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Maternal Zika Virus Infection: Association With Small-for-Gestational-Age Neonates and Preterm Birth

Hannah J. Cooper, MBChB, MPH[1], **Martha Iwamoto, MD, MPH**[1], **Maura Lash, MPH, RN**[1], **Erin E. Conners, PhD, MPH**[1], **Marc Paladini, MPH**[1], **Sally Slavinski, DVM, MPH**[1], **Anne D. Fine, MD**[1], **Joseph Kennedy, MPH**[2], **Dominique Heinke, ScD**[3], **Andrea Ciaranello, MD, MPH**[4], **George R. Seage III, DSc, MPH**[3], **Ellen H. Lee, MD**[1]

[1]Bureau of Communicable Disease, New York City Department of Health and Mental Hygiene, Queens, New York, USA

[2]Bureau of Vital Statistics, New York City Department of Health and Mental Hygiene, New York, New York, USA

[3]Harvard T. H. Chan School of Public Health, Boston, Massachusetts, USA

[4]Medical Practice Evaluation Center, Division of Infectious Disease, Massachusetts General Hospital, Boston, Massachusetts, USA

Abstract

Objectives: To evaluate whether antenatal Zika virus infection is associated with risk of having a small-for-gestational-age (SGA) neonate, risk of preterm birth, and lower mean birth weight of term neonates.

Methods: For this retrospective observational study, we linked birth record data for women who delivered liveborn singleton neonates in New York City (NYC) in 2016 to data for pregnant women with Zika virus infection reported to the NYC Health Department. We restricted the analysis to non-smoking, non-white women and adjusted for maternal characteristics. Among women with antenatal Zika virus infection, we used modified Poisson regression to assess risks of having an SGA neonate and of delivering preterm, and linear regression to assess the association of infection with mean birth weight of term neonates.

Results: Of 116,034 deliveries of singleton neonates in NYC in 2016, 251(0.2%) were to women with antenatal Zika virus infection. A higher percentage of women with Zika virus infection delivered an SGA neonate compared with those without (11.2% vs. 5.8%; adjusted relative risk (RR) 1.8; 95% confidence interval (CI), 1.3 – 2.6). There was no difference in preterm birth prevalence for women with and without Zika virus infection (adjusted RR 1.0; 95% CI, 0.69 – 1.6). Mean birth weight of term neonates born to women with Zika virus infection was 47 grams

Address correspondence to: Ellen H. Lee, MD, 42-09 28th Street, CN# 22A, Queens, New York, 11101. ELee4@health.nyc.gov., Phone: +1 347-396-2630.

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less (95% CI, −105 – 11 grams) ; this difference was not statistically significant in crude or adjusted analyses.

Conclusions: For a cohort of NYC women, antenatal Zika virus infection was associated with an increased risk of having an SGA neonate, but not preterm birth or lower mean birth weight of term neonates. This supports a putative association between Zika virus infection during pregnancy and SGA.

Précis –

Maternal Zika virus infection was associated with increased risk of small-for-gestational-age neonates but not with preterm birth in a cohort of New York City women.

Introduction

Antenatal Zika virus infection can cause devastating birth defects,[1,2] but the full extent of adverse birth outcomes remains to be established. Infections during pregnancy are a recognized cause of low birth weight, small-for-gestational-age (SGA) neonates,[3] and preterm birth.[4] SGA and preterm neonates are at higher risk of morbidity and mortality in infancy and early childhood,[5] as well as chronic disease, such as cardiovascular disease, in later life.[6]

Few published studies have evaluated whether antenatal Zika virus infection is associated with lower birth weight, SGA, and preterm birth. Reported prevalence of these outcomes in cohorts of women with antenatal Zika virus infection has varied considerably and is dependent on the population under study. In Brazil, a case series of 87 microcephalic neonates with congenital Zika virus infection found 29% to be SGA,[7] while among a cohort of 54 women with confirmed antenatal Zika virus infection, there were no SGA neonates.[8] The range in prevalence of preterm birth in cohorts of pregnant women with Zika virus infection from Brazil and the United States was 7–15%;[7–10] in 2016, prevalence in the general U.S. population was 9.9%.[11]

Although New York City (NYC) has not detected local mosquito-borne transmission of Zika virus, over 1,000 imported Zika virus infections were diagnosed in 2016 as a result of the outbreak in the Americas, including 338 cases among pregnant women.[12] Using NYC birth record data, we evaluated whether antenatal Zika virus infection was associated with low birth weight, SGA and preterm birth.

Methods

In this retrospective observational study, we analyzed NYC Health Department Bureau of Vital Statistics birth record data for all liveborn singleton neonates born during 2016 in NYC and surveillance data for cases of Zika virus infection diagnosed in NYC residents in 2016. Beginning in February 2016, the Health Department advised NYC prenatal care providers to screen patients for possible Zika virus exposure (ie, travel to, or unprotected sex with someone who travelled to, an area with mosquito-borne Zika virus transmission) and to obtain Zika virus testing for exposed women.[13] All positive Zika virus results were electronically reported to the Health Department, as required by the NYC Health Code.[14]

Clinical and epidemiologic information was obtained via patient interview. Zika virus testing was recommended for neonates born to women with antenatal Zika virus infection and neonates with clinical findings consistent with congenital Zika virus infection,[1] regardless of maternal Zika virus testing status. Cases of ZIKV in pregnant women were matched to NYC birth records by the Bureau of Vital Statistics to assist routine surveillance activities.

The primary exposure of interest was defined as laboratory evidence of confirmed or probable Zika virus infection during pregnancy or peri-conception, defined as six weeks prior to last menstrual period, or delivery of an neonate with congenital Zika virus infection. Laboratory evidence of confirmed Zika virus infection required either detectable Zika virus RNA on nucleic acid amplification tests of serum, urine, amniotic fluid, or placental tissue; or, non-negative Zika virus antibody capture enzyme-linked immunosorbent assay followed by Zika virus neutralizing antibody titers >10 on plaque reduction neutralization testing (PRNT). Women with PRNT titers >10 for dengue virus in addition to Zika virus were considered to have probable Zika virus infection and were included in the primary analysis but excluded in a sensitivity analysis. Women with no or negative reported Zika virus results were considered to have no Zika virus infection during pregnancy. Infants with laboratory evidence of Zika virus infection and no postnatal exposure to Zika virus before testing were considered to have congenital Zika virus infection. The mothers of these neonates were considered to have confirmed Zika virus infection during pregnancy, regardless of their own Zika virus test results. Zika virus laboratory results were obtained from the Health Department's Bureau of Communicable Disease surveillance database.

Pregnancy- and birth-related data were obtained from NYC birth records. Delivery was classified as preterm (24–36 completed weeks) or term (37-42 completed weeks). SGA was defined as birth weight <10th percentile for gestational age and sex according to INTERGROWTH-21st, an international growth standard.[15,16] Infants with birth weight <400 or >6000 grams, or gestational age <24 or >42 completed weeks were excluded. Mothers were classified by self-reported age, highest educational achievement, race/ethnicity and geographic area of birth. We categorized Dominican Republic separately from other Caribbean countries as a large proportion of all Caribbean-born women delivering in NYC were born in the Dominican Republic.[13] We used 2012–2016 American Community Survey data to classify neighborhood poverty (proportion of residents with household incomes <100% of the Federal Poverty Level) according to census tract of maternal residence for NYC residents. Clinical information for mothers included self-reported smoking status 3 months prior to or during pregnancy, parity, and pre-pregnancy body mass index (BMI). Pre-existing hypertension, gestational hypertension, and pre-eclampsia/eclampsia were categorized as hypertensive disorders; pre-existing and gestational diabetes were categorized as diabetes.

We compared demographic and clinical characteristics between women with and without antenatal Zika virus infection using χ^2 tests. We evaluated the association of antenatal Zika virus infection with SGA and preterm birth using Poisson regression with a robust error variance,[17] and with mean birth weight for term neonates using linear regression. No women with antenatal Zika virus infection self-identified as non-Hispanic White and none reported smoking during or in the 3 months prior to pregnancy, therefore we restricted our analyses to

women of black, Hispanic and other race and ethnicity, and to non-smokers. Because the majority of women with antenatal Zika virus infection were born outside the United States, and nativity is a predictor of adverse birth outcomes in the United States,[18] we also adjusted for geographic area of birth. Based on literature review, for the models with SGA neonate as the outcome, we additionally adjusted for parity (primiparous vs. multiparous) and for the models with preterm birth as the outcome, we additionally adjusted for maternal age.[19–22] We did not include other covariates in these models because of the limited number of SGA and preterm birth outcomes among women with antenatal Zika virus infection.[23] For the birth weight model, we adjusted for geographic area of birth and the following variables: maternal age, parity, race and ethnicity, education, neighborhood poverty, pre-pregnancy BMI, hypertensive disorder, diabetes, completed weeks of gestation and neonate sex.

In a secondary analysis, we assessed whether congenital, and not maternal, Zika virus infection was associated with lower birth weight, SGA, and preterm birth by comparing these outcomes in the subgroup of neonates born to women with antenatal Zika virus infection, by neonate Zika virus test result. Due to the small sample size for these analyses, we did not conduct statistical testing on these data.

We conducted four sensitivity analyses by repeating the primary analyses as follows: 1) to address possible misclassification of Zika virus infection, we restricted the Zika virus-infected group to women with confirmed infection; 2) to reduce potential for undiagnosed Zika virus infection in the unexposed group, we excluded from this group women who had emigrated from a country with a reported Zika virus outbreak in 2015–2016,[24] within 12 months of their neonate's birth; 3) to address potential residual confounding, given nearly all the women with antenatal Zika virus infection were foreign-born, we restricted all analyses to women born in countries with a reported Zika virus outbreak in 2015–2016; and 4) to evaluate whether results were dependent on growth reference characteristics, we used a reference based on a U.S., rather than an international, population.[25]

The sample size for our study was determined by the number of cases of Zika virus identified in pregnant women in NYC during 2016. We set statistical significance at $\alpha = 0.05$. All analyses were conducted in SAS 9.4 (SAS Institute Inc, Cary, NC). This work used previously collected de-identified birth certificate and surveillance data and therefore was classified as exempt from review by the Health Department's Institutional Review Board.

Results

In 2016, a total of 116,034 women gave birth to a singleton neonate in NYC; 251 (0.2%) had antenatal Zika virus infection. After exclusions, 74,955 (64.6%) women remained for analysis (Figure 1). In this cohort, a higher proportion of women with Zika virus infection during pregnancy were in their first pregnancy, age <20 years, identified as non-Hispanic black, and were born outside of the United States (Table 1). Other demographic and clinical variables had comparable distributions in both groups.

Twenty-eight (11.2%) women with Zika virus infection during pregnancy and 4,340 (5.8%) women without Zika virus infection gave birth to an SGA neonate; after adjustment, the risk

of having an SGA neonate was 1.8 times higher for women with antenatal Zika virus infection (95% CI, 1.3 – 2.6) (Table 2). For women with and without antenatal Zika virus infection, prevalence of preterm birth was 8.8% and 7.8%, respectively; there was no association between antenatal Zika virus infection and preterm birth in the adjusted model, however, confidence intervals were wide (RR, 1.0; 95% CI, 0.69 – 1.6). Mean birth weight of the 228 neonates born at term to women with antenatal Zika virus infection was 3256 ± 479 grams compared to 3303 ± 447 grams for the 68,861 term neonates born to women without Zika virus infection; this difference was not significant in crude or adjusted analyses.

Of the 250 neonates born to women with Zika virus infection during pregnancy, 202 (80.8%) had Zika virus testing after birth; 20 neonates (9.9%) had laboratory evidence of congenital Zika virus infection (Table 3). The proportion of neonates born SGA and preterm were similar for neonates with positive and negative Zika virus testing (10.0% vs. 11.5%, and 5.0% vs. 7.1%, respectively), and the difference in mean birth weight between these two groups was 133 grams.

In the sensitivity analysis restricted to the 73 women (29.2% of Zika virus-positive women) with confirmed Zika virus infection (i.e., excluding those with probable Zika virus infection), the adjusted risk ratio of SGA was 2.8 (95% CI, 1.7 – 4.6) (Appendix 1, available online at http://links.lww.com/AOG/B624). Term neonates born to women with confirmed Zika virus infection had lower mean birth weight than those born to women with no Zika virus infection (adjusted difference, −110 grams, 95% CI, −204 – −16 grams). Excluding 3,069 women in the unexposed group who had recently emigrated from a country with mosquito-borne Zika virus transmission gave similar results to the main analyses, as did analyses restricted to 24,323 NYC women who were born in these countries (Appendix 2, available online at http://links.lww.com/AOG/B624). When we defined SGA according to a U.S.-based growth reference,[25] more neonates were classified as SGA (13.4% vs. 5.8% using INTERGROWTH-21st). Using this reference, antenatal Zika virus infection was associated with 1.5 times higher risk of having an SGA neonate (95% CI, 1.1 – 1.9) (Appendix 2, http://links.lww.com/AOG/B624).

Discussion

Women with antenatal Zika virus infection were more likely to have an SGA neonate compared with women with no Zika virus infection in this cohort of non-White women in NYC. This difference remained significant after controlling for parity and region of origin, and was robust across several sensitivity analyses. Prevalence of preterm delivery and birth weight of term neonates were similar in both groups. These findings provide supportive evidence for the hypothesis that antenatal Zika virus infection might be associated with SGA, but do not support an association with preterm birth or birth weight at term.

To date, few studies of antenatal Zika virus infection have compared birth outcomes for women with and without laboratory evidence of Zika virus during pregnancy. Brasil *et al*[9] enrolled women with fever in pregnancy and compared those who tested positive for Zika virus with those with negative Zika virus testing, some of whom were diagnosed with

chikungunya virus. Despite this morbidity in the comparison group, investigators found a non-statistically significant higher proportion of SGA in the Zika virus-positive group (8.6% vs 5.3%, p = .06). Similar to our findings, preterm birth risk in that study did not differ between the two groups. A smaller U.S. study[26] compared 29 women with laboratory evidence of Zika virus infection with women with potential exposure to Zika virus but negative testing and found no difference in birth weight or risk of SGA or preterm birth.

In our cohort, antenatal Zika virus infection was associated with a higher risk of SGA, however only two neonates of 20 with congenital Zika virus infection were SGA. This raises several possible hypotheses. First, antenatal Zika virus infection may be associated with SGA even without congenital Zika virus infection. Studies of other viruses have suggested that maternal infection during pregnancy may impair placental function and affect fetal growth, even without transmission of the virus to the fetus.[3,27,28] In mouse models, Zika virus shows tropism for placental tissue and induces pathologic changes that cause placental insufficiency resulting in fetal growth restriction.[29] Thus, Zika virus might induce growth restriction in the absence of congenital infection, resulting in neonates who are SGA. A study of 66 pregnant women in NYC with possible Zika virus infection found a pattern of femur-sparing fetal growth restriction in the majority, while few neonates had laboratory evidence of congenital Zika virus infection when tested after birth.[30] Second, congenital Zika virus infection may have been under-ascertained in our cohort. In our study, 20% of neonates born to mothers with probable or confirmed Zika virus were not themselves tested for Zika virus. Also, sensitivity of Zika virus testing in neonates is unknown. Though we found that very few SGA neonates born to women with Zika virus infection during pregnancy themselves had laboratory evidence of Zika virus infection, it is possible more SGA neonates were affected by congenital Zika virus infection than were detected by routine testing of neonate serum and urine.

SGA can co-occur with microcephaly, the primary neonate outcome of antenatal Zika virus infection studied to date. For symmetrically small neonates with SGA, head circumference may meet criteria for microcephaly due to growth restriction and not disrupted brain development, particularly if no abnormalities are detected on neuroimaging.[31] Silva *et al.*[32] found fetal growth restriction was strongly associated with microcephaly. Understanding the association of antenatal Zika virus infection and fetal growth can inform the evaluation of neonates with congenital Zika virus exposure and microcephaly. Longitudinal studies of neurodevelopment for infants with congenital Zika virus exposure will be important for understanding whether risk of adverse outcomes differs between SGA and appropriate-for-gestational-age neonates.

SGA is a relative measure dependent on a specific growth reference or standard. Using the INTERGROWTH-21st Growth Standard,[16] recommended by the CDC for the evaluation of neonates with possible Zika virus exposure[33] and commonly used in published studies about Zika virus.[9,34] only 5.8% of neonates in this cohort were in the lowest 10th percentile of birth weight. Reasons for this may include the exclusion of diabetic women and those with BMI >30kg/m^2 from the INTERGROWTH-21st derivation cohort, as these women typically give birth to larger babies.[16,35] Supporting this hypothesis, our sensitivity analysis using a

U.S.-derived growth reference classified over 13% of NYC neonates as SGA. However, the results of our analyses were not sensitive to the growth reference chosen.

Strengths of this study include the relatively large cohort of women with probable or confirmed Zika virus infection and use of birth record data; the latter enabled us to control for maternal nativity, as a high proportion of NYC women diagnosed with antenatal Zika virus infection were born outside the United States. However, the results are subject to several limitations. Some women may have had Zika virus infection but were misclassified as uninfected because they were tested after molecular and serologic evidence could be detected, they were not tested in NYC, or not tested at all. Next, as serologic testing for Zika virus is subject to cross-reactivity with other flaviviruses,[36] some positive Zika virus results might reflect infection with another flavivirus (e.g., dengue), and not Zika virus. However, sensitivity analyses addressing these possible forms of misclassification supported our findings.

Despite the larger size of our cohort, some analyses had sample sizes too small to analyze and confidence intervals that did not allow us to rule out either protective or harmful effects of antenatal Zika virus infection. Although we were able to control for many important predictors of birth weight, residual confounding might have influenced our findings. Medical co-morbidities and smoking during pregnancy often are poorly documented in birth certificate data,[37,38] potentially explaining the very low estimates of smoking in this cohort. Information about maternal characteristics and medical conditions obtained from birth certificates may be inaccurate, therefore models adjusting for these variables may not fully remove confounding. Of note, as the self-reported variables used for the birth certificate are usually documented at the first obstetric visit, most women would have provided these data prior to receiving information on their Zika virus infection status, thereby diminishing potential recall bias related to Zika virus infection status.

Trimester of Zika virus infection during pregnancy may be associated with differential risk of adverse outcomes; however, given the large proportion of women who had an asymptomatic infection and whose laboratory evidence of Zika virus infection was serological and not molecular in nature, we did not have sufficient data on timing of infection to address this question. Lastly, we only included live births in this analysis. Pregnancies affected by fetal growth restriction may result in miscarriage, stillbirth or abortion. As such, an analysis of live births may underestimate the association between antenatal Zika virus infection and growth restriction.

In summary, among women who gave birth in NYC in 2016, we found Zika virus infection during pregnancy was associated with higher risk of SGA. Prospective studies of women with Zika virus infection during pregnancy are needed to validate this finding.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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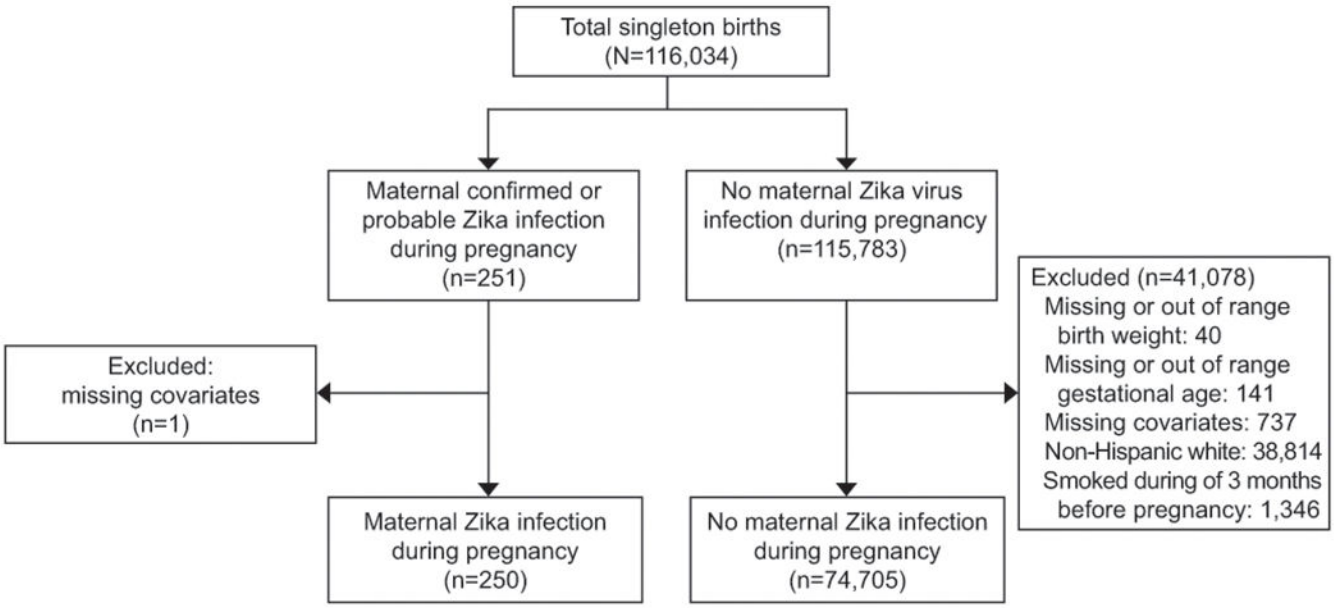

Figure 1:
Singleton deliveries by maternal Zika virus infection status, New York City, 2016.

Table 1:

Characteristics of non-White women who delivered liveborn singleton neonates in New York City, 2016, by Zika virus infection in pregnancy status

	Maternal confirmed and probable Zika virus infection, n (%)	No maternal Zika virus infection, n (%)	P value
Total women	250 (100)	74,705 (100)	
Male neonate	135 (54.0)	38,074 (51.0)	0.34
Nulliparous	121 (48.4)	32,091 (43.0)	0.08
Age			<0.001
<20 years	23 (9.2)	2,892 (3.9)	
20–34 years	175 (70.0)	55,123 (73.8)	
≥35 years	52 (20.8)	16,690 (22.3)	
Race/ethnicity			<0.001
Hispanic	124 (49.6)	32,006 (42.8)	
Black, non-Hispanic	107 (42.8)	20,562 (27.5)	
Other	19 (7.6)	22,127 (29.6)	
Geographic area of birth			<0.001
United States[†]	19 (7.6)	27,721 (37.1)	
Dominican Republic	94 (37.6)	7,415 (9.9)	
Other Caribbean country	112 (44.8)	7,007 (9.4)	
South/Central America	19 (7.6)	10,929 (14.6)	
Rest of world	6 (2.4)	21,633 (29.0)	
Highest education			<0.001
< High school	52 (20.8)	16,498 (22.1)	
High school/GED	80 (32.0)	17,927 (24.0)	
Some college	74 (29.6)	19,183 (25.7)	
Graduated college	44 (17.6)	21,097 (28.2)	
Neighborhood poverty level[*]			0.10
Low (<10%)	30 (12.0)	10,009 (13.4)	
Medium (10–<20%)	61 (24.4)	19,007 (25.4)	
High (20–<30%)	66 (26.4)	17,672 (23.7)	
Very high (30–100%)	86 (34.4)	23,053 (30.9)	
Non-NYC resident	7 (2.8)	4,964 (6.6)	
Hypertensive disorder	22 (8.8)	7,405 (9.9)	0.56
Diabetes	24 (9.6)	8,131 (10.9)	0.52
Pre-pregnancy body mass index			0.48
<18.5 kg/m^2	13 (5.2)	4,046 (5.4)	
18.5–24.9 kg/m^2	108 (43.2)	35,572 (47.6)	
25–29.9 kg/m^2	71 (28.4)	20,132 (27.0)	

	Maternal confirmed and probable Zika virus infection, n (%)	No maternal Zika virus infection, n (%)	P value
≥30 kg/m^2	58 (23.2)	14,955 (20.0)	

Notes: Restricted to women who self-identified as Black, Hispanic or Other race and ethnicity (non-Hispanic White women excluded) and non-smokers. P values reported for χ^2 tests.

*Neighborhood poverty level defined by the % residents in a census tract with incomes below 100% of the Federal Poverty Level. This information was available for NYC residents only.

†Includes Puerto Rico

Table 2:

Singleton birth outcomes for women with and without Zika virus infection, New York City, 2016

Outcome	Maternal Zika virus infection n = 250	No maternal Zika virus infection n = 74,705	Unadjusted risk ratio or mean difference† (95% CI)	Adjusted* risk ratio or mean difference† (95% CI)
Small-for-gestational-age neonates, n (%)	28 (11.2)	4,340 (5.8)	1.9 (1.4 – 2.7)	1.8 (1.3 – 2.6)
Preterm neonates, n (%)	22 (8.8)	5,844 (7.8)	1.1 (0.75 – 1.7)	1.0 (0.69 – 1.6)
Mean birth weight of term neonates ± SD (grams) ‡	3256 ± 479	3303 ± 447	−47 (−105 – 11)	−41 (−94 – 12)

Notes: Restricted to women who self-identified as black, Hispanic and other race and ethnicity (non-Hispanic white women excluded) and non-smokers. SD, standard deviation; CI, confidence interval.

*SGA model adjusted for parity and geographic area of birth. Preterm model adjusted for age and geographic area of birth. Birth weight model adjusted for age, parity, geographic area of birth, race and ethnicity, education, neighborhood poverty, pre-pregnancy body mass index, hypertensive disorder, diabetes, completed weeks gestation and neonatal sex.

†Comparisons of proportion small-for-gestational-age neonates and preterm neonates are risk ratios; comparison of mean birth weight for term neonates is the mean difference

‡Includes neonates born between 37 and 42 completed weeks only. Maternal Zika virus infection, n = 228. No maternal Zika virus infection, n=68,861.

Table 3:

Among singleton neonates born to women with Zika virus infection, risk of SGA, preterm birth and birth weight of term neonates, by neonatal Zika virus test results, New York City, 2016

Outcome	Positive Zika virus test in neonate n = 20	Negative Zika virus test in neonate n = 182
Small-for-gestational-age neonates, n (%)	2 (10.0)	21 (11.5)
Preterm neonates, n (%)	1 (5.0)	13 (7.1)
Mean birth weight of term neonates ± SD (grams) *	3149 ± 556	3282 ± 468

Notes: Because of small numbers and limited power to discern differences, no statistical results were performed on these data.

Of the 250 neonates born to women with Zika virus infection during pregnancy, 48 did not get tested for Zika virus infection after birth and are not included in this table.

* Includes neonates born between 37 and 42 completed weeks only. Positive Zika virus test in neonate, n=19; Negative Zika virus test in neonate, n=169

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