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Prenatal Screening for and Prevalence of Hepatitis B Surface Antigen in Pregnant Women and Prevention of Transmission to Infants Born to Infected Mothers—Guam, 2014

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Abstract

Background.—Perinatal transmission is the major mode of hepatitis B virus (HBV) transmission and drives HBV endemicity in the US territory of Guam. We assessed correlates of prenatal hepatitis B surface antigen (HBsAg) screening and HBsAg positivity among pregnant women and evaluated the care of infants of HBsAg-positive women.

Methods.—Demographic and clinical data were abstracted from the maternal medical records of 966 randomly selected live infants born in 2014. Frequencies were calculated, and prevalence ratios (PRs) and 95% confidence intervals (CIs) were estimated using Poisson regression.

Results.—Among the mothers of the 966 infants, 78.2% were Pacific Islanders, 56.9% were >25 years old (born before universal infant hepatitis B vaccination in Guam), 89.0% received prenatal care (PNC), 96.7% underwent prenatal HBsAg screening, and 2.0% were HBsAg positive. Approximately 15% of the women who did not have PNC were not screened for HBsAg. Receipt of PNC was associated with HBsAg screening (adjusted PR, 1.13 [95% CI, 1.04–1.23]), and

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HBsAg positivity was associated with a maternal age of >25 years (adjusted PR, 6.80 [95% CI, 1.32–35.08]). All 18 infants of the HBsAg-positive mothers received hepatitis B vaccine, and 17 (94.4%) received hepatitis B immunoglobulin.

Conclusion.—Although the prenatal HBsAg screening prevalence in this sample was high, the maternal HBsAg prevalence among women in this sample was more than 14 times and 2 times the prevalence among US-born Pacific Islander/Asian women and all women in the continental United States, respectively. Improving access to PNC, ensuring that all pregnant women in Guam (especially those born before universal hepatitis B vaccination) are screened for HBsAg, and adopting postexposure prophylaxis for infants of HBsAg-positive mothers as standard clinical practice are important for preventing perinatal HBV transmission and reducing HBV endemicity.

Keywords

HBsAg positivity; HBsAg screening; postexposure prophylaxis; pregnant women; Guam

Hepatitis B virus (HBV) infection is endemic in the US territory of Guam [1, 2], 1 of 6 islands that make up the US-affiliated Pacific Islands (USAPI). All islands that comprise the USAPI are considered regions in which HBV is intermediate (2%–7% hepatitis B surface antigen [HBsAg] prevalence) or highly (>7% HBsAg prevalence) endemic [1, 3]. Perinatal transmission is the major mode of HBV transmission in regions in which HBV is endemic [4]. Up to 90% of HBV-infected infants will become chronically infected with HBV, and approximately 25% of them will die prematurely as a result of liver cirrhosis or hepatocellular carcinoma [4-6]. People who are chronically infected with HBV are also reservoirs for continued transmission of HBV [7]. In an effort to address the burden of HBV infection in Guam, hepatitis B vaccination was introduced into its universal infant vaccination schedule in 1988 [1].

Since 1988, the Advisory Committee on Immunization Practices (ACIP) has recommended that all pregnant women receive HBsAg screening early in each pregnancy, regardless of previous HBsAg screening test result or hepatitis B vaccination [8]. HBsAg is a serum marker used to screen for and identify HBV infection in pregnant women. The ACIP also recommends that all infants born to HBsAg-positive mothers receive postexposure prophylaxis (PEP), which consists of hepatitis B vaccine and hepatitis B immunoglobulin (HBIg), within 12 hours of birth [8]. Current US guidelines, instituted in 2015, also recommend hepatitis B virus e antigen (HBeAg) and HBV DNA testing for HBsAg-positive pregnant women and antiviral prophylaxis therapy for those with a high HBV DNA count (>10⁶ copies/ml or >20 000 IU/ml) [9, 10].

Prenatal HBsAg screening is critical for promptly identifying HBsAg-positive women and administering PEP to their infant soon after birth to prevent perinatal HBV transmission. Hepatitis B vaccine provides long-term active immunity to HBV infection, and HBIg provides short-term passive immunity to HBV infection until the infant responds to the vaccine [11, 12]. The purpose of this analysis was to examine the prevalence and correlates of prenatal HBsAg screening and HBsAg positivity among pregnant women in Guam and to describe the care of infants of HBsAg-positive mothers.

METHODS

Data were obtained from the medical records of the largest civilian delivery hospital in Guam. This hospital provided delivery services for approximately 73% of the 3401 births recorded in Guam in 2014. After a sample-size estimation and power analysis, we generated a random sample of 971 (39.2%) of the 2478 live births at the hospital between January 1, 2014, and December 31, 2014. Because our primary outcomes of interest were prenatal HBsAg screening and HBsAg positivity among the mothers of these infants, 1 infant from each of the 5 twin sets delivered in 2014 was removed from the study, which resulted in an analysis sample of 966 live births. Demographic, clinical care, and laboratory data for this analysis were obtained after review and abstraction of the maternal prenatal medical records. Data regarding the administration of hepatitis B vaccine and HBIg to infants born to HBsAg-positive mothers were obtained from the maternal medical records and confirmed with vaccination records at the Guam Department of Public Health and Social Services. Each medical chart was reviewed, and data were abstracted by 1 of 5 abstractors using a standardized chart-abstraction tool. To ensure data quality, 12% of all abstracted data were selected randomly and underwent secondary review by a second abstractor. Any discrepancy in the abstracted data was addressed by a third review of the medical record. Missing elements of laboratory data were obtained, when available, from the testing laboratory.

From the medical charts, we obtained and recorded maternal demographic data (race, age at delivery, highest level of education, employment status, marital status, and health insurance information), maternal clinical data (receipt of prenatal care [PNC], defined as having had 1 PNC visit before admission for delivery, number of PNC visits, number of pregnancies, prenatal HBsAg screening [defined as HBsAg screening any time before birth, including during the admission for delivery], HBeAg and HBV DNA testing, and HBsAgpositive status), and postdelivery care data of infants born to HBsAg-positive mothers (hepatitis B vaccine administered 12 hours after delivery, HBIg administered 12 hours after delivery). Age at delivery was dichotomized at 25 years (25 years and >25 years), because pregnant women who were 25 years old in 2014 were born after routine infant hepatitis B vaccination was initiated in Guam [1]. This investigation was reviewed and approved by the institutional review board of the University of Guam. Descriptive statistics were performed to characterize the sample and determine the prevalence of prenatal HBsAg screening and HBsAg positivity among the pregnant women and the prevalence of hepatitis B vaccination and HBIg administration among infants of HBsAg-positive mothers. Using Poisson regression analysis with robust error variance, we calculated unadjusted prevalence ratios (UPRs) and adjusted prevalence ratios (APRs) with corresponding 95% confidence intervals (CIs) to examine bivariate and multivariate associations between demographic and clinical variables and prenatal HBsAg screening and HBsAg positivity. Statistical significance was set at 0.05, and all analyses were conducted using SAS 9.3 (SAS, Inc, Cary, NC).

RESULTS

Data from 966 pregnant women were included in this analysis. Table 1 lists the characteristics of the sample. Most of the women were Pacific Islander (752 [78.2%]), were

>25 years of age at delivery (542 [56.1%]), had a high school diploma/general equivalency diploma or higher (723 [78.6%]), were unemployed (668 [70.6%]), and were single or divorced (554 [57.5%]). Public insurance (Medicaid or Medically Indigent Program) was the most common type of insurance (514 [53.7%]). Most of the pregnant women (857 [89.0%]) received PNC. Among the women who received PNC, the mean number of PNC visits was 7.6 (range, 1–25). The mean number of total pregnancies was 3.0 (range, 1–13), and 26.7% of the women were primi-gravida. Of the pregnant women, 905 (96.7%) were screened for HBsAg prenatally, of which, 818 (90.4%) were screened during their PNC. Eighty-seven (9.6%) women did not receive PNC but were screened after admission for delivery but before the birth of their infant.

The prevalence of prenatal HBsAg screening and HBsAg positivity according to receipt of PNC was examined. Among the 857 women who received PNC, HBsAg screening data were not available for 23 of them. Of 834 women with available HBsAg screening data, 16 (1.9%) were not screened for HBsAg, and 818 (98.1%) were screened. Of the 106 (10.9%) women who did not receive PNC, HBsAg screening data were not available for 4 of them. Among the 102 women with available HBsAg screening data, 15 (14.7%) were not screened for HBsAg, and 87 (85.2%) were screened after admission for delivery.

Among 899 women with HBsAg screening results available, 18 (2.0%) were HBsAg positive (14 Pacific Islander women and 4 Asian women). Seventeen HBsAg-positive mothers received PNC, and 1 did not receive PNC but was screened after admission for delivery. Of the HBsAg-positive women, 16 (88.9%) were >25 years of age at delivery. All 18 infants of HBsAg-positive mothers received a hepatitis B vaccine, and 17 (94.4%) received HBIg within 12 hours after delivery. None of the HBsAg-positive mothers had clinical or laboratory records to indicate that HBeAg or HBV DNA testing had been performed.

Prenatal HBsAg Screening

Table 2 shows the unadjusted and adjusted associations between prenatal HBsAg screening and demographic and clinical factors. This analysis was restricted to women for whom HBsAg screening data were documented (n = 936). We excluded Hispanic women from the bivariate and multivariate analyses of racial differences because of their small sample size (n = 2). Highest level of education, employment status, health insurance status, receipt of PNC, number of PNC visits, and number of total pregnancies were significantly associated with prenatal HBsAg screening in the bivariate analysis. Pregnant women with less than a high school education (UPR, 0.96 [95% CI, 0.93–0.99]) and those with a high school diploma/general equivalency diploma (UPR, 0.97 [95% CI, 0.95–0.99]) were less likely to have undergone prenatal HBsAg screening than were pregnant women with at least a college degree. Pregnant women who self-paid (UPR, 0.96 [95% CI, 0.93–0.99]) and those with public insurance (UPR, 0.97 [95% CI, 0.95–0.99]) were less likely to have been screened for HBV than were participants with private/military insurance. Pregnant women with a greater number of total pregnancies were also less likely to have been screened (UPR, 0.98 [95% CI, 0.97–0.99]).

Employed pregnant women were more likely to have been screened for HBsAg (UPR, 1.02 [95% CI, 1.01–1.05]) than were unemployed pregnant women. Compared to pregnant women without PNC, pregnant women who received PNC were more likely to have been screened for HBsAg (UPR, 1.15 [95% CI, 1.06–1.25]). Pregnant women with a greater number of PNC visits were also more likely to have been screened for HBsAg (UPR, 1.02 [95% CI, 1.01–1.04]). Race, age at delivery, and marital status were not significantly associated with prenatal HBsAg screening. All significant variables in the bivariate model, except the number of PNC visits, were included in the multivariable model. Number of PNC visits was excluded from the multivariable model because of its strong correlation with receipt of PNC. The multivariable model included highest level of education, employment status, health insurance data, whether PNC was received, and total number of pregnancies. Receipt of PNC remained the only significant predictor of prenatal HBsAg screening (APR, 1.13 [95% CI, 1.04–1.23]) in the multivariable model.

HBsAg Positivity

Table 3 shows the unadjusted and adjusted associations between HBsAg positivity and demographic and clinical factors. This analysis was restricted to women for whom HBsAg screening test results were available (n = 899). In the bivariate model, pregnant women who were >25 years old at delivery were more likely to be HBsAg positive than pregnant women 25 years old at delivery (UPR, 6.44 [95% CI, 1.49–27.85]). HBsAg positivity was not significantly associated with highest level of education, employment status, marital status, health insurance status, receipt of PNC, number of PNC visits, or number of pregnancies. Because no HBsAg-positive women were in the reference group (white), we did not examine the bivariate association between race and HBsAg positivity. Other than age at delivery, we found no significant variables in the bivariate model. In addition to age at delivery, the multivariable model included other variables (highest level of education, marital status, receipt of PNC, and total number of pregnancies) identified on the basis of previous studies that found an association with them and a higher risk of being HBsAg positive [13-15]. In this model, an age of >25 years at delivery remained the only variable that was significantly associated with HBsAg positivity (APR, 6.80 [95% CI, 1.32–35.08]).

DISCUSSION

The prevalence of prenatal HBsAg screening in this sample of pregnant women from Guam was high and similar to the 94% prevalence in the continental United States [16, 17]. The 2% HBsAg prevalence in this analysis is also consistent with population-based data indicating that Guam is a region or intermediate HBV endemicity. HBsAg screening ensures that HBsAg-positive women are identified so that their infants can receive timely PEP to prevent HBV infection [8]. Screening also presents an opportunity to link HBsAg-positive women to hepatitis B-directed care and identify and vaccinate their susceptible sexual and household contacts. Receipt of PNC was the strongest predictor of HBsAg screening in this analysis, which underscores its important role in detecting HBsAg-positive mothers and preventing perinatal HBV transmission. PNC also facilitates the documentation and communication of maternal HBsAg status to the delivery and postnatal healthcare teams

to ensure PEP at birth and continuity of HBV-preventive care (completion of hepatitis B vaccine series and postvaccination serologic testing) for infants of HBsAg-positive mothers.

Although most pregnant women in this sample received PNC, approximately 2% of the women who received PNC and 15% of those who did not receive PNC were not screened for HBsAg. Missed opportunities for screening and preventing perinatal HBV transmission could be addressed by expanding access to PNC and by fully implementing standing hospital policies that require HBsAg screening and proper documentation of its results at a PNC visit or during labor for those without any HBsAg screening record. It is also important that healthcare providers be aware of Guam's intermediate HBV endemicity in women of child-bearing age and the importance of prenatal HBsAg screening in this population.

In this study, women with public insurance, those who self-paid for their healthcare services, and those with a lower level of education were less likely to be screened for HBsAg. Although the cost of HBsAg screening might prevent women who have to make out-of-pocket payments from getting screened, it is less clear why those with public insurance such as Medicaid and the Medically Indigent Program (both of which cover HBsAg screening) were less likely to have been screened. The cost of HBsAg screening also might account for why employed women and women with a higher level of education were more likely to have undergone prenatal HBsAg screening than were unemployed women or women with a lower level of education. Women with a greater number of total pregnancies were less likely to have been screened than were those with fewer pregnancies. Some healthcare providers might wrongly assume that it is unnecessary to screen pregnant women because of a previous negative HBsAg screening result or hepatitis B vaccination; however, risk factors for HBV infection can change between pregnancies, so it is important for healthcare providers to screen for HBsAg in all pregnancies in an effort to identify all HBsAg-positive women.

The maternal HBsAg prevalence of 2.0% in this sample is more than 2 and 14 times the maternal HBsAg prevalence estimate among all women in the continental United States (0.2%–0.9%) and among US-born Pacific Islander and Asian women (0.14%), respectively [17, 18]. Pregnant women who were >25 years old at delivery were more likely to be HBsAg positive than those aged 25 years, presumably because of the positive impact of Guam's initiation of universal infant hepatitis B vaccination in 1988. Previous studies have shown a population-wide decline in HBsAg-positive prevalence after the introduction of universal infant hepatitis B vaccination in areas in which HBV is endemic [19, 20].

In this analysis, all infants born to HBsAg-positive mothers received the hepatitis B vaccine, and all but 1 infant received HBIg within 12 hours after delivery. PEP is an impactful and cost-effective strategy for reducing perinatal HBV transmission and preventing morbidity and death caused by chronic HBV infection [21, 22]. Institutional policies that clearly outline the steps for administering PEP promptly to all infants of HBsAg-positive mothers and properly documenting maternal HBsAg status in maternal records will ensure that all infants at risk receive PEP [17].

We found no data available in the medical records in our study to determine whether HBsAg-positive women underwent HBeAg and HBV DNA testing, because these recommendations were not made until 2015 [9, 10]. A high HBeAg and a high HBV DNA level are important risk factors for perinatal HBV transmission in HBsAg-positive mothers even when PEP is administered [23, 24]. The perinatal HBV transmission risk is approximately 9% in infants of HBeAg-positive women [25] and between 3% and 8% in infants of women with a high HBV DNA level despite PEP [26]. Future studies of the prevention of perinatal HBV infection in Guam and other islands of the USAPI should examine the prevalence of HBeAg and HBV DNA testing in HBsAg-positive pregnant women.

There are limitations to the findings of this study. The generalizability of the study findings is limited because the analytical sample comprised pregnant women with live births in 1 hospital in Guam, although it accounts for most infant deliveries. We used the birth dose of hepatitis B vaccine and HBIg as proxies for protection from HBV infection among infants of HBsAg-positive mothers. However, the complete hepatitis B vaccine series confers maximal protection from HBV infection [16]. We did not conduct postvaccination serologic testing on the infants of HBsAg-positive women to assess vaccine response. Last, although some women who deliver their infants in Guam come from other countries in Asia and the Pacific Islands where HBV is endemic, we could not assess this association with HBsAg positivity because of limited country-of-birth data.

CONCLUSION

Timely identification of HBsAg-positive pregnant women and PEP administration for their infants remain key strategies for controlling HBV infection. In this study, receipt of PNC was the most important predictor of HBsAg screening. Women born before the implementation of universal infant hepatitis B vaccination in Guam were at higher risk of being HBsAg positive; hence, particular importance to HBsAg screening in pregnant women in this age group is warranted. All prenatal healthcare providers should be educated on recommended guidelines for prenatal HBsAg screening and care of HBsAg-positive pregnant women and their infants. Systemic and institutional policies that expand PNC to all pregnant women and the adoption of routine prenatal HBsAg screening for all women might improve the consistent delivery of guideline-concordant care for pregnant women. Given current recommendations, HBeAg and HBV DNA testing of HBsAg-positive pregnant women is important for mitigating perinatal HBV-transmission risk further. Last, delivering recommended follow-up care for all HBsAg-positive mothers and their infants is critical for preventing perinatal HBV transmission and reducing the overall burden of chronic HBV infection in Guam over time.

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 $\label{eq:Table 1.}$ Demographic and Clinical Characteristics of a Random Sample of Pregnant Women From the Largest Civilian Delivery Hospital in Guam, 2014 (N = 966)

Variable	Values ^a
Demographic characteristics	
Race (n [%])	
Pacific Islander	752 (78.2)
Asian	197 (20.5)
White	11 (1.1)
Hispanic	2 (0.2)
Age at delivery	
Range (y)	15–45
Mean (SD) (y)	27.2 (6.2)
25 y (n [%])	424 (43.9)
>25 y (n [%])	542 (56.1)
Highest level of education (n [%])	
Less than high school	197 (21.4)
High school diploma/GED	488 (53.1)
College degree or higher	235 (25.5)
Employment status (n [%])	
Employed	278 (29.4)
Unemployed	668 (70.6)
Marital status (n [%])	
Married	270 (28.1)
Common-law	139 (14.4)
Si ngle/divorced	554 (57.5)
Health insurance (n [%])	
Self-pay	181 (18.9)
Public insurance (Medicaid/Medically Indigent Program)	514 (53.7)
Private/military insurance (n [%])	263 (27.5)
Clinical characteristics	
Receive PNC (n [%]) b	
Yes	857 (89.0)
No	106 (11.0)
PNC visits	
Range	1–25
Mean (SD)	7.6 (4.6)
Pregnancies	
Range	1–13
Mean (SD)	3.0 (2.1)
Prenatal HBsAg screening (n [%]) ^C	
Yes	905 (96.7)

Abara et al.

Variable Values^a 31 (3.3) No Prenatal HBsAg screening among those who received PNC (n [%]) d Yes 818 (98.1) No 16 (1.9) Prenatal HBsAg screening among those who did not receive PNC (n [%]) e Yes 87 (85.3) No 15 (14.7) HBsAg positive (n [%]) Yes 18 (2.0) No 881 (98.0) Age of mother at delivery among HBsAg-positive mothers (n = 18) (n [%]) 2 (11.1) 16 (88.9) >25 y Infants born to HBsAg-positive mothers receiving hepatitis B vaccine 12 h after delivery (n = 18) (n [%]) 18 (100.0) 0(0.0)No Infants born to HBsAg-positive mothers receiving hepatitis B immunoglobulin 12 h after delivery (n = 18) (n [%]) 17 (94.4) No 1 (5.6)

Page 11

Abbreviations: GED, general equivalency diploma; HBsAg, hepatitis B surface antigen; PNC, prenatal care; SD, standard deviation.

^aSums might not equal 966 because of missing data.

One or more prenatal care visit before admission for delivery.

^cIncludes women who were screened during prenatal care and those without prenatal care but who were screened during admission for delivery.

 $d_{\text{Prenatal HBsAg screening data were unavailable for 23 women.}}$

 $^{^{}e}$ Prenatal HBsAg screening data were unavailable for 4 women.

 $\label{eq:Table 2.}$ Factors Associated With Prenatal HBsAg Screening Among a Random Sample of Pregnant Women Selected From the Largest Civilian Delivery Hospital in Guam, 2014 (N = 936)

	Prenatal HBsAg Screening (n)		Prevalence Ratio (95% CI)		
Variable	Yes	No	Unadjusted	Adjusted ^a	
Total	905	31			
Race					
Pacific Islander	711	27	1.07 (0.87-1.32)	_	
Asian	179	3	1.09 (0.89–1.35)	_	
White	9	1	1.00	_	
Age at delivery					
>25 y	500	21	0.98 (0.96–1.01)	_	
25 y	405	10	1.00	_	
Highest level of education					
Less than high school	186	9	0.96 (0.93-0.99)	0.99 (0.95-1.03)	
High school diploma/GED	459	18	0.97 (0.95-0.99)	0.98 (0.96–1.01)	
College degree or higher	220	2	1.00	1.00	
Employment status					
Employed	272	26	1.02 (1.01–1.05)	1.00 (0.97–1.03)	
Unemployed	617	5	1.00	1.00	
Marital status					
Common-law	131	5	0.99 (0.95-1.03)	_	
Single/divorced	524	18	0.99 (0.97-1.02)	_	
Married	248	7	1.00	_	
Health insurance					
Self-pay	155	8	0.96 (0.93-0.99)	0.98 (0.94–1.03)	
Public insurance (Medicaid/Medically Indigent Program)	483	20	0.97 (0.95-0.99)	0.99 (0.97–1.02)	
Private/military insurance	260	3	1.00	1.00	
Received PNC					
Yes	818	16	1.15 (1.06–1.25)	1.13 (1.04–1.23)	
No	87	15	1.00	1.00	
PNC care visits (mean)	7.7	3.9	1.02 (1.01–1.04)	_	
Total pregnancies (mean)	3.0	4.1	0.98 (0.97-0.99)	1.00 (0.99–1.01)	

Abbreviations: CI, confidence interval; HBsAg, hepatitis B surface antigen; GED, general equivalency diploma; PNC, prenatal care.

^aMultivariable model included highest level of education, employment status, health insurance, prenatal care receipt, and total number of pregnancies.

Table 3. Factors Associated With HBsAg Positivity Among a Random Sample of Pregnant Women Selected From the Largest Civilian Delivery Hospital in Guam, 2014 (N = 899)

HBsAg		Positive (n)	Prevalence Ratio (95% CI)	
Variable	Yes	No	Unadjusted	Adjusted ^b
Total	18	881		
Race ^a				
Pacific Islander	14	694	_	_
Asian	4	172	_	_
White	0	9	_	_
Age at delivery				
>25 y	16	482	6.44 (1.49–27.85)	6.80 (1.32–35.08)
25 y	2	399	1.00	1.00
Highest level of education				
Less than high school	6	178	1.18 (0.39–3.61)	1.24 (0.38–4.06)
High school diploma/GED	4	453	0.32 (0.09-1.11)	0.34 (0.09-1.30)
College degree or higher	6	212	1.00	1.00
Employment status				
Employed	4	267	0.70 (0.23-2.11)	_
Unemployed	13	599	1.00	_
Marital status				
Common-law	5	125	3.14 (0.76–12.94)	5.16 (0.99-27.00)
Single/divorced	10	512	1.57 (0.43–5.63)	4.46 (0.93–21.45)
Married	3	242	1.00	1.00
Health insurance				
Self-pay	2	149	1.14 (0.19–6.77)	_
Public insurance (Medicaid/medically indigent program)	13	469	2.33 (0.67-8.10)	_
Private/military insurance	3	256	1.00	_
Receive PNC				
Yes	17	796	1.80 (0.24–13.35)	2.07 (0.29–14.68)
No	1	85	1.00	1.00
PNC visits (mean)	6.4	7.8	0.93 (.83–1.05)	_
Pregnancies (mean)	3.9	3.0	1.00 (.99–1.02)	1.07 (0.91–1.25)

Abbreviations: CI, confidence interval; GED, general equivalency diploma; HBsAg, hepatitis B surface antigen; PNC, prenatal care.

^aUnadjusted and adjusted prevalence ratios were not calculated because of the empty cell for the reference group.

^bMultivariable model included highest level of education, employment status, health insurance, prenatal care receipt, and total number of pregnancies.