and OBJECTIVES:

The aim of the proposed study was to determine the relationship between HIV infection and perinatal morbidity and mortality at Mowbray Maternal Hospital and catchment MOU's.

SPECIFIC OBJECTIVES:

- 1) To compare the Perinatal Mortality Rate in the group of HIV exposed with the HIV negative group and the untested group.
- 2) To determine where possible, the primary obstetric cause of poor outcome and compare this in HIV exposed to the HIV negative group and the untested group.
- 3) To compare the incidence of Neonatal Encephalopathy in the group of HIV exposed with the HIV negative group and the untested group.

STUDY DESIGN:

The study was a retrospective descriptive and comparative study.

Methods:

Study setting.

Mowbray Maternity Hospital is a secondary obstetric unit serving a low to middle income urban population in Cape Town. Four primary Midwife obstetric run units(MOU's) refer to Mowbray hospital. These include Gugulethu MOU, Khayelitsha MOU, Mitchell's Plain MOU and Liesbeeck active birthing unit.

The residential settlements in Cape Town are divided along geographical lines. Each of the mentioned MOUs serves all residents living in the suburbs in close proximity to the MOU. All pregnant women have access to free healthcare provided by the government of South Africa. As soon as the patient establishes that she is pregnant, she has the option of presenting to the particular MOU servicing her residential area in order to access antenatal care. The initial visit at the MOU is regarded as a screening opportunity and is commonly known as the "booking visit". At this visit a qualified midwife will take a focussed history. The exercise is aimed at identifying risk factors in previous pregnancies or past medical history that may adversely affect the index pregnancy. Every MOU is supplied with a list of protocols identifying a range of risk factors in the history that would warrant the referral of the particular patient to the next level of care. A general physical examination and basic observations are done with the same objective. The only special investigations done at this visit include a blood test to ascertain the blood group and rhesus factor; serology to exclude syphilis and a rapid blood test for HIV. An overall risk based on the results of this visit is ascribed to the pregnancy and the patient then referred to the appropriate level of care. The Western Cape Department of Health have as official policy instituted Counselling and Voluntary testing of all pregnant mothers for HIV. Essentially this policy aims to counsel every pregnant mother with regards to the benefits and implications of an HIV test in pregnancy. Unless the

counselled mother declines the test, she will then have an onsite rapid HIV test followed by a second confirmatory test if positive. The policy includes making available the antiretroviral drug, Zidovudine, to all seropositive mothers from 28 weeks gestation as well as Nevirapine as single dose in labour. A blood test measuring the CD4 count is done on all seropositive mothers and those with a CD4 count below 250 are referred for triple antiretroviral therapy. (Since the completion of this study the National Department of Health has increased the threshold for starting antiretroviral triple therapy to a CD4 count of 350). Treatment of the newborn to a seropositive mother is included in the treatment protocol. This is a compromise between cost and reducing antepartum and intrapartum vertical transmission of the virus. As counselling and voluntary testing for HIV infection is standard practice in the Western Cape, the HIV status is recorded in the clinical records for the majority of pregnant mothers.

The perinatal auditing process at Mowbray Maternity Hospital and its referral MOUs is formal. All pregnancies with an adverse perinatal outcome; either stillbirth, early neonatal death or neonatal encephalopathy are reviewed. The process includes a detailed scrutiny of the clinical records pertaining to the index pregnancy by an assigned medical professional. The relevant information is recorded on a specially designed form (the perinatal audit form). At a monthly perinatal audit meeting attended by medical practitioners, nursing staff and administrative staff each case is discussed and an attempt made to identify any avoidable factors and the causes of adverse outcome. Placental histological examination assists in ascertaining the cause.

STUDY POPULATION.

This includes all women delivered at Mowbray Maternity Hospital and its referral MOUs between 01 January 2008 and 31 December 2008.

Cases to be studied were all women where there was an adverse perinatal outcome.

All deliveries born before arrival to any of the above institutions were excluded from the study.

METHOD OF DATA COLLECTION:

The study has, in an anonymous manner, reviewed all perinatal audit forms of patients recorded as having had perinatal mortality or Neonatal encephalopathy between January and December 2008. These forms provided basic demographic details, labour details and HIV status together with the assigned cause of death. Information was abstracted from these forms on to a purpose designed data collection sheet (appendix 1). In cases where perinatal audit forms had not yet been completed the medical records were retrieved and data abstracted from those records.

The Western Cape Department of Health make use of Cradle software to record all delivery details. These records were reviewed in order to quantify the total number of deliveries at Mowbray Maternity Hospital between January 2008 and December 2008. The HIV registers at Mowbray Hospital were consulted in order to quantify the number of deliveries to mothers with an HIV status recorded as positive. The HIV untested sample was quantified by consulting the voluntary counselling and testing (VCT) records for Mowbray Hospital (MMH) and MOUs. These records had recorded the number of patients who declined a voluntary test for HIV during the course of their antenatal care. A number of patients had an untested status by virtue of non attendance of any form of antenatal care (either in private health care or in failing to access antenatal care in any other part of the country eg. Eastern Cape Province). The records of the admission suite at Mowbray Hospital were manually searched and identified patients attending MMH with an "unbooked" status. These numbers were then added to the VCT declined group to make up the untested sample at Mowbray Hospital.

The number of deliveries at the catchment midwife run obstetric units was accessed via the PIPP (Perinatal Problem Identification Program). Perinatal mortality data was also accessed via this system. Voluntary counselling and testing data was requested from the central province health offices where all MOU's send their monthly statistics to. The number of deliveries to HIV positive mothers was recorded in this data as well as the number of deliveries to untested mothers.

DATA COLLECTION FORMS.

The following data was collected for the studied population:

- 1) Age
- 2) parity,
- 3) gravidity,
- 4) results of antenatal syphilis test in patients booked for antenatal care,
- 5) result of HIV test in patients booked for antenatal care and accepting voluntary counselling and testing(VCT).
- 6) booking status.

Delivery data recorded included:

- 1) mode of delivery,
- 2) birth weight at delivery,
- 3) gestational age at delivery,
- 4) delivery outcome and in case of mortality the primary obstetric cause of mortality.

ANALYSIS.

Data was collected using a hand search of clinical records. Data was recorded on a purpose designed data extraction form [Microsoft Excel format].

Descriptive data was analysed using Microsoft Excel statistical.

Detailed statistical analysis was done using the Graphware Prism 3.0 software program.

Frequency data was compared using a standard two by two table. Fisher's exact test, Chi squared tests and odd ratios were calculated.

Demographic data was compared using unpaired Kruskal-Wallis test and one way ANOVA tests.

ETHICS.

Since this is an obstetric audit, it has general ethical permission from the ethics committee of the University of Cape Town. However, the proposal was submitted to this committee for ratification. Ethics approval was granted by the UCT ethics committee (REC.REF 282/2010 –see Appendix).

The Medical Superintendent of Mowbray Maternity gave permission to review clinical records.

RESULTS.

There were a total of 18,870 deliveries at MMH and its catchment MOUs during 2008. There were 379 perinatal deaths combined for the 4 delivering units being studied. The combined perinatal mortality rate for the whole population was therefore 20.1 per 1000 deliveries.

Table 1.Number of deliveries by HIV status at Mowbray Maternity

Hospital and referral MOUs.

INSTITUTION	Total HIV +ve deliveries	Total HIV – ve deliveries	Total untested deliveries	Total number of deliveries
Mowbray maternity hospital	1747 (18,7%)	7044 (75,4%)	547 (5,8%)	9338
Mitchells Plein MOU	368 (8,7%)	3235 (77,1%)	589 (14%)	4192
Khayelitsha MOU	659 (25,8%)	1678 (65,7%)	216 (8,4%)	2553
Guguletu MOU	485 (17,4%)	2011 (72,1%)	291 (10,4%)	2787
TOTAL	3259 (17,2%)	13 968 (74%)	1643(8,7%)	18 870

Delivery statistics at MMH.

During the year January 2008 to December 2008 there were 9338 deliveries at MMH. Of these, 1774 were deliveries to mothers who tested positive for HIV; the rate of deliveries to HIV seropositive mothers was therefore 18,7%.

The number of mothers with an untested HIV status was 547; this was the sum of 126 mothers who were "unbooked" for antenatal care and went on to deliver without the opportunity of having an HIV test, plus 421 mothers who declined an HIV test throughout their antenatal care. The rate of untested mothers was 5,8%.

The total of deliveries to HIV negative women was 7044(75,4% of the total delivered population at MMH).

Delivery statistics at MOUs.

Guguletu MOU.

The total number of deliveries at Guguletu MOU for 2008 was 2787.

The number of deliveries to seropositive mothers was 485. This translates to 17,4% of the total number of deliveries at the MOU.

The number of mothers delivering without an HIV test having been done was 291 (10,4% of the total number of deliveries).

The number of deliveries to HIV negative mothers was 2011(72,1%).

Mitchell's Plain MOU.

The total number of deliveries at MPMOU for 2008 was 4192.

The number of deliveries to HIV positive mothers totalled 368 with a percentage of 8,7%.

The number of untested mothers delivering at MPMOU totalled 589 with a percentage of 14,05%.

Khayelitsha MOU.

There were 2553 deliveries at KMOU during 2008. Of these 659 deliveries were to HIV positive mothers, this is 25.8% of the total number of deliveries.

The number of untested mothers at KMOU for 2008 was 216 (8,4%).

Combined data.

The number of deliveries at the four units combined for 2008 totalled 18 870. The combined number of deliveries to HIV positive mothers was 3259 (17,2%). 13 968 deliveries were to mothers testing negative for HIV(74%). There were 1643 deliveries to mothers with an untested status at a percentage of 8,7%.

Comparison of stillbirth rate by HIV status.

Table 2.

HIV status	Guguletu MOU	Mitchell's Plain MOU	Khayel. MOU	Mowbray Maternity Hospital	Combined SB rate	Odds Ratio*	p-value
	No. SB's (Rates)	No. SB's (Rates)	No.SB's (Rates)	No. SB's (Rates)	Rates		
+ve	8 (16,4)	3 (8,1)	2 (3,0)	43 (24,6)	17,1	2,07 (1,5-2,8)	<0.0001
-ve	13 (6,4)	12 (3,7)	11 (6,5)	81 (11,4)	8,3 per 1000		
No test	26 (89,3)	26 (44,1)	23 (106,4)	52 (95,0)	77,2 per 1000		

*Comparing HIV positive to HIV negative groups.

*All rates = number of stillbirths per 1000 total births.

GUGULETU MOU.

The stillbirth rate in the HIV positive group of mothers at Guguletu MOU was 16,4 per 1000 deliveries. This rate was 6,4 per 1000 in the HIV negative group of mothers. Those without an HIV test had a stillbirth rate of 89,3 per 1000.

Mitchells Plain MOU.

The stillbirth rate at Mitchells Plain MOU in the HIV positive group was 8,1 per 1000. In the HIV negative group this rate was 3,7 per 1000. Those mothers without an HIV test had a rate of 44,1 per 1000.

KHAYELITSHA MOU.

The stillbirth rate at KMOU in the group of HIV positive mothers was 3,0 per 1000 deliveries. The rate in the HIV negative group was 6,5 per 1000 deliveries. Those mothers without an HIV test had a stillbirth rate of 106,4 per 1000.

Mowbray Maternity Hospital.

The stillbirth rate at the referral centre for these primary MOUs was 24,6 per 1000 in the HIV positive group of mothers. For the HIV negative group this rate was 11,4 per 1000. In the untested group the rate was 95 per 1000 deliveries.

COMBINED STILLBIRTH RATES.

Combining the data from all the units being studied showed a combined stillbirth rate of 17,1 per 1000 in the HIV positive group of mothers. The rate in the HIV negative group was 8,3 per 1000 deliveries. Statistical analysis comparing the HIV positive group to their negative counterparts suggested an odds ratio of 2,07. (95%

confidence interval, 1,5-2,8) The calculated P-value was <0,0001. This was statistically significant. In the untested group this rate was 77,2 per 1000.

Comparison of early neonatal death rate by HIV status.

Table 3.

HIV status	Guguletu MOU	Mitchell's Plain MOU	Khayelitsha MOU	Mowbray Maternity Hospital	Combined NND rate	Odds Ratio*	p-value
	No. ENND's (Rate)	No. ENND's (Rate)	No. ENND's (Rate)	No. ENND's (Rate)			
+ve	2 (4,1)	1 (2,7)	1 (1,5)	3 (6,2)	(4,6)	1,46 (0,8- 2,6)	p=0,26
-ve	3 (1,4)	0 (0)	3 (1,7)	11 (5,3)	(3,1)		
untested	1 (3,4)	6 (10,1)	3 (13,8)	10 (12,7)	(10,3)		

*Comparing HIV positive to HIV negative group.

*All rates = number of early neonatal deaths per 1000 live births

Khayelitsha MOU.

The neonatal death rate at Khayelitsha MOU born to mothers with a positive HIV status was 1,5 per 1000. The rate in the group of seronegative mothers was 1,7 per 1000. The untested group had a rate of 13,8 per 1000.

Guguletu MOU.

The neonatal death rate in the HIV positive group was 4,1 per 1000 deliveries. Their negative counterparts had a rate of 1,4 per 1000 deliveries. The untested group had a neonatal death rate of 3,4 per 1000.

Mitchell's Plain Mou.

The neonatal death rate in the HIV positive group at Mitchell's Plain MOU was 2,7 per 1000 deliveries. The untested group had a rate of 10,1 per 1000.

Mowbray Maternity Hospital.

The neonatal death rate in the HIV positive group of mothers delivered at MMH was 6,2 per 1000 deliveries. The corresponding rate in the HIV negative group was 5,3 per 1000. The untested group had a rate of 12,7 per 1000.

Combined neonatal death rates.

The combined neonatal death rate for the five units being studied : HIV positive group 4,6 per 1000 deliveries. In the HIV negative group the combined rate was 3,1 per 1000. In the untested group this rate was found to be 10,3 per 1000. Statistical analysis suggested an odds ratio of 1,46 when comparing the HIV positive with the negative group. (95% confidence interval 0,8 -2,6). The calculated p-value was 0,26.

Comparison of perinatal mortality rate by HIV status for the combined study population.

Table 4.

	HIV positive	HIV negative	Untested	Odds Ratio*	p-value
Stillbirth rate (no.)	17,1 per 1000 (56)	8,3 per 1000 (117)	77,2 per 1000 (127)	2,07 (1,5-2,8)	<0.0001
Early Neonatal Death rate (no.)	4,6 per 1000 (15)	3,1 per 1000 (44)	10,3 per 1000 (20)	1,4 (0,81-2,6)	0.26
Perinatal Mortality rate	21,7 per 1000	11,5 per 1000	87,6 per 1000	1,91 (1,4-2,5)	<0.0001

*Comparing HIV positive to HIV negative group.

The combined perinatal mortality rate in the HIV positive population at the units being studied was 21,7 per 1000 deliveries. The corresponding rate in the HIV negative population was 11,5 per 1000 deliveries. Statistical analysis performed comparing the HIV negative and positive groups with regards to perinatal mortality found an odds ratio of 1,91 (95% confidence interval 1,4-2,5) The calculated p-value was <0,0001. The perinatal mortality rate in the untested group was 87,6 per 1000 deliveries.

(Table 5.) Comparison of Perinatal mortality rate per primary obstetric cause.

Primary obstetric cause	HIV positive	HIV negative	Untested	Odds ratio*	p-value
Preterm Labour (no.)	4,2 per 1000 (14)	3,0 per 1000 (43)	34 per 1000 (56)	1,3 (0.76-2.5)	0.35
Infection (no.)	5,2 per 1000 (17)	1,2 per 1000 (17)	5,4 per 1000 (9)	4,3 (2,19-8,4)	<0.0001
Asphyxia (no.)	3,3 per 1000 (11)	1,8 per 1000 (26)	4,8 per 1000 (8)	1,8 (0.89-3.6)	0.14
IUGR (no.)	3,0 per 1000 (10)	0,6 per 1000 (9)	2,4 per 1000 (4)	4,7 (1.93-11.7)	0.0005
APH (no.)	3,6 per 1000 (12)	1,2 per 1000 (18)	12,1 per 1000 (20)	2,8 (1.37-5.93)	0.006
Unexplained (no.)	2,7 per 1000 (9)	1,8 per 1000 (26)	13,9 per 1000 (23)	1,48 (0.69-3.17)	0.41

Hypertension (no.)	0,3 per 1000 (1)	0,5 per 1000 (8)	4,8 per 1000 (8)	0,5 (0.06-4.2)	0.86
Congenital Abnormality (no.)	0,6 per 1000 (2)	0,5 per 1000 (7)	3,6 per 1000 (6)	1,2 (0.2-5.9)	0.86
Other (no.)	0,0 (0)	0,4 per 1000(6)	4,2 per 1000(7)		

*Comparing HIV positive to HIV negative group.

Preterm labour.

In the HIV positive population preterm labour was responsible for 4,2 per 1000 deaths. In the HIV negative group this rate was found to be 3,0 per 1000. In the untested group 34 per 1000 deliveries were caused primarily by prematurity. The calculated odds ratio was 1,3. The calculated p-value was 0,35.

Infection.

Infection was the primary cause of death in 5,2 per 1000 deliveries in the HIV exposed group. In the corresponding HIV negative group 1,2 per 1000 deliveries were caused primarily by infection. This rate was 5,4 per 1000 in the untested group of patients. The odds ratio calculated was 4,3 comparing HIV positive and HIV negative populations(95% confidence interval between 2,19 and 8,4). The calculated p-value was <0,0001. In the majority of cases, i.e 79,8%, placental histology results were available to confirm the diagnosis of chorio amnionitis.

Asphyxia.

Asphyxia was the cause of death in 3,3 per 1000 deliveries in the HIV positive group. In the HIV negative group it caused mortality in 1,8 per 1000 deliveries. In the untested group this rate was 4,8 per 1000. The odds ratio worked out as 1,8 with a p-value of 0,14.

Intra uterine growth restriction.

IUGR was found to result in mortality in 3,0 per 1000 deliveries in the HIV exposed group as opposed to 0,6 per 1000 deliveries in the HIV negative group. In the untested group this rate was 2,4 per 1000 deliveries. The odds ratio comparing HIV positive to HIV negative groups was 4,7 (95% confidence interval 1,93-11,7) with a p-value of 0,0005.

Antepartum haemorrhage.

Antepartum haemorrhage caused mortality in 3,6 per 1000 deliveries in the HIV positive group as opposed to 1,2 per 1000 in the HIV negative population. In the untested group it was found responsible in 12,1 per 1000 deliveries. The odds ratio was 2,8 (95% confidence interval between 1,37 – 5,93). The p-value was 0,006.

Unexplained.

Unexplained death was coded as primary obstetric cause of mortality in 2,7 per 1000 deliveries in the HIV positive group compared to 1,8 per 1000 in the negative group. 13,9 per 1000 deliveries in the untested group were due to unexplained reasons. The odds ratio was 0,48 with a p-value of 0,41.

Hypertension.

In the HIV positive group 0,3 per 1000 deliveries ended with mortality due to hypertension as opposed to 0,5 per 1000 deliveries in the HIV negative group. In the untested group this rate was 4,8 per 1000 deliveries. The odds ratio was 0,5 with a p-value of 0,86.

Congenital abnormality.

In the HIV exposed group this caused mortality in 0,6 per 1000 deliveries as opposed to 0,5 per 1000 in the HIV negative group. The untested group had a rate of 3,6 per 1000. The odds ratio calculated was 1,2 with a p-value of 0,86.

DEMOGRAPHIC DATA.

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

(Table 6)

	HIV +ve	HIV -ve	Untested	p-value* [non-significant=n/s]
Maternal age (mean[SD])	27,9[5,9]	25,9[5,4]	24,9[6,1]	0.076[n/s]
Birth weight (median)	1400g	2010g	1040g	0.678[n/s]
Gestation	32 weeks	32 weeks	27,5 weeks	0.525[n/s]

(median)				
Gravidity (median)	2	2	11	
Parity (median)	1	1	0	
% patients CD4 count < 350	35,4%	N/A	N/A	
% patients CD4 count <200	12,9%			

*Comparison between HIV +ve and HIV –ve groups.

Table 6 compares the results and statistical analysis of demographic data in the group of mothers with a stillbirth. The p-value is calculated comparing the HIV exposed to the HIV negative group.

Maternal age.

The mean maternal age in the HIV exposed group was 27,9 with a standard deviation of 5,9 years. This opposed to a mean age of 25,9 and a standard deviation of 5,4 in the HIV negative group. The untested group had a mean age of 24,9 and standard deviation of 6,1 years. Comparison between HIV exposed and negative groups showed a non-significant difference and a p-value of 0,076.

Birth weight.

The mean birth weight in the HIV positive group was 1867,5 grams with a standard deviation of 895,7 grams. In the HIV negative group the mean birth weight was 1941,6 grams with a standard deviation of 1006,7 grams. The mean birth weight in the untested group was found to be 1541,1 grams with the standard deviation being 976,5 grams. There was no significant difference in birth weight comparing the HIV positive and negative groups. The p-value was 0,678.

Gestation.

The mean gestational age at delivery in the HIV exposed population was 31,8 weeks with a standard deviation of 5,3 weeks. In the HIV negative group the gestational age at delivery was 32,5 weeks and the standard deviation was 5,7 weeks. The untested group of patients delivered on average at 29,3 weeks of gestation with a standard deviation of 5,4 weeks. A comparison between HIV positive and negative groups showed a non-significant difference with a p-value of 0,525.

Gravidity and parity.

The mean gravidity and parity in the HIV exposed group was 2,2 and 1,2 respectively (standard deviations were 1,1 and 1,0 respectively). In the HIV negative group the means were 2,1 and 1,0 respectively, the standard deviations were 1,3 for both gravidity and parity. In the untested group the mean values were 1,8 and 0,7 respectively. The standard deviations were calculated as 1,1 and 1,0.

CD 4 cell count.

The average lymphocyte cell count displaying CD 4 surface marker was 423,9. The maximum count was found to be 1320 and the minimum 129. The CD 4 count was documented for 67,3% of cases.

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

(Table 7)

	HIV +ve	HIV -ve	Untested	p-value * [non-significant=n/s]
Maternal age (mean[SD])	27,2 [2,8]	26,2 [5,9]	25,2 [6,7]	0.362 [n/s]

Birth weight (median)	900g	1020g	920g	0.208 [n/s]
Gravidity (median)	2	2	3	
Parity (median)	1	1	3	

*Comparison between HIV +ve and HIV –ve groups.

Table 7 compares the demographic data for mothers with an early neonatal death. The calculated p-value compares the HIV exposed to the HIV negative group.

Maternal age.

The mean maternal age for the group testing positive for HIV was 27,2 years with the standard deviation 2,8 years. In the HIV negative group the mean age was 26,2 and the standard deviation 5,9 years. The untested group had the youngest average age of 25,2 years with a standard deviation of 6,7 years. A comparison between the HIV exposed and negative groups showed a non-significant difference with a p-value of 0,362.

Birth weight.

The mean birth weight in the group of HIV positive mothers was 1277 grams with the standard deviation 905,9 grams. The mean birth weight in the HIV negative group was 1641,3 grams with a standard deviation of 1054 grams. In the untested group the average weight at birth was 1222,6 grams with a standard deviation of 562,6 grams. A comparison the HIV positive and negative groups showed a non-significant difference with the p-value 0,208.

Gravidity and parity.

The average gravidity and parity in the HIV exposed group were 3,06 and 1,9 respectively; the standard deviations were 1,4 and 1,5 respectively. In the HIV negative group these averages were 2,0 and 1,0 with standard deviations of 1,0 and 0,9. The averages in the untested group were 2,4 and 1,4 respectively with standard deviations of 1,3 and 1,2 respectively.

NEONATAL ENCEPHALOPATHY.

Comparison of neonatal encephalopathy rate by HIV status and demographic data in this group of parturients.

Table 8.

	HIV +ve	HIV -ve	Untested	Odds Ratio* (CI)	p-value
Neonatal encephalopathy rate (no.)	4,9 per 1000 (16)	2,07 per 1000 (31)	4,86 per 1000 (7)	2.36 (1,28-4,35)	0,008
Maternal age (mean[SD])	25,4[4,6]	23[6,2]	26,8[7,0]	N/A	0,154 (n/s)
Gestation at birth (median)	37,5 weeks	39 weeks	40 weeks	N/A	0,882(n/s)
Birth weight (median)	2920g	3120g	3100g	N/A	0,738(n/s)
% of patients	53,3%				

with CD4 <350					
% of patients with CD4 <200	40%	N/A	N/A		

*Comparing HIV +ve to HIV –ve groups.

Table 8 shows the comparison of the rate of neonatal encephalopathy by HIV status as well as the comparison of demographic data by HIV status of mothers with a neonate diagnosed with neonatal encephalopathy.

Neonatal encephalopathy rate by HIV status.

The rate of neonatal encephalopathy in the group of HIV positive parturients was 4,9 per 1000 deliveries. The rate in the group of HIV negative mothers was 2,07 per 1000 deliveries. In the untested group this rate was calculated as 4,86 per 1000 deliveries. Analysing the difference between the HIV positive and negative groups statistically showed a significant difference. The odds ratio was 2,36 with the 95% confidence interval falling between 1,28 and 4,35. The calculated p-value was 0,008.

DEMOGRAPHIC DATA.

Maternal age.

The average maternal age in the HIV positive population was 25,4 years with a standard deviation of 4,6 years. In the HIV negative population the mean age was 23 years and the standard deviation calculated was 6,2 years. Mean age in the untested group of mothers was 26,8 years with a standard deviation of 7,0 years. A comparison between the HIV positive and negative groups was statistically non-significant. The calculated p-value was 0,154.

Gestation at birth.

The average gestational age at birth in the HIV positive group was 37 weeks with a standard deviation of 2,7 weeks. In the HIV negative group the mean gestational age at delivery was 37,3 weeks with the standard deviation being 4,2 weeks. The mean gestation in the untested group was 38,4 weeks and the standard deviation 2,5 weeks. A comparison between HIV positive and negative groups calculated a non-significant p-value of 0,882.

Birth weight.

The average birth weight in the HIV positive group was 2923 gram with a standard deviation of 732 gram. In the HIV negative group the mean weight at birth was 2957 gram with the standard deviation 770,5 gram. The corresponding values for the untested group was 3140 gram and SD 484,1 gram. The calculated p-value was non-significant at 0,738.

CD 4 count.

The average CD 4 count for individuals in the group of mothers with a neonatal encephalopathy was 379 with a standard deviation of 197.

DISCUSSION.

PERINATAL MORTALITY.

The study shows that there is a statistically significant difference in the perinatal mortality rate between the group of parturients exposed to the Human Immune Deficiency virus and their non-exposed counterparts in the population being studied. This is due to a significantly higher stillbirth rate in the HIV positive group as there was found to be no difference in the neonatal death rate between the two groups as opposed to the significantly higher neonatal death rate (odds ratio 3,61 [CI, 1.76-7.44]) found in the Tshwane study.⁷ The lack of significant difference between the HIV positive and negative groups with regards to neonatal death rate could be due to the high standard of neonatal care at the hospital. The data also indicates no significant differences in demographic factors and birth weight between HIV exposed and negative groups thus excluding these as possible confounding factors for the study findings.

This finding is in keeping with many other published studies including the study done in Tshwane in 2006.^{4,7} These studies were done in resource limited countries but the results were confirmed by a study done by Ellis et al in a large inner city hospital in Atlanta, USA also commenting in the conclusion that a sero positive mother was “more likely to have a perinatal death”.²⁰

Another difference between this study and the Tshwane study was the pattern of primary obstetric cause of mortality. The study in Tshwane found that preterm labour and infection were significantly more common as a cause for perinatal mortality in the HIV positive group compared to their negative counterparts. The Mowbray and referring MOU experience was that infection (i.e chorioamnionitis), intra-uterine growth restriction and ante partum haemorrhage was significantly more common in the HIV group.

This preponderance to chorioamnionitis in an HIV exposed group as a cause for adverse perinatal outcome has been documented in several other studies.^{7,11} One possible theory explaining this trend toward higher incidence of intra uterine infection in an HIV exposed group is the immune suppression caused by the virus leading to ascending infection of membranes and eventually liquor. However the HPTN 024 study by Goldenberg et al analysing the impact of random antibiotics on histological evidence of chorioamnionitis concluded that antibiotic use was not associated with a reduction in histological evidence of chorioamnionitis when a nevirapine anti-retroviral regimen was used.²¹ The Goldenberg study reported on the same cohort in Zambia, Tanzania and Malawi as analysed by Chi et al. This is an important negative finding as it may have been thought possible to reduce the adverse perinatal outcome due to chorioamnionitis in the HIV positive group by prescribing prophylactic antibiotics in labour.

The significantly higher rate of perinatal mortality caused by IUGR in the HIV positive group of patients has been documented in previously conducted studies. Interpretation of this finding is difficult due to most studies having been done in developing countries and confounding factors like poor nutrition and advanced maternal disease have often been blamed for IUGR.^{9,22} The prospective study in Nairobi, Kenya found no increased risk of IUGR in the HIV positive group compared to their negative counterparts.⁴ A more recent study by Iqbal et al found a relationship between CD 4 count and IUGR in a group of HIV infected mothers, the lower the CD 4 count the higher the risk of IUGR.²³ Stratification of the HIV exposed group of patients with regards to CD4 count and the effect it has on IUGR and outcome could be a basis for future study.

It is difficult to explain the finding that antepartum haemorrhage was significantly more common as of obstetric cause for adverse perinatal outcome in the HIV positive population. This finding is also reported in the large cohort in the HPTN 024 trial.²¹

The different trend in perinatal mortality rate at the Khayelitsha MOU is also difficult to explain as the population delivering at this MOU is no different from the

other MOUs. During the data collection phase of the study the impression was that record keeping at Khayelitsha MOU was not of the same standard as the other units. It is thus possible that the differing trend could be the result of inaccurate data from records. However, as the trend at KMOU was the opposite to that at the other units it cannot diminish the significance of the overall results in this study. On the contrary if data at KMOU were more accurate and mirrored the trend at the other units it would emphasize the combined trend.

NEONATAL ENCEPHALOPATHY.

The increased risk of neonatal encephalopathy in the HIV exposed parturients could be due to the immune suppression caused by the virus resulting in higher rates of clinical and subclinical intra uterine infection. The foetus exposed to this environment has a much lower capacity to tolerate the stress of labour without becoming acidotic and suffering the consequences thereof.²⁴ Several studies have found chorio amnionitis to be a risk factor for neonatal^{25,26} encephalopathy.

UNTESTED GROUP.

The results indicate that the group of patients without an HIV test during the pregnancy is at much higher risk of perinatal mortality and morbidity than the other two groups. The untested group consists mainly of a group of patients who were “unbooked” at any medical institution for antenatal care. Several studies have confirmed that a lack of ante natal care is an independent risk factor for adverse pregnancy outcome.²⁷

LIMITATIONS AND STRENGTHS OF THE STUDY.

A limitation of the study was the fact that it was a retrospective study. In addition the lack of adequate record keeping limited the analysis that could be performed on data in the HIV positive population. Only 69% of patients had a CD 4 count recorded. This lack of complete data was due to incomplete record keeping thus limiting the ability to explore an inverse relationship between CD4 count and stillbirth.

It was not possible to collect data regarding smoking history during the pregnancy and its impact as a confounding factor on perinatal outcome is therefore unknown.

IMPLICATIONS OF THE STUDY.

Interpretation of the results of this study indicates that early detection and treatment of HIV in pregnant mothers to prevent the complications of immune suppression would reduce perinatal morbidity and mortality in this at risk group. Maintaining a higher CD4 and a low as possible viral load in these patients should be the goal of antiviral therapy from as early as possible in pregnancy. In an ideal situation this group should have access to prenatal clinics in order to assist in achieving this goal.

A concerted effort by Government to educate the community regarding the dire effect of a lack of ante natal care on pregnancy outcome should be made.

CONCLUSION.

The risk of stillbirth is higher in an HIV exposed population compared to their HIV negative counterparts. Infection, IUGR and ante partum haemorrhage is more common as an obstetric cause for mortality in the HIV positive group.

The untested group of patients in this study was found to be at much higher risk of adverse pregnancy outcome than both HIV positive and HIV negative patients.

APPENDICES.

A} Data collection sheet.

B} Ethics approval for study.

Reference:

- 1) Lawn J, Cousens S, Zupan J. 4 Million neonatal deaths: when? Where? Why? Lancet 2005; 365: 891-900.
- 2) Stanton C, Lawn J, Rahman H et al. Stillbirth rates: delivering estimates in 190 countries. Lancet 2006; 367: 1487-94
- 3) McClure E.M, Nalubamba-Phiri M, Goldenberg R. Stillbirth in developing countries. Int J Gynecol Obstet 94(2006), 82-90.
- 4) Temmerman M, Chomba E. Maternal Human Immunodeficiency Virus 1 Infection and pregnancy outcome. Obstetrics and Gynecology 1994;83:495-501.
- 5) Zupan J. Perinatal mortality in developing countries. N Engl J Med 2005;352: 2047-48.
- 6) UNAIDS. Update on the Global Aids Epidemic 2009. Geneva, Switzerland: UNAIDS, 2009.
- 7) Van Hoorick L, Pattinson RC. The effect of maternal HIV infection on perinatal death in Tshwane in Saving Babies 2003-2005: Fifth perinatal care survey of South Africa. Ed. Pattinson RC. Pretoria. University of Pretoria. MRC. CDC; 2007.
- 8) Saving Mothers 2004-2007. Fourth report on confidential enquiries into maternal deaths in South Africa. Department of Health. Pretoria 2010.
- 9) Habib N, Daltveit T. Maternal HIV status and pregnancy outcomes in north eastern Tanzania: a registry-based study. BJOG 2008;115:616-624.
- 10) Brocklehurst P. The association between maternal HIV infection and perinatal outcome: a systematic review of the literature and meta-analysis. Br Journal Obstets and Gynecol 1998;105:836-848.
- 11) Kumar R, Uduman S, Khurrana A. Impact of HIV-1 infection on perinatal outcome. International Journal of Gynecology and Obstetrics 49(1995):137-143.
- 12) Chi B, Wang L, Read J. Predictors of stillbirth in sub-Saharan Africa. Obstetrics and Gynecology 110(5), November 2007, pp 989-997.
- 13) Bultereys M, Chao A, Muneyemana S et al. Maternal human immunodeficiency virus 1 infection and intra uterine growth: a prospective cohort study in Butare, Rwanda. Pediatric Infectious Diseases Journal . 1994 Feb; 13(2): 94-100.
- 14) Lambert J.S, Watts D.H, Mefenson L et al. Risk factors for preterm birth, low birth weight, and intra uterine growth restriction in infants born to HIV-infected pregnant women

- receiving Zidovudine. Pediatric AIDS Clinical Trials Group 185 Team. AIDS. 2000.July:14(10): 1389-99.
- 15) Fawcus S, Van Coeverden de Groot H, Isaacs S.A 50 year audit of maternal mortality in the PMNS,Cape Town(1953-2002).BJOG 2005,112:1257-1263.
 - 16) Moss W et al.Researsh priorities for the reduction of Perinatal and neonatal morbidity and mortality in developing country communities. Journal of Perinatology.2002;22:484-495.
 - 17) Nelson K, Leviton A. How much of neonatal encephalopathy is due to birth asphyxia? Am J Dis Child. 1991;145(11)1325-31.
 - 18) Nelson K, Leviton A. How much of neonatal encephalopathy is due to birth asphyxia? Am J Dis Child. 1991;145(11)1325-31.
 - 19) Sarnat H, Sarnat M. Neonatal encephalopathy following fetal distress. A clinical and encephalographic study,Arch Neurol 33(1976),pp. 696-705.
 - 20) Ellis J, Williams H, Graves W. Human Immunodeficiency virus infection is a risk factor for adverse perinatal outcome. Am J Obstet Gynecol 186(2002), 903-906.
 - 21) Goldenberg R, Mudenda V, Read J. HPTN 024 study: Histologic chorioamnionitis, antibiotic and adverse fetal outcomes in a predominantly HIV-1- infected African population. Am J Obstet Gynecol 195(2006), 1065-1074.
 - 22) Stratton P, Tuomala R, Abboud R et al.Obstetric and newborn outcomes in a cohort of HIV infected women: a report of the women and infants transmission study. J Acquir Immune Defic Syndr Retrovirol 1999;20: 179-86.
 - 23) Iqbal S, Kriebs J. Predictors of fetal growth in maternal HIV disease. Am J Perinatology.2010 Aug;27(7)517-23.
 - 24) Fenichel G. Hypoxic-Ischemic encephalopathy in the newborn. Arch Neurol. May 1983;(40)261-66.
 - 25) Wu Y, Colford Jr J, Chorio amnionitis as risk factor for cerebral palsy; a meta analysis. JAMA 2000; 284(11)1417-24.
 - 26) Badawi N, Kuriczuk JJ et al. Intrapartum risk factors for newborn encephalopathy: the Western Australian case-control study. Br Med J 1998;317: 1554-8.
 - 27) Weiner R, Rausman C, Dorman E et al. Labour complications remain the most important risk factor for perinatal mortality in rural Kenya.Bulletin of World Health Organisation.2003;81:7.

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