Published in final edited form as:

Pediatr Infect Dis J. 2019 May ; 38(5): 500–502. doi:10.1097/INF.0000000000002253.

Maternal Perinatal HIV Infection is Associated with Increased Infectious Morbidity in HIV-Exposed Uninfected Infants

Kathleen M. Powis, MD^{1,2}, Amy L. Slogrove, PhD³, Ibeawuchi Okorafor, MD⁴, Lily Millen, BA⁵, Roberto Posada, MD⁶, Jocelyn Childs, LCSW-R⁷, Elaine J. Abrams, MD⁸, Rhoda S. Sperling, MD⁵, and Jennifer Jao, MD^{4,5}

¹Massachusetts General Hospital, Departments of Internal Medicine and Pediatrics, Boston, MA, USA

²Harvard T.H. Chan School of Public Health, Department of Immunology and Infectious Diseases, Boston, MA, USA

³Stellenbosch University, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch, South Africa

⁴Icahn School of Medicine at Mount Sinai, Department of Medicine, New York, NY, USA

⁵Icahn School of Medicine at Mount Sinai, Department of Obstetrics, Gynecology, and Reproductive Science, New York, NY, US

⁶Icahn School of Medicine at Mount Sinai, Department of Pediatrics, New York, NY, USA

⁷Icahn School of Medicine at Mount Sinai, Department of Social Work, New York, NY, USA

⁸ICAP at Columbia, Mailman School of Public Health and College of Physicians and Surgeons, Columbia University, New York, NY, USA

Abstract

More women with perinatally-acquired HIV are giving birth. We evaluated infectious cause hospitalizations (ICH) in HIV-uninfected infants of perinatally HIV-infected (HEU-P), non-perinatally HIV-infected (HEU-N), and HIV-uninfected women (HUU) through 12 months-of-life at an urban tertiary health center. HEU-P infants experienced higher ICH risk compared to HEU-N and HUU infants. Identification of biological and structural drivers of differences are needed.

Keywords

HIV-exposed infants

Correspondence: Kathleen M. Powis, MD, MPH, MBA, Massachusetts General Hospital, 125 Nashua Street, Office 8426, Boston, MA 02114, Telephone number: (617) 643-2054, Fax number: (617) 643-8398, kpowis@mgh.harvard.edu.

Conflicts of Interest: EJA has participated on advisory boards for ViiV and Merck. No other authors have any potential conflicts of interest to report.

Introduction

Worldwide in 2016 approximately 650,000 adolescent girls were living with perinatally-acquired HIV (PHIV).¹ As this population reaches reproductive age, a generation of HIV-exposed uninfected (HEU) infants born to women living with PHIV (HEU-P) is emerging, with some conflicting birth outcomes data^{2,3} and limited postnatal data. HIV-uninfected infants of non-perinatally HIV-infected women (HEU-N) are at greater risk for infectious morbidity with more severe disease than HIV-unexposed uninfected (HUU) infants.⁴ Drivers of excess infectious morbidity among HEU-N infants are multifactorial representing a complex array of intrauterine and early postnatal exposures. In utero environments, potentially perturbed by HIV-related chronic inflammation, maternal immune compromise, and antiretroviral (ARV) exposure, may contribute to poor transplacental transfer of protective maternal pathogen-specific antibodies and adversely affect early life immunologic responses, increasing infectious morbidity risk.⁵ Additionally, HEU infants are more likely to be born preterm, small-for-gestational-age (SGA), or of low birth weight, factors known to increase infectious morbidity.⁶

It is reasonable to expect potentiation of infectious morbidity risk factors among HEU-P infants born to women with lifelong HIV, frequently with a complicated disease course and complex antiretroviral therapy (ART) by the time they reach reproductive age. Yet, prevalence of infectious morbidity in HEU-P infants, and whether risk differs from that of HEU-N and HUU infants has not been studied. The objective of this study was to assess the association between maternal HIV status [maternal PHIV vs. non-perinatally acquired HIV (NPHIV) vs. HIV-uninfected] and infant infectious morbidity in the first year of life in a tertiary care center in the U.S.

Materials and Methods

Study Population

We enrolled pregnant women living with HIV (WLHIV) and HIV-uninfected pregnant women receiving care at Mount Sinai Obstetrical Clinic and their infants who received pediatric follow-up at Mount Sinai Medical Center (MSMC) in New York City from 2009–2015. The Obstetrical Clinic provides clinical care to WLHIV and HIV-uninfected pregnant women in the same catchment area with similar socioeconomic circumstances, including insurance coverage. Maternal eligibility for this sub-study required a live, singleton delivery at ≥ 28 weeks gestational age (GA), with exclusion of HIV-infected infants.

The study was approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai.

Primary Outcome

We evaluated the prevalence of at least one infectious cause hospitalization (ICH) during the first 12 months-of-life in HEU and HUU infants. Hospitalization, identified via maternal report, was defined as either failure to leave the hospital after birth due to infectious causes or admission to a hospital for >24 hours. Hospitalization details were collected via medical

record review from Mount Sinai hospital records as well as outside institutions, when records were available.

Predictor Measurements

Our main exposure of interest was maternal HIV status, categorized as maternal PHIV vs. NPHIV vs. HIV-uninfected according to medical records or patient report. Other potential confounders, including socio-demographics and substance use during pregnancy, were determined by medical record review. Substance use was defined as any tobacco, alcohol, or other substance use during pregnancy. For WLHIV, data on pregnancy nadir CD4 cell counts and HIV RNA levels (using <400 copies/mL to define viral suppression), as well as ART use throughout pregnancy was collected. Birth weight-for-age (WAZ) and length-for-age (LAZ) Z-scores were calculated based on U.S. standards.⁷ GA at birth was assessed by routine ultrasound in all women, and preterm birth was defined as delivery before 37 weeks GA.

Statistical Analysis

Characteristics of women at first pregnancy were compared using Wilcoxon test, Chi-square, or Fisher's exact test as appropriate. Generalized Estimating Equation modeling was used to evaluate the effect of maternal HIV status on infant ICH and account for the clustering of repeat pregnancies in the same woman. Statistical analyses were performed using SAS® 9.4 (SAS Institute, Cary, NC.).

Results

A total of 206 infants [29 HEU-P (born to 20 women with PHIV), 112 HEU-N (born to 86 women with NPHIV) and 65 HIV-unexposed uninfected infants (born to 65 HIV uninfected women)] enrolled from 2009–2015 met study eligibility criteria. (Table 1) PHIV women at first pregnancy were younger (median age in years 22 vs. 29 vs. 23 respectively, $p<0.01$) and more likely to be African-American (70% vs. 63% vs. 43% respectively, $p<0.01$) compared to NPHIV and HIV-uninfected women. NPHIV women were more likely to report heroin/cocaine (9% vs. 0% vs 0% respectively, $p<0.01$) and tobacco (20% vs. 10% vs, 3% respectively, $p=0.01$) use during pregnancy and present with Hepatitis B co-infection (8% vs. 0% vs, 2%) compared to PHIV and HIV-uninfected women. Among WLHIV, PHIV women were more likely to have a CD4 nadir <50 cells/mm³ during pregnancy (25% vs. 1%, $p<0.01$) and to have received an ART regimen consisting of 3 ARV classes (35% vs. 0%, $p=0.01$) compared to NPHIV women. HEU-P infants were more likely to be born SGA (31% vs. 13% vs. 8% respectively, $p=0.01$) and exhibit lower birth WAZ (−0.88 vs. −0.37 vs, −0.30 respectively, $p=0.02$) and LAZ (−0.48 vs. −0.14 vs. 0.10 respectively, $p=0.01$) than HEU-N and HUU infants. HEU infants were more likely to be born preterm than HUU infants (21% for HEU-P and HEU-N vs, 6% for HUU, $p=0.03$). HEU-N were more likely to be in the custody of someone other than the biological mother in the first year of life (17% vs. 14% vs. 2% respectively, $p<0.01$) compared to HEU-P and HUU infants.

Overall, 21% of HEU-P, 4% of HEU-N and 12% of HUU infants had at least one ICH ($p<0.01$) in the first 12 months-of-life. ICH etiologies included viral syndrome with cough or upper respiratory symptoms (53%), bronchiolitis or pneumonia (26%), viral

gastroenteritis (16%), and sepsis (5%). Three participants had ICH within the first 3 months of life, including one HEU-P infant who died on the second day of life of *Klebsiella* sepsis and pneumonia. After adjusting for maternal age, education, black race, substance use during pregnancy, infant SGA, prematurity, guardian other than biological mother, and infant outpatient visits during the first year of life, HEU-P infants remained at increased risk for ICH compared to HEU-N infants [adjusted odds ratio (aOR)=7.45, 95% Confidence Interval (CI):1.58-35.04], without significant difference in ICH risk observed between HUU and HEU-N infants [aOR 2.82, 95% CI:0.70-11.41]. In sub-group multivariable analysis of HEU infants, this relationship persisted after additional adjustment for maternal CD4 and HIV RNA level (aOR=10.24, 95% CI:1.66-63.31).

Discussion

In this cohort of PHIV, NPHIV and HIV-uninfected women and their infants from an urban tertiary health center in the U.S, we observed a 7-fold greater probability of an ICH for HEU-P compared to HEU-N infants. Consistent with previous reports, preterm birth was substantially higher in both HEU-P and HEU-N infants compared to HUU infants.⁸ Additionally, HEU-P infants were more often SGA with lower birth WAZ and LAZ than both HEU-N and HUU infants. Of note, when we restricted the analysis to appropriate-for-gestational age infants, results remained the same.

There was no difference in the number of ambulatory care visits in the first year of life between the three groups, indicating frequency of minor infectious events was similar between groups, suggesting that HEU-P infants experience more severe infectious events warranting hospitalization. However, a low threshold for admission may exist amongst clinician's caring for HEU-P infants. In this study, severity of infectious illness was not assessed. However, a South African study employed a novel infection severity grading tool and reported that common infectious diseases manifest with greater severity in HEU compared with HUU infants.⁹ Further studies that incorporate infectious disease severity grading tools would be valuable in identifying differences in ICH between HEU-P and HEU-N infants.

The risk of ICH remained 10-fold greater in HEU-P compared to HEU-N infants after adjusting for markers of HIV-disease severity, including pregnancy nadir CD4 count and HIV RNA level, an important adjustment given PHIV mothers were more likely to have a pregnancy CD4 nadir < 50 cells/mm³. It is notable that neither maternal CD4 count nor HIV RNA level were associated with ICH, though neither of these may be the best measure for longstanding immune perturbation in women with PHIV. Though we were unable to determine the cause of the observed increase in ICH in HEU-P infants, we hypothesize that chronic inflammation and vascular consequences of lifelong HIV in women with PHIV could adversely impact the HEU-P fetal intrauterine immune environment.^{10,11} Furthermore, PHIV women often receive complex ART regimens during pregnancy of which, the placental and fetal effects are only beginning to be studied.

Our study has notable limitations. The imbalance in race between the control group and women living with HIV introduced risk of residual confounding. However, if race was

driving ICH risk then the HEU-N group (with 63% African-America) should have experienced a significantly greater risk of ICH than the HUU group. This was not the case. Secondly, this is a small study from a single healthcare center. Also, underlying microbiologic causes of infectious events were not evaluated. Larger studies structured to define infectious etiologies and compare ICH to an infant's HIV-exposure status and immunization history may identify opportunities for interventions to prevent HEU-P infant health disparities.

To our knowledge, this is the first study to evaluate infectious morbidity in HEU-P infants, indicating an increased risk for ICH in these infants. As survival continues to improve for children, adolescents, and young adults with PHIV across the globe, larger studies in high HIV burden settings will be needed to better characterize and understand the implications of maternal PHIV on pregnancy and offspring outcomes from infancy into adulthood.

Acknowledgments

JJ received salary support from the National Institute of Child Health and Human Development 1K23HD070760-01A1 during the preparation of this manuscript. ALS received salary support from the Fogarty International Center of the National Institutes of Health (1K43TW010683-01). This study was supported by the Icahn School of Medicine at Mount Sinai Dean's Office and ConduITS - the Institutes for Translational Sciences (CTSA) (UL1TR001433)

REFERENCES

1. Park YJ et al. The structure of the C-terminal domain of the largest editosome interaction protein and its role in promoting RNA binding by RNA-editing ligase L2. *Nucleic Acids Res* 40, 6966–6977, doi:10.1093/nar/gks369 (2012). [PubMed: 22561373]
2. Jao J et al. Birth Weight and Preterm Delivery Outcomes of Perinatally vs Nonperinatally Human Immunodeficiency Virus-Infected Pregnant Women in the United States: Results From the PHACS SMARTT Study and IMPAACT P1025 Protocol. *Clin Infect Dis* 65, 982–989, doi:10.1093/cid/cix488 (2017). [PubMed: 28575201]
3. Jao J et al. Small for gestational age birth outcomes in pregnant women with perinatally acquired HIV. *AIDS* 26, 855–859, doi:10.1097/QAD.0b013e328351f6ef (2012). [PubMed: 22313958]
4. Slogrove AL, Goetghebuer T, Cotton MF, Singer J & Bettinger JA Pattern of Infectious Morbidity in HIV-Exposed Uninfected Infants and Children. *Front Immunol* 7, 164, doi:10.3389/fimmu.2016.00164 (2016). [PubMed: 27199989]
5. Bunders MJ et al. Fetal exposure to HIV-1 alters chemokine receptor expression by CD4+T cells and increases susceptibility to HIV-1. *Sci Rep* 4, 6690, doi:10.1038/srep06690 (2014). [PubMed: 25341640]
6. Zash R et al. Reassuring Birth Outcomes With Tenofovir/Emtricitabine/Efavirenz Used for Prevention of Mother-to-Child Transmission of HIV in Botswana. *J Acquir Immune Defic Syndr* 71, 428–436, doi:10.1097/QAI.0000000000000847 (2016). [PubMed: 26379069]
7. Olsen IE, Groveman SA, Lawson ML, Clark RH & Zemel BS New intrauterine growth curves based on United States data. *Pediatrics* 125, e214–224, doi:10.1542/peds.2009-0913 (2010). [PubMed: 20100760]
8. Uthman OA et al. Timing of initiation of antiretroviral therapy and adverse pregnancy outcomes: a systematic review and meta-analysis. *Lancet HIV* 4, e21–e30, doi:10.1016/S2352-3018(16)30195-3 (2017). [PubMed: 27864000]
9. Slogrove A et al. A Prospective Cohort Study of Common Childhood Infections in South African HIV Exposed Uninfected and HIV Unexposed Infants. *The Pediatric Infectious Disease Journal* In Press, doi:10.1097/INF.0000000000001391 (2017).

10. Yan J, Zhang S, Sun J, Xu J & Zhang X Irreversible phenotypic perturbation and functional impairment of B cells during HIV-1 infection. *Frontiers of medicine* 11, 536–547, doi:10.1007/s11684-017-0592-x (2017). [PubMed: 29181691]
11. Quiros-Roldan E et al. Effects of combined antiretroviral therapy on B- and T-cell release from production sites in long-term treated HIV-1+ patients. *Journal of translational medicine* 10, 94, doi:10.1186/1479-5876-10-94 (2012). [PubMed: 22591651]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1.

Characteristics of Women at First Pregnancy and Infants

<i>PREGNANT WOMEN</i>				
	PHIV (n=20)	NPHIV (n=86)	HIV-uninfected (n=65)	<i>p</i> value
Age of Mother, years	22.4 (20.2-24.5)	29.2 (23.5 – 34.8)	23.2 (20.5-27.7)	<i><0.01</i>
Race				<i><0.01</i>
African American	14 (70%)	54 (63%)	28 (43%)	
Hispanic	6 (30%)	26 (30%)	32 (49%)	
White/ Other	0 (0%)	6 (7%)	5 (8%)	
Highest Education Level				<i>0.16</i>
Some College or Higher	6 (30%)	32 (37%)	33 (51%)	
High School Diploma/ GED	6 (30%)	19 (22%)	17 (26%)	
Some High School or Lower	8 (40%)	35 (41%)	15 (23%)	
Employed	4 (20%)	18 (21%)	21 (32%)	<i>0.24</i>
Gravida	1 (1-2)	3 (2-5)	2 (1-4)	<i><0.01</i>
Any Substance Use During Pregnancy				
Heroin/Cocaine	0 (0%)	8 (9%)	0 (0%)	<i><0.01</i>
Marijuana	0 (0%)	11 (13%)	3 (5%)	<i>0.07</i>
Alcohol	0 (0%)	3 (3%)	0 (0%)	<i>0.22</i>
Tobacco	2 (10%)	17 (20%)	2 (3%)	<i>0.01</i>
Maternal Height, cm	156 (154-160)	160 (155-165)	163 (155-168)	<i>0.10</i>
Maternal Pre-Pregnancy BMI, kg/m ²	24 (23-26)	28 (23-33)	24 (22-29)	<i>0.03</i>
History of Opportunistic Infections	4 (20%)	6 (7%)	---	<i>0.09</i>
Nadir CD4 cells during pregnancy, cells/mm ³			---	<i><0.01</i>
<50 cells/mm ³	5 (25%)	1 (1%)	---	
50-200 cells/mm ³	3 (15%)	14 (16%)	---	
201-350 cells/mm ³	6 (30%)	23 (27%)	---	
>350 cells/mm ³	6 (30%)	48 (56%)	---	
HIV RNA level <400 copies/mL at delivery	15 (75%)	76 (88%)	---	<i>0.15</i>
Log10 HIV RNA level at delivery	1.3 (1.3-2.7)	1.3 (1.3-1.3)	---	<i>0.14</i>
On 3 classes of ARV during pregnancy	7 (35%)	0 (0%)	---	<i><0.01</i>
Hepatitis B infection	0 (0%)	7 (8%)	1 (2%)	<i>0.02</i>
Hepatitis C infection	2 (10%)	8 (9%)	0 (0%)	<i>0.01</i>
<i>INFANTS</i>				
	HEU-P (n=28)	HEU-N (n=112)	HUU (n=65)	<i>p</i> value
GA at First Prenatal Visit, weeks	8 (7-10)	11 (8-16)	12 (9-15)	<i>0.01</i>
Female	13 (46%)	51 (46%)	36 (55%)	<i>0.43</i>
APGAR score at 5 minutes	9 (9-9)	9 (9-9)	9 (9-9)	<i>0.90</i>
Preterm (<37 weeks GA)	5 (18%)	24 (21%)	4 (6%)	<i>0.03</i>
SGA at Birth	9 (32%)	14 (13%)	5 (8%)	<i>0.01</i>

<i>INFANTS</i>				
	HEU-P (n=28)	HEU-N (n=112)	HUU (n=65)	<i>p</i> value
Birth WAZ	−0.89 (−1.57, −0.19)	−0.37 (−0.82, 0.20)	−0.30 (−0.81, 0.32)	<i>0.02</i>
Birth LAZ	−0.48 (−1.12, 0.09)	−0.14 (−0.87, 0.44)	0.10 (−0.55, 0.69)	<i>0.02</i>
In custody of someone other than biological mother	4 (14%)	19 (17%)	1 (2%)	<i><0.01</i>
Vaccines not up to date at 6 months	4 (14%)	10 (9%)	4 (6%)	<i>0.44</i>
>10 Ambulatory Care Visits in First Year	4 (14%)	18 (16%)	14 (22%)	<i>0.58</i>
Ever Hospitalized for Infectious Cause in First Year	5 (18%)	5 (4%)	8 (12%)	<i><0.01</i>

Continuous variables expressed as median (interquartile range) and categorical variables as no. (%); P-values from Wilcoxon test or t test for continuous variables and Chi-square or Fisher's exact for categorical variables as appropriate.

ARV=Antiretrovirals, BMI=Body Mass Index, GA=Gestational Age, HEU=HIV-exposed uninfected, HUU=HIV unexposed uninfected, LAZ=Length-for-age z score, PHIV=Perinatally HIV-infected, NPHIV=Non-Perinatally HIV-infected, SGA=Small for gestational age, WAZ=Weight-for-age z score, WLZ=Weight-for-length z score