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Small for Gestational Age Birth Outcomes in Pregnant Women with Perinatally Acquired HIV

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Introduction

With the introduction of combination antiretroviral therapy (cART), morbidity and mortality have declined in individuals with perinatally acquired HIV (PAH), allowing many to reach reproductive ages [1-3] Women with PAH who have conceived represent a particularly challenging subset of patients. In comparison to women with behaviorally acquired HIV (BAH), they often harbor complex psychosocial and reproductive health needs [4-5], possess more advanced HIV disease [8], and exhibit distinct immunological alterations – a maturational delay in cell-mediated immunity [6-7] as well as persistent CD8+ cellular activation. [7-8] Pregnancy and neonatal outcomes in women with PAH have not been well documented and of particular concern is poor intrauterine growth. [9-10] Small for gestational age (SGA) birth weight (BW) has been associated with a variety of poor health outcomes including increased neonatal morbidity and mortality [11-12], childhood neurocognitive deficits [13-14], and long term metabolic consequences such as diabetes and cardiovascular disease [15-17]. This paper evaluates the rates of SGA infants born to women with PAH vs. BAH at a single health facility in New York City.

Methods

Study Population

Part of an urban tertiary center, the Mount Sinai Obstetrics-Infectious Disease (OB-ID) clinic provides comprehensive obstetrical and HIV care to HIV-infected pregnant women. This analysis includes all HIV-infected pregnant women who received prenatal care and

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delivered their baby at our institution from January 2004- April 2011. Pregnancies ending in spontaneous/therapeutic abortions and intra-uterine fetal demise (IUFD) were excluded from primary analysis. Pregnancies with multiple gestations were also excluded.[18]

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

Primary Outcome

Using routinely collected birth weight data from delivery records and gestational age calculated by last menstrual period or ultrasound dating (the latter if there was a discrepancy), we evaluated the incidence of small for gestational age (SGA) births in pregnant women with PAH vs. BAH. SGA was defined as birth weight $<10^{th}$ percentile based on U.S. gender-specific standards [19].

Predictor Measurements

Our main exposure of interest was the documented mode of HIV acquisition; subjects were categorized as having PAH or BAH according to medical records or patient report. Rates of other risk factors for fetal growth restriction including age, race [20], self-reported substance abuse prior to and during pregnancy [21-22], and history of past or current psychiatric disorders including depression [23] were determined by review of the medical record. Substance use was defined as any tobacco, alcohol, or illicit drug use. We collected data on the CD4 cell count, HIV RNA levels, history of opportunistic infections, and information regarding cART recorded throughout the pregnancy and at delivery. Nadir CD4 cell count during the pregnancy was analyzed. HIV RNA levels at delivery were defined as suppressed if they were <400 copies/mL. Second-line cART regimens were defined as containing either enfuvirtide, etravirine, darunavir, or raltegravir.

Statistical Analysis

Baseline characteristics of the pregnant women with PAH vs. BAH were compared using Wilcoxon test, Chi-square, or Fisher's exact test as appropriate. We applied Generalized Estimating Equation (GEE) models [24] to assess the unadjusted association between PAH and SGA while accounting for repeated measures (due to multiple pregnancies) within study subjects. We then repeated the analysis adjusting for established risk factors of SGA BW including age, substance abuse during pregnancy, nadir CD4 cell count ≤200 cells/mm^3 during pregnancy, viral suppression at delivery, and use of second-line cART during pregnancy. A secondary analysis was then performed on the larger sample of all pregnancies including those resulting in termination or IUFD. For this analysis, we used a combined outcome of SGA birth, termination, or IUFD. Statistical analyses were performed using IBM® SPSS® Statistics 19.

Results

Between January 2004 and April 2011, 79 pregnant women (17 PAH, 62 BAH) received care at the Mount Sinai OB-ID clinic, resulting in 100 pregnancies. After excluding 9 spontaneous/induced abortions (from three women with PAH and five with BAH), two pregnancies resulting in IUFD (from two women with BAH), and one twin pregnancy, 87 live births from 74 women were included in the analysis. This primary analytic sample included 14 women with PAH representing 17 live births and 60 women with BAH representing 70 births. Maternal baseline characteristics at the time of their first pregnancy are shown in Table 1. Women with perinatal HIV acquisition were younger ($p<0.001$) but had similar racial and marital status distribution. Self-reported substance use before and during pregnancy also did not differ significantly between groups. Not surprisingly, women

with PAH were more likely to have had a history of opportunistic infections (p=0.008), experience a nadir CD4 cell count ≤200 cells/mm^3 during pregnancy (p=0.01), and require second-line cART (p<0.001). Ninety-three percent (13/14) of women with PAH and 92% (55/60) of those with BAH received protease-inhibitor (PI)-based cART during their first pregnancy. Two women in the PAH group were co-infected with Hepatitis C; none had Hepatitis B. Amongst women in the BAH group, one was co-infected with Hepatitis B, eight with Hepatitis C, and one with both Hepatitis B and C. Rates of past or current psychiatric disorders including depression were similar in both groups as well (24% in PAH vs. 34% in BAH group, p=0.42; data not shown.)

Vertical transmission rates were 0% [97.5% Confidence Interval (CI): 0.0-0.22] in the PAH group and 2.9% (95% CI: 0.01-0.10) in the BAH group. Roughly half of the pregnancies were delivered via C-section, eight of which were emergent. Rates of C-section did not differ between groups. One neonate (born to a woman with PAH) had a 5-minute Apgar score <8. One pregnancy (from a woman with BAH) was complicated by pre-eclampsia.

Median gestational age was 38 weeks [InterQuartile Range (IQR): 36-39] and did not differ between groups. Median BW in the PAH group was 2460 g (IQR: 2260-2868), while that of the BAH group was 2910 g (IQR: 2622-3413) (p=0.18) The overall rate of SGA births was 23% (20/87). Thirty-one percent (27/87) were premature (<37 weeks). Among women with PAH, 47% of infants (8/17) were SGA, 29% (5/17) were premature, and two were both premature and SGA. Rates of prematurity were similar between groups (29% in PAH vs. 31% in BAH.)

Live births to women with PAH and women on second-line cART during pregnancy were more likely to be born SGA in our unadjusted analysis [odds ratio (OR) =4.13, 95% CI: 1.38-12.41 and OR=5.12, 95% CI: 1.34-19.57 respectively]. After adjusting for mother's age, substance use during pregnancy, nadir CD4 cell count during pregnancy, viral suppression at delivery, and use of second-line cART during pregnancy, the relationship between PAH and SGA BW persisted with an adjusted OR of 5.67 (95% CI: 1.03-31.61) (Table 2). Substance abuse during pregnancy (OR=3.68, 95% CI: 1.04-13.04) was also a risk factor for SGA BW in our adjusted analysis, but use of second-line cART did not remain a significant predictor of SGA BW. We found similar results in a secondary analysis, using a combined outcome of SGA birth as well as pregnancies resulting in termination or IUFD.

Discussion

In this study of HIV-infected pregnant women, we found that SGA birth weight occurred frequently and that PAH in the mother and substance abuse during pregnancy were both significant risk factors for an SGA birth outcome, even after adjusting for other known or suspected risk factors.

Since the first case of a successful pregnancy outcome was reported in a woman with PAH in 1998 [25] a growing number of reports have emerged describing pregnancy in vertically HIV-infected women. Our findings are largely consistent with other case series in the literature in developed countries. With the exception of one study where rates of SGA births in women with PAH were lower (12%)[26], other studies in developed countries have reported increased rates of low birth weight (LBW) (<2500g) [27] and median BWs (2667-2688g) of children born to women with PAH similar to those in our study. [28-29] However, BW outcomes in women with PAH are conflicting in resource-limited countries. A Brazilian study demonstrated LBWs in women with PAH[30] and a study in India reported median birth weights close to national norms.[31] The overall rate of preterm birth

in our cohort (31%) was higher than rates found in the U.S. among HIV-infected pregnant women (18-22%). [32-33] However, rates of preterm birth in women with PAH in developed countries are similar to those found in our study (13.3 – 36%). [26-29] In addition, other studies reported similar trends in CD4 cell counts both before (mean initial CD4 cell count 144-314 cells/mm^3) [27-28] and during the pregnancy (136-394 cells/mm^3) [28-31, 34] in women with PAH as seen in our cohort. Reported rates of maternal virologic suppression at delivery, however, were lower in most other series [27-30] than those seen in our study.

Fetal growth restriction is not a benign condition. SGA BW has been associated with increased overall morbidity and mortality. [11, 35] Prematurity in SGA infants confers even greater risks of neonatal morbidity and mortality. [36-37] Long term adverse health outcomes reported in SGA infants include childhood neuro-developmental delay [14, 38] and long-term risks for adult illnesses including hypertension, heart disease, obesity and diabetes.[16-17, 39-40] HIV-exposed children born SGA may thus merit increased surveillance throughout adulthood.

It is not entirely clear why there was an association of PAH with SGA BW even after controlling for known risk factors. Neither a low CD4 nadir during pregnancy nor maternal viremia at delivery appeared to predict SGA BW, suggesting that the prenatal environment of the pregnant woman with PAH may uniquely affect intrauterine growth. The sustained chronicity of altered immunologic function in the mother with PAH may play a role in creating a hostile *in utero* environment for the growing fetus.

Our study was limited by the small cohort size and retrospective study design. Since we determined the mode of HIV acquirement in some via patient report, there is the possibility of misclassification bias. In addition, our assessment of substance use prior to and during the pregnancy may have been affected by recall bias as it was based on patient report and not toxicology screens. Other known risk factors for SGA BW, such as maternal height were also not available in all subjects. Lastly, the racial/ethnic composition of our cohort was largely limited to Blacks and Hispanics, reflective of our clinical demographics.

In conclusion, pregnant women with PAH represent a complex population of patients whose prenatal care requires a high level of monitoring for pregnancy complications including poor intrauterine growth. Further studies aimed at understanding the uniqueness of this *in utero* environment are warranted to elucidate mechanisms by which intrauterine growth may be compromised in the offspring of women with PAH.

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Table 1

Baseline Characteristics of Mothers in Cohort

	Perinatally Acquired HIV (n=14)	Behaviorally Acquired HIV (n=60)	P-value
Age of Mother, years (Median) (IQR)	20 (19-23)	30 (23-37)	< 0.001
Race, No. (%)			0.8
White	0 (0)	1 (2)	
African American	10 (71)	38 (59)	
Hispanic	4 (29)	25 (39)	
Asian	0 (0)	1 (2)	
Marital Status, No. (%)			0.3
Single	13 (93)	47 (79)	
Married	0 (0)	11 (18)	
Living with partner	1 (7)	2 (3)	
Substance Abuse, No. (%)			0.6
Prior to pregnancy	6 (43)	31 (52)	
During pregnancy	1 (7)	10 (17)	
Maternal Height, cm (Median) (IQR)	155 (154-159)	162 (155-168)‡	0.71
History of Opportunistic Infections, No. (%)	6 (43)	6 (10)	0.008
Nadir CD4+ cells/mm^3 during pregnancy (Median, IQR)	271 (38-374)	391 (283-544)	
Nadir CD4+ cells ≤200 cells/mm^3 during pregnancy	9 (64)	5 (36)	0.01
HIV RNA level <400 copies/mL at delivery	10 (71)	52 (87)	0.2
Combination ART (cART), No. (%)			
Second-line cART *	6 (43)	0 (0)	<0.001

P-values from Wilcoxon test for continuous variables and Chi-square or Fisher's exact for categorical variables.

‡ n=53 women with BAH

* Second-line cART includes: Enfuvirtide, Etravirine, Darunavir, and Raltegravir

Table 2

Multivariate GEE[†] Analysis of Small for Gestational Age Births

	Odds Ratio (95% CI)	
Risk Factor	**Unadjusted**	**Adjusted**
Age of mother (1 year increment)	0.98 (0.92-1.04)	1.02 (0.94-1.11)
Perinatally acquired HIV	4.13 (1.38-12.41)	5.67 (1.03-31.61)
Substance abuse during pregnancy	2.67 (0.87-8.16)	3.68 (1.04-13.04)
Nadir CD4 ≤200 cells/mm^3 during pregnancy	2.02 (0.64-6.36)	0.77 (0.09-6.46)
HIV RNA level <400 copies/mL at delivery	1.64 (0.49-5.49)	2.02 (0.58-7.02)
Second line cART[*] during pregnancy	5.12 (1.34-19.57)	1.91 (0.22-16.75)

[†]GEE= Generalized Estimating Equation

[*]Second-line cART includes: Enfuvirtide, Etravirine, Darunvavir, and Raltegravir