Journal of Clinical Cases and Reports

Clinical Research | Vol 3 Iss 4

Evaluation of the Relationship between Clinical Outcome of Early Neonatal Sepsis and HIV Exposure in Homa bay County Referral Hospital, Western Kenya

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Abstract

Background: Maternal HIV is the leading cause of both maternal and child morbidity in Sub-Saharan Africa and very little is known about the relationship of HIV exposure and early neonatal sepsis.

Objective: To describe the association between maternal HIV and probable or confirmed early neonatal sepsis in Homa Bay County Referral Hospital, Western Kenya.

Design: Hospital based cross- sectional study.

Study Setting: Homa Bay County Referral Hospital.

Subjects/Participants: One hundred and forty two (142) neonates aged 24 hours to 96 hours.

Results: Data purposively collected included, characteristics of women and newborns at enrollment, by maternal HIV status and HIV- positive women and their newborns, prevalence of probable or confirmed sepsis, factors in association between maternal HIV infection and probable sepsis in newborns and associations between HIV exposure and probable or confirmed sepsis among newborns and HIV-exposed newborns, 0(0.00%) HIV-positive by 24-hours PCR, prevalence of positive culture 1.6% in HIV-exposed, 1.7% HIV-unexposed with a prevalence ratio: 1.11 (95% CI: 0.05, 8.00) *p*-value = 0.8615. There was no statistical relationship between clinical outcomes of early neonatal sepsis to HIV exposure.

Conclusion: There was no association between maternal HIV and probable or confirmed early neonatal sepsis in Homa Bay County Referral Hospital, Western Kenya.

Keywords: ***Maternal HIV; Neonatal sepsis; Mother-to-child transmission***

Received Date: October 24, 2019; **Accepted Date:** November 11, 2019; **Published Date:** November 18, 2019

Citation: Jacqueline Mulongo Naulikha, Evaluation of the Relationship between Clinical Outcome of Early Neonatal Sepsis and HIV Exposure in Homa bay County Referral Hospital, Western Kenya. J Clin Cases Rep 3(4): 139-145.

Introduction

In 2011, an estimated 330,000 children became newly infected with HIV Worldwide [1]. Over 90% of these infections were acquired through mother-to-child transmission (MTCT), and more than 90% of these occurred in sub-Saharan Africa [1,2]. Worldwide, it is estimated that HIV accounts for 1.5% of all deaths in infants younger than twelve months of age; and 4.9% of deaths in one to four-year-old children's [3]. Kenya is among the 22 countries that collectively account for 90% of all pregnant women living with HIV. The country accounts for 4% of all new paediatric HIV infections globally, and each year an estimated 13,000 new HIV infections occur among Kenyan children 94). Before 1995, perinatally infected infants had a 50 percent chance of developing AIDS by three years of age and a 90 percent chance of dying by the 10^{th} birthday [2]. From 1992 to 1997, the number of AIDS cases in children declined by 66 percent, primarily because of major advances in management resulting in to decreased vertical transmission of HIV during pregnancy [2]. The risk of peri-natal HIV infection can vary from 1 percent to 33 percent, depending on interventions and maternal disease state [4].

The early identification of HIV infection, the administration of Highly Active Anti-Retroviral Therapy, the suppression of viral loads to undetectable levels, and the prevention of opportunistic infections all have shown to prolong life and prevent morbidity in adults. In theory, the principle of viral load suppression would apply to infants as well as adults. However, the management of HIV exposed children in association with sepsis is a rapidly evolving area with limited data.

Materials and Methods

This was a hospital based cross sectional study in Homa Bay County Referral Hospital, Western Kenya, from June 2015 to January 2016. The participants were enrolled from New borne units, Post-natal wards and Outpatient. Mother Neonate pair was enrolled based on maternal and neonatal risk factors. Informed consent was obtained from the Mother before inclusion in to the study. Information on demographics, history of pregnancy, diseases and outcome of the neonates were extracted from the patients' files, blood was obtained for blood cultures and Neonatal HIV, PCR. Neonatal clinical outcomes in relation to HIV and bacteremia was analyzed using Chi-square, associations of demographics clinical outcomes, bacteremia and HIV was explored using univariate analysis and logistic regression.

Ethical clearance was obtained from Kenya medical research institute (KEMRI) and University of Washington IRB- instate of research board. Informed consent was obtained from mothers before enrollment in to the study.

Standardized questionnaire were used to obtain demographic and clinical information which included details abstracted from the infant medical records and a head-to-toe neonatal physical examination. Neonatal variables that were collected at entry included location of birth, admission diagnosis, gestational age at birth, birth weight, HIV status of the Mother. Other data that were collected included medical complications, antibiotic use, laboratory and culture results, and discharge diagnosis. Maternal data were abstracted from obstetric records and included maternal age, frequency at antenatal care, demographics, obstetrical history, HIV status, CD_4 count, Highly Active Anti-Retroviral Therapy (HAART) at the time of delivery and gestational age was estimated using reported last menstrual period (LMP). Prematurity was defined as an infant delivered <37 weeks gestation. Birth weight was categorized as normal (>2500 gram), low (1500 gram - 2500 gram), very low (1000 gram - 1499 gram). Infants were considered HIV-exposed if their mother had a positive HIV test any time prior to delivery or immediately post-partum. HIV-unexposed infants included those whose mothers had a documented negative HIV test during

pregnancy or immediately post-partum. Infants born to women with no documented HIV test were considered to have unknown HIV exposure.

Results

A total of 142 participants were enrolled in the study, out of which 23 (46.9) were HIV exposed, 52 (66.7) were HIV unexposed. HIV exposed Preterm (<37 weeks) were 13(26.5) and 23(24.9) were HIV unexposed.

Table 1 shows the demographic features and Antenatal characteristic of HIV positive and HIV negative mothers. HIV positive were more likely to attend antenatal clinic as compared to HIV negative mothers 48(51.6). The mean maternal ages between HIV positive and HIV negative mothers was comparable 20 years - 35 years, 44(89.8) being HIV positive mothers and 60(64.5) HIV negative. Majority of the mothers in this age group had completed primary school education 41(83.7) HIV positive and 56(60.2) HIV negative respectively. The rate of HIV disclosure was high in both groups. HIV positive women 30(61.2) and HIV negative women 68(78.1) had known their partners HIV status. From the HIV positive mothers 2(4.1) were having their first birth compared to 48(51.9) HIV negative mothers having their first births. Antibiotics use during pregnancy was high in HIV positive mothers compared to HIV negative mothers 17(34.7) to 15(16.1) respectively. With equal number of mothers using antibiotics during intra-partum are 3(6.1) and 3(3.1). Caesarean section was the preferred mode of delivery (with or without vaginal attempt) in the two cohorts with 24(49.0) in HIV positive mothers and 41(44.1) in HIV negative mothers. The enrollment criteria of neonates into the study were based on the intra-partum and new born factors. Intra-partum factors were 29(59.2%) for positive HIV status and 35(37.6%) for negative HIV status. Newborn factors were 7(14.3%) for HIV positive, 10(10.8%) for HIV negative. For the Neonates enrollment age (hours) median IQR (16,46) minimum: 6, maximum: 83 for HIV exposed and HIV unexposed 32(17,45) minimum: 3, maximum: 8.

Characteristic	N	HIV+ Freq. (%) or Median (IQR) (N=49)	N	HIV+ Freq. (%) or Median (IQR) (N=93)
Maternal age	49		93	
< 20		2 (4.1)		29 (31.2)
20 - 35		44 (89.8)		60 (64.5)
35+		3 (6.1)		4 (4.3)
Mother completed primary school or less	49	41 (83.7)	93	56 (60.2)
Household income< 10, 000 Ksh	47	27 (57.5)	75	33 (44.0)
Father HIV status	49		93	
Known neg.		3 (6.1)		68 (78.1)
Known post.		30 (61.2)		1 (1.1)
Decline to state		16 (32.6)		24 (25.8)
First birth	49	2 (4.1)	93	48 (51.6)
1+ ANC visit	49	48 (98.0)	93	90 (96.8)
Maternal antibiotics in pregnancy	49	17 (34.7)	93	15 (16.1)
Referred/transferred to facility	49	22 (44.9)	93	41 (44.1)
Traveled 1+ hours to hospital	49	27 (55.1)	93	44 (47.3)
Intra-partum antibiotics	49	3 (6.1)	93	3 (3.2)
Caesarean section (with or without vaginal attempt)	49	24 (49.0)	93	41 (44.1)

Enrollment criteria	49		93	
Intra-partum factors only		29 (59.2)		35 (37.6)
Newborn factors only		7 (14.3)		10 (10.8)
Intra-partum and newborn factors		13 (26.5)		48 (51.6)
Preterm (< 37 weeks)	49	13 (26.5)	93	23 (24.7)
Low or very low birth weight	49	16 (32.6)	93	26 (28.0)
Newborn age at enrollment (hours) (median, IQR)		24 (16, 46) min: 6, max: 83		32 (17, 45) min: 3, max: 89
Newborn antibiotics prior to blood draw	49	15 (49.6)	90	54 (60.0)

Table 1: Characteristics of women and newborns at enrollment, by maternal HIV status (N = 142).

Table 2 illustrates characteristics of HIV positive mothers and their newborns (N = 49). Majority of the women new their partners HIV status, those with HIV positive partners were 30(61.2) and those who did not know their partners status or declined to state were 16(32.7). Most recent CD_4 count (median, IQR) 24 462.5(361,720) minimum: 145; maximum: 1300.Women who were on cotrimoxazole 43(87.8) and those taking HAART 39(79.6). All the newborns received nevirapine 49(100.0).

Characteristic	N	Freq. (%) or Median (IQR)
Partner known HIV+	49	30 (61.2)
Partner unknown status or decline to state		16 (32.7)
Most recent CD4 count (median, IQR)	24	462.5 (361, 720) min: 145; max: 1300
Time since most recent CD4 count (months) (median, IQR)	11	5.9 (3.8, 8.5) min: 1.1, max: 16.3
Currently taking Contrimoxazole	49	43 (87.8)
Currently taking HAART	49	39 (79.6)
Newborn received Navirapine	49	49 (100.0)

Table 2: Characteristics of HIV positive women and their newborns (N = 49).

All the neonates enrolled into the study within the first 24 hours of life were tested for HIV, from the 49 neonates HIV-exposed there was 0 (0.00 %) HIV-positive by 24-hr PCR of this neonates, prevalence of probable or confirmed sepsis was 23(46.7), with a prevalence ratio of 0.70 (95% CI: 0.05, 0.51, 0.98) p-value 0.0375 as compared to HIV- unexposed 52(66.7) as indicate in Table 3.

Characteristic	Probable or confirmed sepsis [1] Frequency (%)	Unadjusted Prevalence Ratio (95% CI) [2]	p-value [3]	p-value [4]	Adjusted Prevalence Ratio (95% CI) [5,6]	p-value [7]
Homa Bay (n=142)						
HIV-exposed	23 (46.9)	0.70 (0.51, 0.98)	0.0375	0.0305	0.71 (0.51, 0.99)	0.0433
HIV-unexposed	52 (66.7)					

Table 3: Prevalence of probable or confirmed sepsis by HIV exposure status.

As per table 4 analysis there was no difference in the role of potential mediating factors in the association between maternal HIV infection and probable sepsis in newborns.

Potential Mediating Factor	Direct Effect of maternal HIV (95% CI) [1,2]	Natural Indirect Effect (Causal Mediation Effect) of maternal HIV (95% CI) [3]	Total Causal Effect of maternal HIV (95% CI) [4]	% of Total Effect of maternal HIV mediated by factor (95% CI)
Maternal Cotrimoxazole use	0.00(-0.39,0.38)	-0.19(-0.57,0.18)	-0.19(-0.35,-0.03)	1.01(0.51,4.72)
Maternal HAART use	-0.17(-0.57,0.24)	-0.02(-0.39,0.33)	-0.19(-0.35,-0.03)	0.13(0.06,0.51)
Newborn antibiotic exposure	-0.03(-0.17,0.11)	-0.18(-0.33,-0.06)	-0.21(-0.39,0.03)	0.86(0.45,4.30)
Preterm birth	-0.20(-0.36,0.05)	0.00(-0.03,0.04)	-0.20(-0.34,0.03)	-0.02(-0.08,.01)
Low birth weight	-0.20(-0.36,0.04)	0.00(-0.03,0.04)	-0.20(-0.36,-0.03)	0.00(0.00,0.00)

Table 4: Analysis of the role of potential mediating factors in the association between maternal HIV infection and probable sepsis in newborns (N = 142).

From Table 5 there seem to be very little or no association between HIV exposure and probable or confirmed sepsis among the newborns a part from the mothers who were on cotrimoxazole who had a prevalence 1.00 (0.56, 1.79) with a *p-value* of 1. There was no statistical significance in the association of maternal level of education for HIV exposure and probable or confirmed sepsis where we had a prevalence of 0.70(0.51, 0.98) with a *p-value* of 0.0375.

Discussion

The study sample represented 23(46.9) of HIV exposed and 52(66.7) of unexposed neonates of the 142 mother neonate pair enrolled in the study in Homa Bay County Referral Hospital from June 2016 to January 2017. In this study the education level of mothers seemed lower as compared to mothers enrolled in similar studies in Cameroon and Zambia [1]. In both studies, the level of education never had a statistical significance on the association of HIV exposure and probable or confirmed sepsis; neither did their level of education affect their antenatal attendance, use of Cotrimoxazole, and Nevirapine for their Newborns. Despite Homa Bay County being one of the counties with high rates of HIV infections in Kenya, persons living with HIV were well informed about HIV care, which was noted in this study during pregnancy. Antenatal visits were well attended by the mothers 48(98.0) HAART 39(79.6). Neonatal dosage of Nevirapine 49(100.0) might have had a positive impact on the outcome of the newborns. This showed no effect of maternal HIV status on newborn at 0(0.00%) with HIV-positive by 24-hr PCR.

The management of infants whose mothers were infected with the human immunodeficiency virus (HIV) involved minimizing the risk of vertical transmission of HIV, detecting neonatal HIV infection early, and preventing opportunistic infections [4]. Maternal anti-retroviral drug therapy during pregnancy and labour, followed by neonatal Nevirapine therapy could significantly decrease the risk of vertical transmission. Elective Caesarean section may also prevent vertical transmission of HIV. In this study we had 48% of Neonates tested for HIV and receiving Nevirapine syrup at birth. These neonates also received antibiotics before their blood samples were taken for culture. The administration of antibiotics may also have had an impact of the culture results thus affecting the direct effect of Maternal HIV association with Neonatal sepsis. Women who had good virologic control during pregnancy and labour by use of HAART, Antibiotics, had lower viral loads, good CD_4 count, and the mode of delivery may also prevent the neonatal from any invasive procedures [5]. Looking at our study, the association of Maternal HIV and Neonatal sepsis could not be ascertained as the measures pertaining care and Prevention of Mother to child transmission were well taken care of [6].

Women with HIV were originally thought to give birth to infants who showed evidence of stunted growth, low birth weight, or were more likely to be preterm [1,3]. However, in this study there was no statistical significance of association between maternal HIV and number of Preterm babies 13(26.5) and lower birth weight 16(32.6) as other factors may also have been responsible for low birth weight babies, which could have included malnutrition, coexisting infection, illicit drug, tobacco or alcohol use, of which no data was collected [7].

The prevalence of premature births varied with HIV positive mothers at 26.5% and HIV negative mothers at 23% with no statistical significance. Our findings were similar to Termmeman et al. [17], who noticed a difference of 21.1% in HIV positive mothers compared to 9.4% in HIV negative mothers [7-15]. In a similar study Haeri et al. [18] found that prematurity was more common among HIV-positive women than uninfected mothers (OR = 2.27, 95% CI = 1.22 - 4.25) [16,17].

The reported non association of maternal HIV in association with probable or confirmed sepsis was not different from other studies done in the developed countries [9]. Very low rates were reported in the developed countries which could be explained by the high quality of life and quality health care and Hospital services in these countries which were also not different from the study done in Boston which revealed 14.7% of 7226 of neonates that were evaluated for early neonatal sepsis [8,10].

Characteristic	Prevalence Ratio (95% CI) [2]	*p*-value [3]
Crude analysis	0.70 (0.51, 0.98)	0.0375
Adjusted for maternal education (completed primary or less *vs.* attended more)	0.71 (0.51, 0.99)	0.0433
Adjusted for maternal age (3 category)	0.70 (0.50, 0.99)	0.0427
Adjusted for household income (<10,000 Ksh *vs.* 10,000+ Ksh)	0.69 (0.49, 0.97)	0.0309
Adjusted for travel time to facility (1+ hours *vs.* <1 hour)	0.70 (0.70, 0.97)	0.0326
Adjusted for paternal HIV status (known neg., known post., don't know/decline)	0.74 (0.42, 1.28)	0.2776
Adjusted for parity (first birth *vs.* higher-order)	0.68 (0.48, 0.96)	0.0265
Adjusted for maternal antibiotics in pregnancy (any *vs.* none)	0.72 (0.51, 1.00)	0.0507
Adjusted for maternal Cotrimoxazole use (current) (mediator)	1.00 (0.56, 1.79)	1.00
Adjusted for maternal HAART use (current) (mediator)	0.75 (0.40, 1.42)	0.3755
Adjusted for maternal CD_4 count (mediator) [6]	0.57 (0.05, 6.16)	0.6421
Adjusted for low birth weight (low or very low *vs.* not low or very low) (mediator)	0.69 (0.50, 0.94) [5]	0.0172
Adjusted for preterm birth (mediator)	0.73 (0.52, 1.02)	0.0663
Adjusted for delivery mode (mediator)	0.74 (0.56, 0.97) [5]	0.0295
Adjusted for newborn age at enrollment (hours, continuous)	0.69 (0.50, 0.97)	0.0321
Adjusted for newborn antibiotic exposure (mediator) [5]	0.94 (0.73, 1.22) [5]	0.6588

Table 5: Crude and adjusted associations between HIV exposure and probable or confirmed sepsis among newborns (N = 142).

Advanced maternal age has been associated with early neonatal sepsis [11]. A study done by Jiang et al. [14] noted that once a woman's child bearing age is postponed, with the extended period between the sexually mature phase and childbirth and an increase in the proportion of unplanned pregnancies, many women have induced abortions [12]. This can lead to adverse effects on pregnant women and their newborns during delivery and following childbirth hence an increase in risk factors for neonatal sepsis [13]. On the contrary, the mean maternal age of this study participant was 25-35 years which may also explain the lower sepsis rates in this study as compared to other studies [16-18].

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