Nicotine & Tobacco Research, Volume 15, Number 1 (January 2013) *177–184*

Original Investigation

Cigarette Smoking and Fetal Morbidity Outcomes in a Large Cohort of HIV-Infected Mothers

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Received September 11, 2011; accepted March 11, 2012

Abstract

Background: Reproductive-age women comprise approximately 25% of all persons living with HIV/AIDS in the United States. HIV infection and smoking during pregnancy are independent risk factors for adverse fetal outcomes. We examined predictors of fetal growth restriction among infants born to HIV-infected mothers who smoke cigarettes in pregnancy.

Methods: We analyzed hospital discharge data linked to birth records from the state of Florida for 1998–2007 ($N = 1{,}645{,}209$). The outcomes of interest included: low and very low birth weight (LBW and VLBW), preterm and very preterm birth (PTB and VPTB), and small for gestational age (SGA). We calculated adjusted rate ratios (*ARR*) for these outcomes by HIV/AIDS status, smoking status, and sociodemographic variables. We also examined the association between the observed fetal morbidity outcomes and the interaction between HIV/AIDS and smoking status. We employed the generalized estimating equation framework to correct for intracluster correlations.

Results: All fetal morbidity outcomes were more common in mothers who had HIV/AIDS, regardless of smoking status. Maternal HIV status and cigarette use were independent predictors of LBW, PTB, and SGA, with morbidity effects more prominent in HIV-infected mothers who smoke cigarettes. We observed a significant interaction between maternal HIV and smoking status, in which mothers who were HIV positive and smoked during pregnancy experienced the greatest risks for LBW (*ARR* = 2.24 [1.89–2.65]), SGA (*ARR* = 1.95 [1.67–2.29]), and PTB (*ARR* = 1.70 [1.42–2.03]).

Conclusions: HIV-infected mothers who smoke cigarettes during pregnancy have a heightened risk for adverse fetal morbidity outcomes. There is a need for integration of smoking cessation interventions into ongoing HIV/AIDS programs.

Introduction

More than one million individuals currently live with the HIV in the United States, and approximately 25% are women of childbearing age (UNAIDS, 2010). HIV infection is a recognized risk factor for numerous adverse perinatal outcomes, including low birth weight (LBW), small for gestational age (SGA), and preterm delivery (Salihu et al., 2010). LBW and preterm birth (PTB), in turn, are major contributors to substantial mortality and morbidity in newborns (McCormick, Litt, Smith, & Zupancic, 2011), with up to 75% of all perinatal mortality and greater than 50% of long-term morbidity attributable to PTB alone (McCormick, 1985; Goldenberg, Culhane, Iams, & Romero, 2008).

Another prominent risk factor for adverse fetal outcomes is maternal smoking. Smoking during pregnancy is associated with LBW, PTB, premature rupture of the membranes, placenta previa, and placental abruption, among other morbidities (Aliyu, Salihu, Wilson, & Kirby, 2007; Centers for Disease Control and Prevention [CDC], 2002; Polakowski, Akinbami, & Mendola, 2009). Rates of cigarette smoking are much higher in women with HIV infection than in HIV-negative women (Feldman et al., 2006). In addition, HIV-infected mothers who smoke respond less favorably to treatment with antiretrovirals than their nonsmoking counterparts (Feldman et al., 2006) and have an increased risk for maternal–child transmission of HIV (Turner, Hauck, Fanning, & Markson, 1997).

Published data are scant regarding the relationship between maternal smoking and HIV infection as risk factors for adverse fetal growth. Understanding this relationship is important, as cigarette smoking cessation programs targeting HIV-infected persons are feasible, as well as efficacious (Elzi et al., 2006; Vidrine, Marks, Arduino, & Gritz, 2011).

doi:10.1093/ntr/nts105
Advance Access publication May 9, 2012
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The purpose of this study is to determine whether tobacco use in pregnancy modifies the association between maternal HIV infection and selected fetal morbidity outcomes (LBW and very low birth weight [VLBW], PTB and very preterm delivery [VPTB], and SGA) in a large population-based cohort of mothers.

Methods

This analysis was conducted using the de-identified Florida linked hospital discharge and vital records data files. The Hospital Inpatient Discharge Data were obtained from the Florida Agency for Health Care Administration and linked to Florida vital records spanning the decade from 1998 through 2007. The data linkage process has been validated internally and found to be 97.6% successful (Salihu et al., 2012). We assessed the quality of the linked data by investigating the accuracy of important variables using a sample of medical charts obtained from a randomly selected list of hospitals within the state of Florida as reference. The variables in the linked data files showed a high level of correlation with those in the abstracted charts. The vital statistics data provided all maternal sociodemographic information (age, educational level, race/ethnicity, marital status, and prenatal care) and infant characteristics (birth weight and gestational age). All medical complications of pregnancy and drug and alcohol abuse were abstracted from the inpatient discharge data, as this data source was considered an accurate source of information on hospital discharge diagnoses and procedures. Tobacco use during pregnancy was abstracted from both data sources.

The linked data set contains only singleton live births as listed on both the hospital discharge data and the vital records. We categorized the study population into exposed and comparison groups based on maternal HIV and tobacco use status. The exposed group consisted of women who were HIV positive and smoked tobacco during pregnancy (0.1%). These women were compared with those who were HIV/AIDS negative and nonsmokers (89.8%), those who were HIV/AIDS negative and smokers (10.0%), and those who were HIV/AIDS positive and nonsmokers (0.3%). International Classification of Disease (ICD) -9 codes were used to identify all cases of HIV/AIDS (ICD-9 codes: V08, 042–044, 079.53). While tobacco use was abstracted from both data sources, within the hospital inpatient discharge data, ICD-9 codes that denote tobacco use disorder or excessive tobacco use that is harmful to a person's health or social functioning (305.10), complicates pregnancy, childbirth, or puerperium (649.00–04), or has toxic effects (989.84) were utilized in this study. Gestational age was restricted to between 20 and 44 completed weeks gestation at the time of delivery, and birth weight was restricted to a range of 125 g–6,000 g at birth.

The main outcomes of interest in this study were fetal growth parameters: LBW, VLBW, PTB, VPTB, and SGA. VLBW and LBW were defined as infant birth weight less than 1,500 and less than 2,500 g, respectively. PTB was defined as birth before 37 completed weeks of gestation, while VPTB were births before 32 completed weeks of gestation. SGA was defined as infants weighing below the 10th percentile of birth weight for their gestational age using normalized growth curves (Alexander, Kogan, Martin, & Papiernik, 1998).

Race/ethnicity, marital status, educational attainment, maternal age, adequacy of prenatal care, drug and alcohol use, and the presence of complications during pregnancy were selected as risk factors for this analysis. Race/ethnicity was categorized into three groups: "Hispanic" for any woman listed as ethnic "Hispanic" on birth certificate, regardless of racial classification; all woman listed as "White" and not Hispanic were classified as "White;" all women listed as "Black" and not Hispanic were classified as "Black." Due to low prevalence, other races/ethnicities were excluded from the study population. Education was classified as those with at least a high school degree (≥12 years) and those without a high school degree (<12 years); those with missing information regarding educational status were included in the latter category (<12 years). Age was dichotomized into less than 35 years and 35 years or more. Adequacy of prenatal care was assessed using the Revised-Graduated Index of prenatal care utilization (R-GINDEX). This index assesses the adequacy of care on the basis of the trimester that prenatal care began, the number of visits and the gestational age of infant at birth (Alexander & Kotelchuck, 1996). In this study, inadequate prenatal care utilization refers to women who either had missing prenatal care information, had a prenatal care but the level was considered suboptimal, or mothers who had no prenatal care at all.

Pregnancy complications in this study were identified within the hospital inpatient discharge data using ICD-9 codes and included preeclampsia (ICD-9 codes: 642.4, 642.5), eclampsia (ICD-9 codes: 642.6), pregnancy-induced hypertension (ICD-9 codes: 642.3, 642.7, 642.9), chronic hypertension (ICD-9 codes: 642.0, 401.0, 401.1, 401.9, 642.1, 642.2, 742.7), diabetes mellitus (ICD-9 codes: 250, 648.0), gestational diabetes (ICD-9 codes: 648.8), placenta previa (ICD-9 codes: 641.0, 641.1, 762.0), placenta abruption (ICD-9 codes: 641.2, 762.1), endocrine disorders (ICD-9 codes: 240–246,251,252, 253,255, 259.3, 577,628.1, and 648.1), cardiomyopathy (ICD-9 codes: 425.0-425.9), and prolonged rupture of membrane (ICD-9 codes: 658.20, 658.21, 658.23).

Alcohol abuse and drug abuse were also determined using ICD-9 codes. Alcohol abuse was defined by codes that indicate: acute alcohol intoxication (303.00–03); alcohol dependence (303.90–93); nondependent alcohol abuse, such as "binge drinking" (305.00–03); alcohol-induced mental disorders (291.0–5, 9; 291.81–82, 89); and alcohol affecting the fetus or newborn via placenta or breast milk (760.71). ICD-9 codes signifying drug dependence complicating pregnancy, childbirth, or the puerperium or postdelivery period (648.30–648.34) were utilized to determine drug abuse.

Statistical Analysis

We calculated the frequencies of maternal sociodemographic factors, as well as birth outcomes, and computed chi-square *p* values for differences between the four exposure categories (HIV/AIDS positive/smoker, HIV/AIDS positive/nonsmoker, HIV/AIDS negative/smoker, and HIV/AIDS negative/nonsmoker). We also compared the presence of pregnancy complications by exposure category. We then calculated rate ratios for the fetal growth parameters among all births and the rate ratios for the interaction between HIV/AIDS status and fetal growth parameters by sociodemographic characteristics using one of the categories as referent. Since prevalence of HIV/AIDS among

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pregnant women in Florida is epidemiologically a rare event, we assumed a Poisson distribution for our data, namely, that the probability (Pr) of HIV/AIDS among mothers at birth (y) per 100,000 live births is equal to some number r is given by:

$$\Pr(y = r) = \lambda r e^{-\lambda / r!}$$

Where λ is the expected value (mean) of y and $r! = r(r-1)(r-2)\ldots$16

We then used the variance derived from the Poisson formula to generate the *SE*s and *CI*s around the rate estimates. The Generalized Estimating Equation was used to correct for intracluster correlation, since a proportion of the women contributed more than one birth during the study period (Clayton & Hills, 1993). The covariates included in our model are maternal race/ethnicity, maternal age, marital status, education status, alcohol, drug, and tobacco abuse and pregnancy complications. The GENMOD procedure in SAS v. 9.1(SAS Institute, Inc., Cary, NC) was used to conduct this analysis. All tests of hypotheses were two tailed with a Type 1 error rate of 5%. Prior to initiation, this study received approval from the Institutional Review Board at the University of South Florida.

Results

Analysis was conducted on 1,700,734 singleton live births occurring from 1998 through 2007 in Florida. We excluded all records with missing birth weight or gestational age, as well as records of women who were not of Black, White, or Hispanic race/ethnicity, yielding a final sample size of 1,645,209 records. During the study period, a total of 648 cases of HIV/AIDS-infected mothers who smoked during pregnancy were documented (0.04%). Blacks accounted for 61% of this total, yet represented only 23% of the women who gave birth during the study period. White and Hispanic women represented 33% and 7% of all the HIV/AIDS/smoker cases, respectively, but comprised 52% and 25% of the population (Table 1). Tobacco use and HIV/AIDS infection were common among women who were unmarried, younger than 35, without a high school degree, or with documented alcohol or drug abuse (Table 1). HIV-positive smokers had a significantly greater frequency of feto-infant morbidity outcomes (LBW, VLBW, PTB, and SGA) than their uninfected counterparts (Table 1), with the exception of VPTB, which was more frequent among smokers who were HIV/AIDS negative. Infants born to HIV-positive mothers who smoked

Table 1. Demographics of Women Who Delivered Between 1998 and 2007 in the State of Florida by HIV/AIDS and Tobacco Use Status

N = 1,645,209	HIV/AIDS-positive smokers, *n* (%)	HIV/AIDS-negative smokers, *n* (%)	HIV/AIDS-positive nonsmokers, *n* (%)	HIV/AIDS-negative nonsmokers, *n* (%)	*p* Value[a]
Total	648 (0.1)	163,777 (10.0)	4,047 (0.3)	1,476,737 (89.8)	
Race					
White	211 (32.6)	138,110 (84.3)	391 (9.7)	765,671 (51.9)	**<.01**
Black	393 (60.7)	16,649 (10.1)	3,123 (77.1)	343,108 (23.2)	
Hispanic	44 (6.8)	9,018 (5.5)	533 (13.2)	367,958 (24.9)	
Age					
<35 years	543 (83.8)	145,889 (89.1)	3,584 (88.6)	1,261,221 (85.4)	**<.01**
≥35 years	105 (16.2)	17,887 (10.9)	463 (11.4)	233,354 (14.1)	
Marital status					
Married	122 (18.8)	65,427 (40.0)	990 (24.5)	918,872 (62.2)	**<.01**
Unmarried	526 (81.2)	98,350 (60.0)	3,057 (75.5)	557,865 (37.8)	
Education					
High school degree (≥12 years)	71 (10.0)	36,232 (22.1)	746 (18.4)	749,468 (50.8)	**<.01**
No high school degree (<12 years)	577 (89.0)	127,545 (77.9)	3,301 (81.6)	727,269 (49.3)	
Parity					
Nulliparous	502 (77.5)	107,716 (65.8)	2,928 (72.4)	842,023 (57.0)	**<.01**
Multiparous	146 (22.5)	56,061 (34.2)	1,119 (27.7)	634,714 (43.0)	
Substance use					
Alcohol abuse	33 (5.1)	1,832 (1.1)	14 (0.4)	1,101 (0.1)	**<.01**
Drug abuse	18 (2.8)	1,115 (0.7)	9 (0.2)	676 (0.1)	**<.01**
Prenatal care					
Adequate	152 (23.5)	53,191 (32.5)	1,117 (27.7)	563,962 (38.2)	**<.01**
Inadequate	496 (76.5)	110,586 (67.5)	2,930 (72.3)	912,775 (61.8)	
Birth outcomes[b]					
LBW	135 (20.8)	16,316 (10.0)	558 (13.8)	87,827 (6.0)	**<.01**
VLBW	16 (2.47)	1,961 (1.2)	92 (2.3)	14,265 (1.0)	**<.01**
PTB	123 (19.0)	16,726 (10.2)	579 (14.3)	125,106 (8.5)	**<.01**
VPTB	13 (2.01)	2,249 (11.6)	108 (2.7)	16,967 (1.2)	**<.01**
SGA	154 (23.77)	25,127 (15.4)	707 (17.5)	120,827 (8.2)	**<.01**

Note. [a]Significant values in bold font. *p* values of <.05 considered significant. *p* values computed by chi-square test.

[b]Birth outcomes: LBW = low birth weight, <2,500 g; VLBW = very low birth weight, <1,500 g; PTB = preterm birth, <37 completed weeks gestation; VPTB = very preterm birth, <32 completed weeks gestation; SGA = small for gestational age.

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were 431 g smaller than those born to HIV-negative smokers (2889 g vs. 3320 g, $p < .0001$) and were also born earlier (mean gestational age: 37.7 weeks vs. 38.6 weeks, $p < .0001$).

Table 2 provides the frequencies of selected pregnancy complications among HIV-infected and -uninfected mothers who used tobacco during pregnancy. Overall, pregnancy complications were observed to be significantly higher among HIV-infected women, irrespective of their smoking status (HIV/AIDS-positive smokers, 23.8%; HIV/AIDS-positive nonsmokers, 25.9%; HIV/AIDS-negative smokers, 18.6%; and HIV/AIDS-negative nonsmokers, 21.1%; $p < .01$). Anemia, diabetes mellitus, chronic hypertension, preeclampsia, and preterm premature rupture of membranes were more common among mothers with HIV/AIDS, regardless of their smoking status, whereas gestational diabetes and pregnancy-induced hypertension, and were more common among women who were negative for HIV/AIDS. Placental abruption occurred more frequently among mothers who smoked during pregnancy, irrespective of their HIV status. Eclampsia, placental previa, and cardiomyopathy were observed at similar rates among HIV/AIDS-positive and -negative mothers.

Significantly elevated risk estimates for LBW, PTB, and SGA were observed among HIV-positive mothers, as well as mothers who smoked cigarettes during pregnancy (Table 3). Among the three racial/ethnic groups included in this study, Black women had the highest risk for all feto-infant morbidity outcomes. Advanced maternal age, unmarried status, lower educational attainment, alcohol abuse, and the presence of pregnancy complications were associated with higher risk for impaired fetal growth parameters. Drug abuse was not associated with any of the outcomes retained for analysis.

Table 4 summarizes the results for interaction of maternal HIV/AIDS and smoking status with respect to feto-infant morbidity outcomes. Overall, HIV-infected mothers who smoked had approximately a twofold elevated risk for LBW (*ARR* = 2.24 [1.89–2.65]), PTB (*ARR* = 1.70 [1.42–2.03]), and SGA (*ARR* = 1.95 [1.67–2.29]) compared with those who were nonsmokers and negative for HIV/AIDS. Furthermore, the risk estimates for LBW and PTB among mothers who were both HIV positive and smoked cigarettes were 43%–79% higher than those of mothers who were either HIV positive or smokers. For SGA, the risk estimates for smokers were similar, regardless of their HIV status.

Discussion

In this large retrospective cohort study, we report elevated risks for LBW, PTB, and SGA among infants delivered to HIV-infected mothers who reported smoking during pregnancy, an important modifiable risk factor for intrauterine growth retardation. Our findings are in agreement with at least two other studies. Floridia et al. (2008) found smoking in pregnancy to add to the independent effect of HIV on birth weight; HIV-infected women who smoked more than 10 cigarettes/day had a twofold increased risk of delivering an infant with gestational age–adjusted birth weight Z-score values below the 10th percentile. Our results also concur with those from The Pediatric AIDS Clinical Trials Group, who documented a 3.6-fold risk of intrauterine growth retardation associated with cigarette smoking during pregnancy in HIV-positive women (Lambert et al., 2000).

Higher rates of LBW (Ellis, Williams, Graves, & Lindsay, 2002; Leroy et al., 1998; Markson et al., 1996; Mwanyumba et al., 2001) and PTB (Ellis et al., 2002; Leroy et al., 1998; Taha et al., 1995) have been reported among HIV-infected pregnant women compared with the general population of pregnant women. The mechanism by which HIV infection could predispose to LBW and/or PTB is not fully established, but possible mechanisms have been postulated. These include the intrauterine growth delay associated with HIV virus itself (as is seen in

Table 2. Pregnancy Complications by HIV/AIDS and Tobacco Use Status (Florida, 1998–2007)[a]

Pregnancy complications	HIV/AIDS-positive smokers, *n* (%), *N* = 648	HIV/AIDS-negative smokers, *n* (%), *N* = 163,777	HIV/AIDS-positive nonsmokers, *n* (%), *N* = 4,047	HIV/AIDS-negative nonsmokers, *n* (%), *N* = 1,476,737	*p* Value[a]
Anemia	67 (10.3)	8,509 (5.2)	468 (11.6)	88,744 (6.0)	**<.01**
Gestational diabetes	15 (2.3)	6,547 (4.0)	114 (2.8)	64,809 (4.4)	**<.01**
Diabetes mellitus	6 (0.9)	1,079 (0.7)	41 (1.0)	10,572 (0.8)	**.01**
Pregnancy-induced hypertension	12 (1.9)	4,614 (2.8)	91 (2.3)	52,547 (3.6)	**<.01**
Chronic hypertension	20 (3.1)	1,696 (1.0)	109 (2.7)	18,822 (1.3)	**<.01**
Preeclampsia	27 (4.2)	5,312 (3.2)	221 (5.5)	64,758 (4.4)	**<.01**
Eclampsia	1 (0.2)	138 (0.1)	5 (0.1)	1,469 (0.2)	.27
Placenta previa	5 (0.8)	939 (0.6)	19 (0.5)	7,842 (0.6)	.11
Placental abruption	7 (1.1)	2,437 (1.5)	39 (1.0)	12,801 (0.9)	**<.01**
Endocrine disorders	7 (1.1)	1,521 (0.9)	31 (0.8)	22,061 (1.5)	**<.01**
Cardiomyopathy	0 (0.0)	49 (0.03)	3 (0.1)	358 (0.02)	.11
PPROM	9 (1.4)	2,174 (1.3)	72 (1.8)	15,783 (1.1)	**<.01**
All complications[b]	154 (23.8)	30,514 (18.6)	1,046 (25.9)	311,100 (21.1)	**<.01**

Note. [a]Significant values in bold font. *p* values of <.05 considered significant. *p* values computed by chi-square test.

[b]All complications refers to a composite variable denoting that the mother experienced at least one of the listed pregnancy complications (preeclampsia, eclampsia, gestational diabetes, pregnancy-induced hypertension, chronic hypertension, diabetes mellitus, placenta abruption, placenta previa, endocrine disorders, cardiomyopathy, PPROM = preterm premature rupture of membranes).

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Table 3. Adjusted Rate Ratios (*ARR*) for the Association Between Maternal HIV/AIDS Status and Fetal Growth Parameters Among Singleton Births (Florida, 1998–2007)[a]

	LBW[b], *ARR* (95% *CI*)	VLBW[b], *ARR* (95% *CI*)	PTB[b], *ARR* (95% *CI*)	VPTB[b], *ARR* (95% CI)	SGA[b], *ARR* (95% *CI*)
Maternal HIV/AIDS status					
Negative	Referent	Referent	Referent	Referent	Referent
Positive	**1.41 (1.31–1.53)**	**1.24 (1.03–1.51)**	**1.29 (1.20–1.39)**	**1.27 (1.03–1.47)**	**1.28 (1.20–1.37)**
Maternal smoking status					
Nonsmoker	Referent	Referent	Referent	Referent	Referent
Smoker	**1.78 (1.75–1.81)**	**1.43 (1.36–1.51)**	**1.24 (1.22–1.26)**	**1.34 (1.28–1.41)**	**1.99 (1.96–2.01)**
Race/ethnicity					
White	Referent	Referent	Referent	Referent	Referent
Black	**1.81 (1.78–1.84)**	**2.32 (2.23–2.41)**	**1.37 (1.35–1.38)**	**2.15 (2.07–2.22)**	**1.91 (1.89–1.94)**
Hispanic	**1.16 (1.14–1.18)**	**1.28 (1.23–1.34)**	**1.03 (1.02–1.04)**	**1.26 (1.21–1.31)**	**1.25 (1.24–1.27)**
Age					
<35 years	Referent	Referent	Referent	Referent	Referent
≥35 years	**1.12 (1.10–1.14)**	**1.20 (1.15–1.25)**	**1.10 (1.09–1.12)**	**1.17 (1.13–1.22)**	**1.03 (1.02–1.05)**
Marital status					
Married	Referent	Referent	Referent	Referent	Referent
Unmarried	**1.26 (1.24–1.28)**	**1.28 (1.24–1.33)**	**1.11 (1.10–1.13)**	**1.27 (1.23–1.31)**	**1.27 (1.25–1.28)**
Education					
High school degree (≥12 years)	Referent	Referent	Referent	Referent	Referent
No high school degree (<12 years)	**1.15 (1.14–1.17)**	**1.13 (1.09–1.17)**	**1.08 (1.07–1.10)**	**1.15 (1.11–1.19)**	**1.17 (1.16–1.18)**
Alcohol abuse					
Yes	**2.18 (1.93–2.46)**	**2.54 (1.88–3.41)**	**1.74 (1.53–1.99)**	**2.35 (1.76–3.15)**	**1.56 (1.39–1.76)**
No	Referent	Referent	Referent	Referent	Referent
Drug abuse					
Yes	0.97 (0.83–1.32)	0.90 (0.61–1.34)	1.12 (0.95–1.32)	1.12 (0.78–1.62)	1.03 (0.88–1.20)
No	Referent	Referent	Referent	Referent	Referent
Pregnancy complications[c]					
Yes	**2.77 (2.74–2.81)**	**5.31 (5.13–5.48)**	**2.68 (2.65–2.70)**	**4.48 (4.36–4.61)**	**1.31 (1.30–1.33)**
No	Referent	Referent	Referent	Referent	Referent

Note. [a]Significant values are in bold font.

[b]Birth outcomes: *LBW* = low birth weight, <2,500 g; VLBW = very low birth weight, <1,500 g; PTB = preterm birth, <37 completed weeks gestation; VPTB = very preterm birth, <32 completed weeks gestation; SGA = small for gestational age.

[c]Pregnancy complications: Anemia, preeclampsia, eclampsia, gestational diabetes, pregnancy-induced hypertension, chronic hypertension, diabetes mellitus, placental abruption, placenta previa, endocrine disorders, cardiomyopathy, preterm premature rupture of membranes.

other intrauterine viral infections, e.g., cytomegalovirus; Galask, Larsen, & Ohm, 1993), possible effects on uteroplacental blood supply and/or maternal physiology (Johnstone, Raab, & Hamilton, 1996), obstetric policies for HIV-infected mothers that encourage cesarean delivery before term, and the use of maternal combination antiretroviral therapy (especially protease inhibitors; Floridia et al., 2008). The additional effect of cigarette smoking on fetal morbidity associated with HIV infection could be attributed to the synergistic intrauterine effect of cigarettes on fetal growth, in addition to the heightened risk of mother–child transmission of HIV connected with cigarette use (Burns et al., 1994) and the association between smoking in pregnancy and conditions that impair placental blood flow (e.g., premature rupture of the membranes, placenta previa, and placental abruption).

The strengths of this study include a large sample size (1,700,734 singleton live births) that improved the generalizability of our findings and permitted sufficient power for analysis of risk across cofactors. Previous analyses addressing this topic in the United States were conducted on relatively small study populations in selected health care settings. An additional strength is the use of hospital discharge and vital records data files that were linked via a validated linkage process, which improves the internal validity of our findings. In terms of limitations, we lacked information on maternal immune status (CD4 T-lymphocyte counts), which has been associated with LBW in some studies (Cailhol et al., 2009). In addition, infants who are HIV-infected may be more likely to be LBW (Brocklehurst & French, 1998; Markson et al., 1996; Minkoff & Mofenson 1994). Unfortunately, information on infant HIV status was not available in our data files. Another limitation present in this study is our inability to adjust for certain maternal risk factors for LBW, such as nutritional status of the mother during pregnancy and prepregnancy weight.

In summary, our findings emphasize the need to address maternal smoking in HIV-infected pregnant women. Health care providers who serve HIV-infected women should consider integrating smoking cessation programs into their HIV care services. Trials of smoking cessation interventions tailored to persons living with HIV/AIDS show that both traditional

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Table 4. Adjusted Rate Ratios (*ARR*) for the Association Between the Co-occurrence of Maternal HIV/AIDS Status and Cigarette Smoking and Fetal Growth Parameters Among Singleton Births (Florida, 1998–2007)[a]

	LBW[b], *ARR* (95% *CI*)	VLBW[b], *ARR* (95% *CI*)	PTB[b], *ARR* (95% *CI*)	VPTB[b], *ARR* (95% *CI*)	SGA[b], *ARR* (95% *CI*)
Maternal HIV/AIDS status and smoking status					
HIV/AIDS + smokers	**2.24 (1.89–2.65)**	1.46 (0.89–2.38)	**1.70 (1.42–2.03)**	1.02 (0.59–1.75)	**1.95 (1.67–2.29)**
HIV/AIDS − smokers	**1.78 (1.74–1.81)**	**1.43 (1.36–1.51)**	**1.24 (1.22–1.26)**	**1.34 (1.28–1.41)**	**1.99 (1.96–2.02)**
HIV/AIDS + nonsmokers	**1.45 (1.33–1.57)**	**1.28 (1.04–1.57)**	**1.27 (1.17–1.37)**	**1.31 (1.09–1.59)**	**1.37 (1.27–1.47)**
HIV/AIDS − nonsmokers	Referent	Referent	Referent	Referent	Referent
Race/ethnicity					
White	Referent	Referent	Referent	Referent	Referent
Black	**1.81 (1.79–1.84)**	**2.32 (2.23–2.41)**	**1.37 (1.35–1.39)**	**2.15 (2.08–2.23)**	**1.91 (1.89–1.94)**
Hispanic	**1.16 (1.14–1.18)**	**1.28 (1.22–1.34)**	**1.03 (1.01–1.04)**	**1.26 (1.21–1.31)**	**1.25 (1.24–1.27)**
Age					
<35 years	Referent	Referent	Referent	Referent	Referent
≥35 years	**1.12 (1.10–1.14)**	**1.20 (1.15–1.25)**	**1.10 (1.009–1.12)**	**1.17 (1.13–1.22)**	**1.03 (1.02–1.05)**
Marital status					
Married	Referent	Referent	Referent	Referent	Referent
Unmarried	**1.28 (1.26–1.30)**	1.31 (1.27–1.36)	**1.13 (1.11–1.14)**	**1.30 (1.25–1.34)**	**1.27 (1.26–1.29)**
Education					
High school degree (≥12 years)	Referent	Referent	Referent	Referent	Referent
No high school degree (<12 years)	**1.16 (1.15–1.18)**	**1.15 (1.11–1.19)**	**1.09 (1.08–1.11)**	**1.17 (1.13–1.20)**	**1.17 (1.16–1.19)**
Alcohol abuse					
Yes	**2.14 (1.90–2.42)**	**2.47 (1.83–3.32)**	**1.72 (1.51–1.96)**	**2.30 (1.72–3.08)**	**1.56 (1.39–1.76)**
No	Referent	Referent	Referent	Referent	Referent
Drug abuse					
Yes	0.98 (0.84–1.15)	0.92 (0.62–1.36)	1.13 (0.96–1.34)	**1.14 (0.79–1.65)**	1.03 (0.89–1.20)
No	Referent	Referent	Referent	Referent	Referent
Pregnancy complications[d]					
Yes	**2.76 (2.72–2.79)**	**5.26 (5.10–5.43)**	**2.67 (2.64–2.69)**	**4.45 (4.32–4.58)**	**1.31 (1.30–1.33)**
No	Referent	Referent	Referent	Referent	Referent

Note. [a]Significant values are in bold font.

[b]Birth outcomes: LBW = low birth weight, <2,500 g; VLBW = very low birth weight, <1,500 g; PTB = preterm birth, <37 completed weeks gestation; VPTB = very preterm birth, <32 completed weeks gestation; SGA = small for gestational age.

[c]Insufficient cell size.

[d]Pregnancy complications: anemia, preeclampsia, eclampsia, gestational diabetes, pregnancy-induced hypertension, chronic hypertension, diabetes mellitus, placenta abruption, placenta previa, endocrine disorders, cardiomyopathy, preterm premature rupture of membranes.

and novel smoking cessation approaches are feasible and can significantly impact smoking abstinence rates (Cummins, Trotter, Moussa, & Turham, 2005; Lazev, Vidrine, Arduino, & Gritz, 2004; Wewers, Neidig, & Kihm, 2000). Smoking cessation efforts targeting HIV-infected women could therefore represent a useful behavioral approach to reducing the burden of fetal morbidity in our communities.

Declaration of Interests

The authors declare no conflict of interest.

Acknowledgments

The abstract for this study was presented at the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Rome, Italy, July 17–20, 2011.

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