Original Article

Looking beyond prevention of parent to child transmission: Impact of maternal factors on growth of HIV-exposed uninfected infant

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Abstract

Background: Compared to HIV-infected children, relatively little has been described regarding the health status, particularly growth of HIV-exposed but uninfected children in resource-limited settings. This is particularly relevant with widespread implementation of the prevention of parent to child transmission program. **Methods:** At a tertiary care health institute in India, a cohort of 44 HIV-exposed but uninfected children were followed through 6 months of age. The anthropometric parameters weight, length, and head circumference were investigated at birth, 3 weeks, 6 weeks, 3 months, and 6 months point of time. The information on maternal characteristics such as HIV clinical staging, CD4 count, and maternal weight were recorded. The linear regression analysis was applied to estimate the influence of maternal characteristics on infant anthropometric parameters. **Results:** Anthropometric parameters (weight, length and head circumference) were significantly reduced in uninfected new-borns of mothers in HIV Clinical stage III and IV and weight <50 kg compared to mothers in HIV Clinical stage I and II and weight >50 kg. Analysis conducted to find the effect of maternal immunosuppression on infant growth reveals a significant difference at CD4 300 cells/mm³ and not at established cut-off of CD4 350 cells/mm³. This trend of difference continued at 6 weeks, 3 months, and 6 months. The multiple linear regression analysis model demonstrated maternal HIV clinical stage and weight as predictors for birth weight and length, respectively. **Conclusions:** Advanced HIV disease in the mother is associated with poor infant growth in HIV-exposed, but uninfected children at a critical growth phase in life. These results underscore the importance, especially in resource-constrained settings, of early HIV diagnosis and interventions to halt disease progression in all pregnant women.

Key words: HIV-exposed infants, maternal HIV, PPTCT

INTRODUCTION

Of an estimated 27 million pregnancies in India less than a quarter have HIV counseling and testing.[1] It is estimated that there are between 22,000 and 61,000 HIV pregnant women living with HIV in India.[1,2] With improving prevention of parent to child transmission (PPTCT) program services, perinatal transmission of HIV has decreased and the vast majority of infants born to known HIV-infected mothers are HIV-exposed but uninfected. At the same time, there remains a huge gap between the number of estimated HIV infections in pregnant women versus those actually diagnosed and availing of PPTCT services.[3,4] Resultant, a subset of HIV-infected pregnant women remains undiagnosed and untreated allowing disease progression, malnutrition, and immunosuppression.[1]

Compared to the cohort of HIV-infected children, the health status of HIV-exposed but uninfected

children is relatively less published especially in Indian context.[5,6]

The present study was planned to assess the impact of maternal factors such as clinical stage of the HIV disease, CD4 count, and weight during pregnancy in HIV-infected mothers on anthropometric parameters of HIV-exposed but uninfected infants.[5-7]

METHODS

Study duration and settings
This prospective cohort study of HIV-exposed (documented maternal HIV infection) but uninfected children was conducted from December 2009 to June 2011 at the HIV care clinic of an urban, tertiary care hospital in Western India.

Study design and participants
All HIV-infected mothers who delivered during the study period and consented to the study were enrolled along with their infants. The data of infants who remained HIV negative at 18 months of age were analyzed to be reported in this manuscript.

Study methods
All women who came to the Antenatal outpatient department (OPD) were enrolled in PPTCT center for pretest counseling and HIV testing by third generation enzyme-linked immunosorbent essay (ELISA) test with three test kits, sequentially as per the NACO protocol, was done for those who gave consent.[8] The results were shared after the posttest counseling, and all women were referred for Antenatal Care to Obstetrics and Gynecology OPD. The women, who were diagnosed as HIV positive, were referred to the antiretroviral therapy (ART) center also for care, support, and linkages. A complete HIV-related clinical and laboratory assessment was done for all women. Clinical staging was done as per the WHO classification.[9] The immunological status of the mother was determined by the CD4 cell count. The eligibility for therapeutic ART was determined. Those mothers who were not eligible for ART were given antiretroviral prophylaxis.[8]

Antiretroviral prophylaxis (single dose nevirapine prophylaxis) mother-baby pair was provided to mother and newborn according to the NACO guidelines. The infant feeding was continued as per the choice of the mother after she was informed about the benefits versus risk of breastfeeding.[9]

Anthropometric measurements (weight, height, and head circumference) of all neonates were done immediately after birth preferably by same investigator. Infants were weighed on an electronic weighing scale up to nearest 10 g. Length was taken by infantometer up to the nearest centimeter. A non-elastic tape was used to record head circumference in centimeters. The ponderal index was calculated from the recorded height and weight using the formula of weight in g $\times$ 100/length in cm.

All infants were followed monthly at the ART center to evaluate growth and development, immunization, chemoprophylaxis for opportunistic infections and to provide nutrition counseling. In addition to the routine care and support to the mother and infant, the anthropometric measurements were repeated at 6 weeks, 3 months, and 6 months in the nursery following the same protocol and with the same standardized instruments used at birth. All infants were on exclusive breastfeeding during this period.

Infant HIV diagnosis was ruled out using HIV DNA polymerase chain reaction on dried blood spot at 6 weeks and 6 months of age. In addition, all infants were tested for antibodies against HIV by ELISA at 18 months of age and deemed HIV negative only if they had a negative HIV ELISA.[9]

Ethical issues
The approval from Institutional Review Board was taken before the commencement of the study. The study participants were explained in detail about the study, and informed consent of all mothers was obtained. All data were kept confidential at all stages of study.

Data collection and analysis
Data were collected, and entry was started during the study period to ensure minimal errors and also to have a backup data. Data entry was done in two separate software, Microsoft Excel and International Business Machines Corporation SPSS (Statistical Package for Social Studies). The descriptive statistics of all variables were calculated. Growth indicators of infant were analyzed with maternal factors to find an association between them by parametric tests like compare means with the help of independent *t*-test. The median analysis was performed by nonparametric tests for independent samples like Mann–Whitney tests. The data were checked for assumptions of parametric tests such as normality and equal variance when groups were unequal. The statistical difference was considered for $P < 0.05$.

Multivariate analysis of repeated measures ANOVA was also done to compare the growth of infants according to mothers' immunological and clinical

staging. Linear regression model was constructed to predict the impact of maternal characteristics on infant anthropometric measurements. Only the factors with $P < 0.05$ were reported with their regression coefficient (B) in final regression model.

RESULTS

The present study describes the analysis of total 44 HIV-positive mothers and their HIV-exposed infants. The distribution of infants according to the immunological and HIV clinical stage of mothers is shown in the Table 1.

Table 1: Distribution of HIV-exposed infants according to the characteristics of mothers

Mothers' characteristics (*n*=44)	*n*	Percentage
Mother's CD4 count		
<350 cells/mm^3	17	38.6
≥350 cells/mm^3	27	61.4
<300 cells/mm^3	13	29.5
≥300 cells/mm^3	31	70.5
Mother's clinical stage		
Stage I and II (not eligible for therapeutic ART)	30	68.2
Stage III and IV (advanced stage-eligible for therapeutic ART)	14	31.4
Mother's weight		
<50 kg	9	20.5
≥50 kg	35	79.5

ART=Antiretroviral therapy; HIV=Human Immunodeficency Virus; CD4=Cluster of Differentiation4

Table 2: Descriptive statistics of mothers' weight and CD4 count

Mother's characteristic	Median	Mean±2SD	Range
Mothers' weight	55.3	55.4±11.1	45-65.4
CD4 count	397.50	427.9±444.6	13-909

SD=Standard deviation; CD4=Cluster of Differentiation4

The median weight of mothers was 55.3 kg and their median CD4 count was 397.50 cells/mm^3 [Table 2].

Mean and Median values of weight, length, head circumference, and ponderal index at birth of babies born to mothers with clinical stage I/II, CD4 >350 cells/mm^3, and maternal weight >50 kg were higher than mothers in clinical stage III/IV, CD4 <350 cells/mm^3 and weight <50 kg. Findings from further analysis reveal the difference in anthropometric indicators of infants becomes statistically and clinically significant at low maternal weight, advanced HIV clinical stage and CD4 <300 cells/mm^3 [Table 3].

The anthropometric measurements were taken at 6 weeks, 3 months, and 6 months. Thirty-nine infants came for follow-up at 6 months. The analysis done according to maternal characteristics showed, lower parameters of infants born to mothers having CD4 count <300 cells/mm^3 and advanced HIV clinical stage III and IV [Table 4].

The regression analysis was done with maternal characteristics as predictor (independent) variables and infant characteristics as outcome (dependent) variables [Table 5]. In the final model, birth weight was more by 0.293 g in infants born to mothers with clinical stage I and II during pregnancy as compared with mothers who have progressed to stage III and IV ($P = 0.04$). The length of baby at birth was associated with maternal weight, and 0.139 cm increase in the length of the infant was observed for unit increase in weight of mother ($P = 0.02$).

DISCUSSIONS AND CONCLUSIONS

HIV-positive status during pregnancy is a coexisting

Table 3: Distribution of anthropometric measurements of infants at birth according to immunological and HIV clinical stage of the mother

Anthropometric measurements of infants at birth	Immunological and HIV status of the mother					
	Mother's clinical stage I/II			Mother's clinical stage III/IV		
	Mean±2SD	Median	Number of infants	Mean±2SD	Median	Number of infants
Birth weight[a,b]	2.51±0.81	2.58	30	2.22±0.94	2.25	14
Length at birth[a,b]	47.5±3.78	48.00	30	46.2±3.2	45.75	14
Head circumference	33.2±2.66	33.50	30	32.7±2.8	33.00	14
Ponderal index	2.32±0.46	2.33	30	2.21±0.46	2.30	14
	Mother's CD4 count>350			Mother's CD4 count<350		
Birth weight	2.48±0.78	2.55	27	2.33±1.04	2.50	17
Length at birth	47.30±3.66	48.00	27	46.79±5.47	48.0	17
Head circumference	33.11±2.70	33.50	27	32.91±2.79	33.50	17
Ponderal index	2.32±0.44	2.34	27	2.23±0.48	2.26	17

[a]$P<0.05$ (compare means by *t*-test), [b]$P<0.05$ (compare median by nonparametric tests of significance i.e., Mann-Whitney test). SD=Standard deviation; HIV=Human Immunodeficiency Virus

Table 4: Distribution of anthropometric measurements of infants at 6 months according to immunological and HIV clinical stage of mother

Anthropometric measurements of infants at 6 months	Immunological and HIV status of mother					
	Mother's clinical stage I/II			Mother's clinical stage III/IV		
	Mean±2SD	Median	Number of infants	Mean±2SD	Median	Number of infants
Weight (kg)	6.07±1.18	5.96	27	5.97±0.90	6.03	12
Length (cm)	63.94±4.10	64.00	27	62.88±4.04	63.00	12
Head circumference (cm)	41.93±2.08	42.00	27	41.88±2.80	42.25	12
	Mother's CD4 count>350			Mother's CD4 count<350		
Weight (kg)	6.05±1.20	5.96	27	6.03±0.92	6.05	12
Length (cm)	63.85±4.28	63.50	27	63.23±3.98	63.00	12
Head circumference (cm)	41.90±2.08	42.00	27	41.93±2.74	42.00	12
	Mother's weight>50 kg			Mother's weight<50 kg		
Weight (kg)	6.12±1.07	6.00	31	5.75±1.06	5.73	8
Length (cm)	63.9±3.98	64.00	31	62.5±4.40	61.50	8
Head circumference (cm)	42.0±2.04	42.00	31	41.56±3.28	41.50	8

SD=Standard deviation; HIV=Human Immunodeficency Virus; CD4=Cluster of Differentiation4

Table 5: Multiple linear regression analysis of length, weight, and head circumference of HIV-exposed infants according to maternal CD4 count, HIV clinical stage, and weight as predictors

Model*	B (unstandardized coefficient)	SE (B)	Standardized coefficients (β)	P
Mother's clinical stage (dependent variable is birth weight)	−0.293	−0.139	−0.310	0.04
Mother's weight (dependent variable is length at birth)	0.139	0.57	0.350	0.02

SE=Standard error; HIV=Human Immunodeficency Virus; CD4=Cluster of Differentiation4

condition and makes the mother and pregnancy outcome even more vulnerable. Therefore, it is logical that even uninfected infant of HIV-infected mother has compromised health status compared to nonexposed counterparts. The need to document the impact of maternal factors on growth and development of HIV-exposed uninfected children prompted the present study.

The comparison of anthropometric measurements at birth of infants demonstrates significantly lower values for babies of mothers with poor immunological, clinical staging, and weight. This is in line with findings of other authors on outcomes of HIV-exposed babies and confirms that the HIV positivity during pregnancy has an adverse impact on perinatal outcome of HIV-exposed and uninfected infant also[6,7]

The current study further shows that the growth parameters of HIV-exposed infants of mothers having weight <50 kg, clinical stage III and IV and CD4 count <300 cells/mm³ do not catch-up with the growth parameters of their counterparts even after follow-up at 6 months of age. This is contrary to the findings of the cohort study done in Congo, which shows that uninfected infants attain the health status of nonexposed infants later in life.[10] The present study results highlight the importance of reviewing the health status of HIV-exposed uninfected children in our settings and developing interventions to address the observed growth delay.

The multiple linear regression analysis was done to estimate differences in anthropometric parameters of infant (dependent and outcome variables) for maternal factors; weight, clinical staging, and immunological staging (independent and predictor variables). Birth weight and length were significantly associated with maternal clinical stage of HIV and maternal weight, respectively, as per the multiple linear regression model in the present study. Other studies confirm similar findings in HIV-exposed but infected infants.[5-7,10,11]

Birth weight is considered as the best indicator for predicting the infant growth and survival. The present study shows that the birth weight of infants born to mothers with better immunological and clinical staging was significantly higher, and this difference remained as a trend even at 6 months of age [Table 3]. The impact on birth weight through 6 months of age, we report in HIV-exposed uninfected infants, potentially can impact childhood morbidity and mortality.

The current study proves the impact of HIV-positive mothers' disease stage characteristics on infant growth parameters at birth and beyond which underscores the need of interventions to be offered at earlier stage of HIV disease so that the mother does not progress to advanced stage of disease and the fetal outcome is uncompromised.

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