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Association of Body Mass Index of HIV-1-Infected Pregnant Women and Infant Weight, Body Mass Index, Length, and Head Circumference: The NISDI Perinatal Study

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Abstract

This study assessed the relationship between the body mass index (BMI) of HIV-1-infected women and their infants' perinatal outcomes. The study population consisted of women enrolled in the NICHD International Site Development Initiative (NISDI) Perinatal Study with data allowing calculation of the BMI adjusted for length of gestation (adjBMI), who delivered singleton infants. Outcome variables included infant growth parameters at birth (weight, BMI, length and head circumference) and gestational age. Of 697 women from Argentina, the Bahamas, Brazil and Mexico who were included in the analysis, the adjBMI was classified as underweight for 109 (15.6%), normal for 418 (60.0%), overweight for 88 (12.6%) and obese for 82 (11.8%). Median infant birth weight, BMI, birth length and head circumference differed significantly according to maternal adjBMI ($P \leq 0.0002$). Underweight mothers gave birth to infants with lower weight, lower BMI, shorter length and smaller head circumference, while infants born to normal, overweight and obese mothers were of similar size.

Keywords

maternal BMI; low birth weight; preterm; HIV-exposed infants; HIV-infected pregnant women

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1. Introduction

Increasing numbers of women have acquired HIV-1 infection over the past few years. With the feminization of the HIV-1 epidemic, women from different social and cultural settings are becoming infected every day, with consequent harm to their general health and family life. Malnutrition is a complex and frequent event during the course of HIV-1 infection and has multiple causes [1]. Maternal malnutrition is associated with increased risks of illness, disability and death for the fetus and infant [2].

Maternal HIV-1 infection and receipt of antiretrovirals (ARVs) during pregnancy have been reported to be associated with an increased risk of preterm birth and low birth weight [3,4,5, 6]. Although many cohorts of HIV-1-infected pregnant women have been followed in different parts of the world, published data regarding their nutritional status are limited. In 1999, a study from Africa reported that underweight, HIV-1-infected pregnant women have a greater risk of delivering low birth weight infants [7].

The objectives of this analysis were to describe the body mass index (BMI) adjusted for length of gestation (adjBMI) of HIV-1-infected pregnant women enrolled in the NICHD International Site Development Initiative (NISDI) Perinatal Study, and to investigate the association of adjBMI with infant outcomes (gestational age, infant BMI at birth, and birth weight, length, and head circumference).

2. Materials and Methods

2.1 Subjects and Definitions

The NISDI Perinatal Study is a prospective cohort study of HIV-1-infected women and their infants at sites in Latin America and the Caribbean [8]. At study entry, women are interviewed for social, clinical and obstetric history, and study visits include a physical examination and laboratory evaluations (hematology, biochemistry, CD4/CD8 and viral load measurements). The protocol was approved by the ethical review board at each site, the sponsoring institution (National Institute of Child Health and Human Development), and the data management center (Westat).

The study population comprised HIV-1-infected women who delivered live born, singleton infants between September 2002 and March 2005. BMI at enrollment was adjusted for length of gestation (adjBMI) using an algorithm available from the Ministry of Health of Argentina [9]. Categories of adjBMI (kg/m^2) were: underweight (≥ 10 to < 19.8), normal (≥ 19.8 to < 26.1), overweight (≥ 26.1 to < 29) and obese (≥ 29 to < 50). Outcome variables were infant growth parameters at birth (weight, length, BMI and head circumference) and gestational age. The maternal ARV regimen received at the time of enrollment was categorized as follows: one or two nucleoside reverse transcriptase inhibitors (NRTIs), two NRTIs with one non-nucleoside reverse transcriptase inhibitor (NNRTI) (HAART/NNRTI), two NRTIs with one PI (HAART/PI), or "Other".

2.2 Statistical analysis

The association of maternal adjBMI at enrollment with categorical variables was evaluated using the Fisher-Freeman-Halton [10] exact test. The Fisher-Freeman-Halton exact test, a generalization of Fisher's exact test for greater than 2×2 tables, was used to assess independence between maternal adjBMI and the categorical covariates. For variables measured on a continuous scale, the Kruskal-Wallis test was used to assess statistical significance [11]. The Kruskal-Wallis test, a non-parametric counterpart to analysis of variance (ANOVA), tests whether the sample means are from the same population against the alternative that they come

from different populations. All analyses were carried out using SAS, Version 8, with P values of 0.05 or less used to define statistical significance [12].

3. Results

Of 803 women enrolled in the NISDI Perinatal Study, 723 had delivered as of March 2005. Of these 723 women, 697 delivered live born singleton infants, and these mother-infant pairs represent the study population. Sixty-six percent of these women were enrolled in Brazil, 25 percent in Argentina, 6% in the Bahamas and 3% in Mexico. At enrollment, 109 (15.6%) women were underweight, 418 (60.0%) had normal weight, 88 (12.6%) were overweight, and 82 (11.8%) were obese. There was a significant difference in adjBMI distribution ($p < 0.0001$) according to country of origin, with a larger proportion of those from the Bahamas being obese and the majority of mothers from Argentina, Brazil and Mexico being of normal weight; 17.4% of women from Brazil and 14.0% from Argentina were underweight. Women from the Bahamas and Mexico were less likely to be underweight (7.3% and 8.3%, respectively).

The median age at enrollment was 27 years. Significant differences in the median age at enrollment were observed among adjBMI groups ($P < 0.0001$); the median age of those who were underweight was the lowest (24 years) while that of obese women was highest (29 years). There were no significant associations between years of formal education completed or number of household members and maternal adjBMI ($P > 0.4$), but gainful employment outside the home was significantly associated with maternal adjBMI. A larger proportion of gainfully employed women were overweight or obese when compared to those not employed, while a higher proportion of women not employed outside the home were underweight ($P = 0.012$).

HIV-1-related characteristics according to maternal adjBMI are shown in Table 1. Although statistically significant differences in clinical and virologic measures of HIV-1 disease progression according to maternal adjBMI at enrollment were not observed, there were significant differences in immunologic measures of disease progression. Generally, those who were overweight or obese had the highest lymphocyte counts, as well as CD4+ and CD8+ counts, while those who were underweight or of normal weight had the lowest values ($P < 0.02$). The maternal ARV regimen received at enrollment was not associated with maternal adjBMI at enrollment ($P = 0.13$). Since plasma viral load can be directly affected by the receipt of antiretrovirals (ARVs), the plasma HIV-1 RNA concentration at enrollment also was examined among adjBMI groups according to whether or not the subject received ARVs prior to enrollment. Those who were not receiving ARVs at enrollment had higher viral loads than those receiving ARVs at enrollment, but the viral loads did not differ according to maternal adjBMI within these two strata ($P > 0.1$) (data not shown).

Laboratory measures at enrollment according to maternal adjBMI are shown in Table 2. Maternal adjBMI at enrollment was significantly associated with bicarbonate, blood urea nitrogen (BUN), cholesterol and hemoglobin ($P < 0.05$). Median bicarbonate levels were lower among overweight and obese mothers than among those who were underweight or of normal weight, while the median BUN value was highest among normal weight mothers and lowest among obese mothers. The median total cholesterol level at enrollment was lowest among underweight and normal weight mothers and highest among overweight and obese mothers. The median hemoglobin value was lowest among underweight mothers compared to normal, overweight and obese mothers whose median levels were similar.

Overall, 63 infants (9.2%) were born preterm (< 37 weeks) and 89 infants (12.9%) were born with low birth weight (< 2500 grams). As shown in Table 3, median infant birth weight, BMI, length and head circumference at birth differed significantly according to maternal adjBMI ($P \leq 0.0002$). Underweight mothers delivered the lightest babies; birth weight was similar

among those who were of normal weight or who were overweight, while the median birth weight was highest for obese women. Underweight mothers gave birth to babies with the lowest BMI, shortest length and smallest head circumference.

4. Discussion

In this study, maternal BMI adjusted for gestational age was associated with infant birth weight, length, BMI, and head circumference. Underweight women tended to deliver smaller infants than other women.

The incidence of low birth weight and preterm birth has been previously investigated in the NISDI population [13]. In this published analysis, variables associated with the occurrence of preterm birth included country of residence, maternal clinical disease stage, maternal plasma viral load, diabetes, mode of delivery and hypertension. In addition to maternal underweight, risk factors for low birth weight included pre-eclampsia/eclampsia, non-elective cesarean section and maternal diabetes. The present analysis focused on the effect of maternal nutritional status, evaluated by BMI adjusted for gestational age, on infant outcomes treated as continuous measures.

The proportion of underweight HIV-1-infected women at enrollment (almost 16%) is much higher than the 5.7% found among HIV-1-uninfected, pregnant women in Brazil between 1991 and 1995 [14]. Unfortunately information is not available concerning the nutritional status of pregnant women in other Latin American countries.

The high proportion of underweight women in our study could represent a manifestation of HIV-1 disease itself. However, we did not observe a significant association between HIV-1 clinical stage and adjBMI. Alternatively, the high proportion of underweight women in the study likely reflects the fact that, in many parts of the world, the HIV-1 epidemic is spreading faster among people of lower socioeconomic status. Although women from all social strata in Brazil are being affected by the HIV-1 epidemic, infection is more prevalent among the most socially disenfranchised segments of the population, as measured by the number of years of formal education completed [15]. Our finding that HIV-1-infected pregnant women who were underweight tended to be younger is consistent with previously reported results regarding Brazilian pregnant women without HIV-1 infection [14] and is particularly relevant in countries where youths are initiating sexual activity early in life and socio-cultural factors lead to pregnancy at young ages. The importance of social aspects with regard to the high frequency of underweight pregnant women in our study population is underscored by the association of gainful employment during pregnancy and higher adjBMI.

Nutritional status has been identified as a predictor of levels of T-cell subclasses among HIV-1-uninfected women [16]. In this study, underweight and normal weight women had lower CD4+ count values when compared to obese women, but we found no association between maternal adjBMI and clinical stage or viral load. BMI assesses the body's fat mass, and thus our results are consistent with the report by McDermott et al [17] in which a positive linear relationship was observed between fat mass and CD4+ counts among HIV-1-infected adults. Our observed association of adjBMI with CD4+ counts could be related to many known causes of nutritional impairment in patients with more advanced HIV-1 disease and must be interpreted with caution, since we do not have information about pre-pregnancy weight or possible weight loss in the recent past. Metabolic consequences of antiretroviral treatment also should be considered since women with lower CD4+ values could be more heavily exposed to these drugs and have altered body composition.

Maternal adjBMI was associated with several laboratory measures (bicarbonate, BUN, glucose, cholesterol, and hemoglobin). Bicarbonate was included in the biochemistry panel for

these HIV-1-infected pregnant women to monitor lactic acidosis associated with ARV toxicity. The association of median bicarbonate levels and adjBMI is difficult to interpret since most of available literature in this field concerns patients with chronic kidney disease. For example, a French research group also found a negative correlation of bicarbonate with albumin, pre-albumin, BMI and lean body mass when evaluating chronic kidney disease patients receiving dialysis [18]. Since BUN is a laboratory marker of dietary protein intake, the finding of the lowest median BUN value among obese women raises a question about the protein content of diets among obese pregnant women in Latin America, although no difference in total protein or albumin was found among adjBMI groups. The higher median total cholesterol values among overweight and obese women emphasizes the importance of evaluating diet during antenatal clinic visits. Hemoglobin is frequently used as a parameter to evaluate the nutritional status of pregnant women and, in a study of pregnant adolescents in Tanzania, there was a strong correlation between maternal hemoglobin values and infant birth weight [19]. In Zimbabwe, maternal arm fat, used as a proxy for body fat mass, was a predictor of infant birth weight, while maternal age, arm muscle area, and hemoglobin level were not associated with infant birth weight [20].

The overall rate of preterm birth (9.2%) is lower than that of the general population in Brazil in 2004 (16.2%) [21], and also lower than that reported in other series of HIV-1-infected pregnant women: Rwanda (22.7%) [22], the U.S. (17%) [23], and Europe (25% between 2000–2004) [6]. However, our observed rate of low birth weight (12.9%) is similar to that of the HIV-1-uninfected black population in the U.S. (13%) [24], Latin America (10–20%) [25] and Brazil (10.4%) [21]. It is also similar to that reported in other studies of HIV-1-infected women in Tanzania (11%) [26,27], the U.S. (13%) [23], and Kenya (9.6%) [28].

Prematurity and low birth weight are associated with increased childhood morbidity and mortality, including hospitalization for [29] and mortality from infectious diseases [30]. In addition, fetal under-nutrition predisposes to adult hypertension, diabetes, obesity and coronary artery disease [reviewed in 31]. Our results confirm the importance of nutritional evaluation during antenatal care of HIV-1-infected women. Antiretroviral and obstetrical interventions have dramatically changed the life expectancy of infants born to HIV-1 infected women, but among populations of young people living in mid-developed countries, HIV-1 infection and social impairment occur in parallel and increase risk to family health.

Further research on micronutrient deficiency in HIV-1-infected pregnant women and its possible effect on fetus/infant growth and general health are needed. The use of nutrition interventions to correct possible deficiencies should improve the quality of life and the growth of HIV-1-exposed infants. Nutritional interventions may be particularly important among HIV-1-infected pregnant adolescents and younger women, especially in developing countries.

List of Abbreviations

AdjBMI, body mass index adjusted for length of gestation
 ARV, antiretroviral
 BMI, body mass index
 BUN, blood urea nitrogen
 HAART, highly active antiretroviral therapy
 HIV-1, human immunodeficiency virus type 1
 NICHD, National Institute of Child Health and Human Development
 NISDI, NICHD International Site Development Initiative
 NNRTI, non-nucleoside reverse transcriptase inhibitor
 NRTI, nucleoside reverse transcriptase inhibitors
 PI, protease inhibitor

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HIV-1-related characteristics of pregnant women at enrollment, overall and according to maternal body mass index adjusted for length of gestation (adjBMI) at enrollment

Table 1

Enrollment characteristic	Overall N=697	Maternal adjBMI (kg/m ²) at Enrollment			P value ¹
		Underweight (≥10.0 - <19.8) n=109	Normal (≥19.8 - <26.1) n=418	Over-Weight (≥26.1 - <29.0) n=88	
Duration of HIV-1 diagnosis prior to enrollment (months):					
Mean (SD)	18.9 (26.9)	16.2 (23.3)	20.2 (27.8)	15.1 (22.4)	
Median	5.0	4.0	5.0	4.0	0.56
CDC disease classification: n (%)					
Category A	599	91 (16.2)	351 (88.6)	83 (13.9)	
Category B	42	7 (16.7)	29 (69.0)	2 (4.8)	
Category C	56	11 (19.6)	38 (67.9)	3 (5.4)	0.21
Plasma HIV-1 RNA concentration (copies/mL):					
Mean (SD)	19037 (78608)	15179 (53015)	19675 (84660)	23851 (83524)	
Median	452.0	653.0	470.5	227.0	0.32
Absolute lymphocyte count (cells/mL):					
Mean (SD)	1494 (502)	1383 (474)	1475 (469)	1580 (574)	
Median	1440	1321	1433	1575	0.0011
CD4+ absolute count (cells/mm³):					
Mean (SD)	428 (221)	421 (208)	409 (212)	503 (271)	
Median	397	384	378	456	0.011
Antiretroviral regimen received at enrollment²: n (%)					
None	161	28 (17.4)	97 (60.3)	18 (11.2)	
1 NRTI	57	11 (19.3)	24 (42.1)	12 (21.1)	
2 NRTIs	30	4 (13.3)	21 (70.0)	2 (6.7)	
2 NRTIs + 1 NNRTI	190	23 (12.1)	112 (59.0)	27 (14.2)	
2 NRTIs + 1 PI	247	43 (17.4)	156 (63.2)	26 (10.5)	
Other	12	0	8 (66.7)	3 (25.0)	0.13

¹ The p-values for associations between maternal BMI at enrollment and categorical characteristics are based on the Fisher-Freeman-Halton exact test, while those for associations with continuous scaled characteristics are based on the non-parametric Kruskal-Wallis test of equality of means.

² Maternal ARV regimen at the time of enrollment was categorized as: one or two nucleoside reverse transcriptase inhibitors (NRTIs), two NRTIs with one non-nucleoside reverse transcriptase inhibitor (NNRTI) (HAART/NNRTI), two NRTIs with one PI (HAART/PI), or "Other".

Table 2
Laboratory measures of pregnant women at enrollment, overall and according to maternal body mass index adjusted for length of gestation (adjBMI) at enrollment

Enrollment laboratory measure	Overall N=697	Maternal adjBMI (kg/m ²) at Enrollment			P value ¹
		Underweight (≥10.0 - <19.8) n=109	Normal (≥19.8 - <26.1) n=418	Over-Weight (≥26.1 - <29.0) n=88	
Bicarbonate (mmol/l):					
Mean (SD)	22.64 (2.58)	23.13 (2.06)	22.64 (2.50)	22.41 (3.54)	22.11 (2.30)
Median	23.00	23.00	23.00	22.00	22.00
BUN (mmol/l):					
Mean (SD)	3.84 (2.55)	3.50 (1.83)	4.03 (2.69)	3.77 (2.77)	3.34 (2.30)
Median	2.86	2.86	3.21	2.86	2.50
Glucose (mmol/l):					
Mean (SD)	4.27 (0.77)	4.16 (0.92)	4.28 (0.68)	4.21 (0.83)	4.42 (0.90)
Median	4.16	4.11	4.22	4.11	4.33
AST/SGOT (μkat/l):					
Mean (SD)	0.35 (0.23)	0.37 (0.29)	0.36 (0.23)	0.34 (0.15)	0.33 (0.20)
Median	0.30	0.30	0.30	0.30	0.29
ALT/SGPT (μkat/l):					
Mean (SD)	0.36 (0.26)	0.40 (0.34)	0.35 (0.24)	0.35 (0.20)	0.41 (0.30)
Median	0.32	0.32	0.32	0.32	0.38
Albumin (g/dL):					
Mean (SD)	33.75 (4.31)	33.28 (4.15)	33.92 (4.32)	34.11 (4.74)	33.12 (3.95)
Median	34.00	33.00	34.00	35.00	33.00
Total protein (g/dl):					
Mean (SD)	71.0 (6.1)	71.2 (6.0)	71.0 (5.9)	70.6 (7.5)	71.5 (5.7)
Median	70.0	71.0	70.0	69.0	71.0
Cholesterol (mmol/l):					
Mean (SD)	5.32 (1.16)	5.24 (1.25)	5.24 (1.12)	5.56 (1.15)	5.61 (1.19)
Median	5.20	5.16	5.17	5.59	5.57
Triacylglycerol (mmol/l):					
Mean (SD)	2.18 (0.98)	2.14 (0.98)	2.20 (1.04)	2.11 (0.81)	2.19 (0.86)
Median	2.01	1.90	2.03	1.96	2.07
Hemoglobin (mmol/l):					
Mean (SD)	6.83 (0.78)	6.66 (0.81)	6.82 (0.79)	6.91 (0.76)	6.95 (0.71)
Median	6.83	6.70	6.86	6.95	7.01

¹The p-values for associations between maternal adjBMI and laboratory measures at enrollment are based on the non-parametric Kruskal-Wallis test of equality of means.

Infant outcomes, overall and according to maternal body mass index adjusted for length of gestation (adjBMI) at enrollment

Table 3

Infant outcome	Maternal adjBMI (kg/m ²) at Enrollment				P value ^f
	Overall N=697	Underweight (≥10.0 - <19.8) n=109	Normal (≥19.8 - <26.1) n=418	Over-Weight (≥26.1 - <29.0) n=88	
Gestational age at birth (weeks):					
Mean (SD)	38.4 (1.7)	38.0 (2.0)	38.5 (1.5)	38.5 (1.6)	38.4 (2.3)
Median	39.0	38.0	39.0	39.0	39.0
Birth weight (grams):					
Mean (SD)	3005 (519)	2753 (567)	3022 (466)	3142 (496)	3105 (625)
Median	3000	2700	3000	3000	3200
BMI at birth:					
Mean (SD)	13.0 (1.6)	12.4 (1.7)	13.0 (1.6)	13.3 (1.3)	13.1 (2.0)
Median	13.0	12.5	13.1	13.2	13.1
Birth length (centimeters):					
Mean (SD)	48.0 (2.7)	46.9 (3.0)	48.2 (2.5)	48.5 (2.5)	48.5 (3.1)
Median	48.0	47.0	48.0	48.8	49.0
Head circumference at birth (centimeters):					
Mean (SD)	33.9 (1.7)	33.2 (1.9)	34.0 (1.5)	34.3 (1.4)	34.1 (2.1)
Median	34.0	33.5	34.0	34.5	34.0

^fThe p-values for associations between maternal adjBMI at enrollment and infant outcomes are based on the non-parametric Kruskal-Wallis test of equality of means.