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Infectious Disease: *Original Research*

Maternal Zika Virus Infection

Association With Small-for-Gestational-Age Neonates and Preterm Birth

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OBJECTIVE: 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 in 2016 to data for pregnant women with Zika virus infection reported to the New York City Health Department. We restricted the analysis to nonsmoking, nonwhite 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 New York City 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% 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 g less (95% CI −105 to 11 g); this difference was not statistically significant in crude or adjusted analyses.

CONCLUSION: For a cohort of New York City 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.

(Obstet Gynecol 2019;134:1197–204)

DOI: 10.1097/AOG.0000000000003577

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] Small-for-gestational-age and preterm neonates are at higher risk of morbidity and mortality in infancy

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This publication was supported (in part) by the Epidemiology and Laboratory Capacity (ELC) for Infectious Diseases Cooperative Agreement (Grant Number: NU50CK000407) funded by the Centers for Disease Control and Prevention (CDC). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of CDC or the Department of Health and Human Services. Dominique Heinke was supported in part by Training Grant T32HD060454 from the National Institutes of Health and Training Grant T03MC07648 from the Health Resources and Services Administration of the U.S. Department of Health and Human Services.

The authors thank the New York City health care community, without which this work would not be possible; Sharon K. Greene, PhD, MPH, who provided epidemiologic consultation; and the following New York City Health Department staff who contributed to this work: Danielle Bloch, Sandhya Clarke, Gili Hrusa, Corinne Thompson, and Public Health Laboratory Zika testing staff.

Each author has confirmed compliance with the journal's requirements for authorship.

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Financial Disclosure

The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/19

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 neonates with microcephaly and congenital Zika virus infection found 29% to be SGA,[7] whereas, 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 has not detected local mosquito-borne transmission of Zika virus, more than 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 New York City 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 New York City Health Department Bureau of Vital Statistics birth record data for all liveborn singleton neonates born during 2016 in New York City and surveillance data for cases of Zika virus infection diagnosed in New York City residents in 2016. Beginning in February 2016, the Health Department advised New York City 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 New York City 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 Zika virus in pregnant women were matched to New York City 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 6 weeks before the last menstrual period, or delivery of a 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 greater than 10 on plaque reduction neutralization testing. Women with plaque reduction neutralization testing titers greater than 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. Neonates 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 New York City birth records. Delivery was classified as preterm (24–36 completed weeks of gestation) or term (37–42 completed weeks of gestation). Small-for-gestational-age was defined as birth weight less than the 10th percentile for gestational age and sex according to INTERGROWTH-21st, an international growth standard.[15,16] Neonates with birth weight less than 400 g or higher than 6,000 g, or gestational age less than 24 or greater than 42 completed weeks of gestation 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 New York City 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 less than 100% of the federal poverty level) according to census tract of maternal residence for New York City residents. Clinical information for mothers included self-reported smoking status 3 months before or during pregnancy,

parity, and prepregnancy body mass index (BMI, calculated as weight in kilograms divided by height in meters squared). Preexisting hypertension, gestational hypertension, and preeclampsia or eclampsia were categorized as hypertensive disorders; preexisting 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 before pregnancy, therefore we restricted our analyses to women of black, Hispanic, and other race and ethnicity, and to nonsmokers. 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, prepregnancy 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. Owing 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 that 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 New York City during 2016. We set statistical significance at $\alpha=0.05$. All analyses were conducted in SAS 9.4. 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 New York City; 251 (0.2%) had antenatal Zika virus infection. After exclusions, 74,955 (64.6%) women remained for analysis (Fig. 1). In this cohort, a higher proportion of women with antenatal Zika virus infection were in their first pregnancy, aged younger than 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 antenatal Zika virus infection 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, CIs were wide (relative risk 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 3,256±479 g vs 3,303±447 g 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 antenatal Zika virus infection, 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

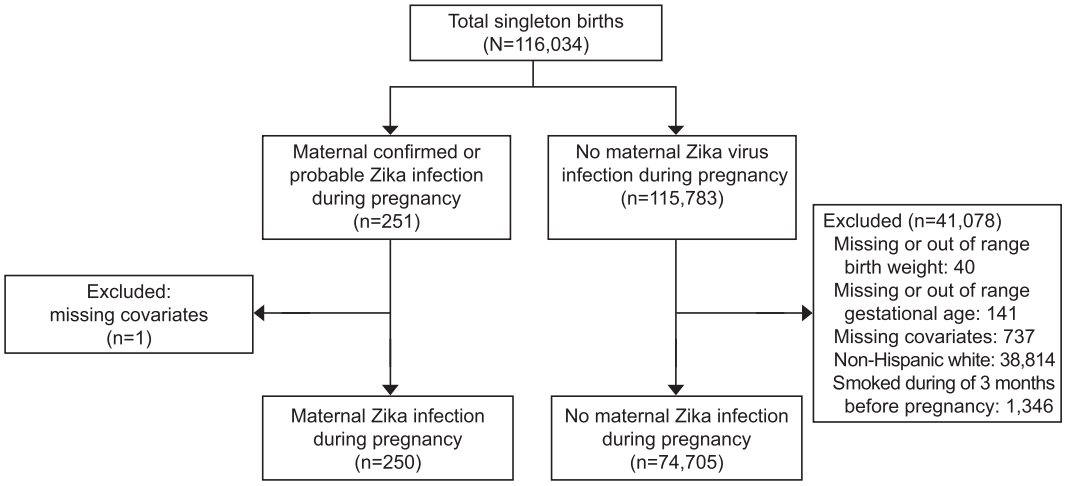

Fig. 1. Singleton deliveries by maternal Zika virus infection status, New York City, 2016.
Cooper. Maternal Zika Virus Infection and SGA. Obstet Gynecol 2019.

SGA and preterm were similar for neonates with positive and negative Zika virus test results (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 g.

In the sensitivity analysis restricted to the 73 women (29.2% of Zika virus–positive women) with confirmed Zika virus infection (ie, 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 g, 95% CI −204 to −16 g). 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 New York City 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 nonwhite women in New York City. 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 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 test results, some of whom were diagnosed with chikungunya virus. Despite this morbidity in the comparison group, investigators found a not-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 test results 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

Table 1. Characteristics of Nonwhite Women Who Delivered Liveborn Singleton Neonates in New York City, 2016, by Zika Virus Infection in Pregnancy Status

Characteristic	Maternal Confirmed and Probable Zika Virus Infection	No Maternal Zika Virus Infection	*P*
Total women	250 (100)	74,705 (100)	
Male neonate	135 (54.0)	38,074 (51.0)	.34
Nulliparous	121 (48.4)	32,091 (43.0)	.08
Age (y)			<.001
Younger than 20	23 (9.2)	2,892 (3.9)	
20–34	175 (70.0)	55,123 (73.8)	
35 or older	52 (20.8)	16,690 (22.3)	
Race–ethnicity			<.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			<.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 or Central America	19 (7.6)	10,929 (14.6)	
Rest of world	6 (2.4)	21,633 (29.0)	
Highest education			<.001
Less than high school	52 (20.8)	16,498 (22.1)	
High school or high school equivalency certificate	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†			.10
Low (less than 10%)	30 (12.0)	10,009 (13.4)	
Medium (10 to less than 20%)	61 (24.4)	19,007 (25.4)	
High (20 to less than 30%)	66 (26.4)	17,672 (23.7)	
Very high (30–100%)	86 (34.4)	23,053 (30.9)	
Non–New York City resident	7 (2.8)	4,964 (6.6)	
Hypertensive disorder	22 (8.8)	7,405 (9.9)	.56
Diabetes	24 (9.6)	8,131 (10.9)	.52
Prepregnancy BMI (kg/m^2)			.48
Less than 18.5	13 (5.2)	4,046 (5.4)	
18.5–24.9	108 (43.2)	35,572 (47.6)	
25–29.9	71 (28.4)	20,132 (27.0)	
30 or higher	58 (23.2)	14,955 (20.0)	

BMI, body mass index.
Data are n (%) unless otherwise specified.
Restricted to women who self-identified as black, Hispanic or other race–ethnicity (non-Hispanic white women excluded) and nonsmokers. *P* values reported for χ^2 tests.
* Includes Puerto Rico.
† Neighborhood poverty level defined by the percentage of residents in a census tract with incomes less than 100% of the federal poverty level. This information was available for New York City residents only.

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 New York City with possible Zika virus infection found a pattern of femur-sparing fetal growth restriction in the majority, whereas 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 antenatal Zika virus infection themselves had laboratory evidence of Zika virus infection, it is possible more SGA neonates were affected by

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 RR or Mean Difference (95% CI)*	Adjusted† RR or Mean Difference (95% CI)*
SGA neonate	28 (11.2)	4,340 (5.8)	1.9 (1.4 to 2.7)	1.8 (1.3 to 2.6)
Preterm neonate	22 (8.8)	5,844 (7.8)	1.1 (0.75 to 1.7)	1.0 (0.69 to 1.6)
Birth weight of term neonates (g)‡	3,256±479	3,303±447	−47 (−105 to 11)	−41 (−94 to 12)

RR, risk ratio; SGA, small for gestational age.
Data are n (%) or mean±SD unless otherwise specified.
Restricted to women who self-identified as black, Hispanic and other race and ethnicity (non-Hispanic white women excluded) and nonsmokers.
* Comparisons of proportion of SGA neonates and preterm neonates are shown as RRs; comparison of mean birth weight for term neonates is shown as mean difference.
† Small-for-gestational-age 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, prepregnancy body mass index, hypertensive disorder, diabetes, completed weeks of gestation, and neonatal sex.
‡ Includes neonates born between 37 and 42 completed weeks of gestation only. Maternal Zika virus infection, n=228. No maternal Zika virus infection, n=68,861.

congenital Zika virus infection than were detected by routine testing of neonate serum and urine.

Small-for-gestational-age 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 owing 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.

Small-for-gestational-age 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 women with diabetes and those with BMIs higher than 30 from the INTERGROWTH-21st derivation cohort, because these women typically give birth to larger neonates.[16,35] Supporting this hypothesis, our sensitivity analysis using a U.S.-derived growth reference classified more than 13% of New York City neonates as SGA. However,

Table 3. Among Singleton Neonates Born to Women With Zika Virus Infection, Risk of Small-For-Gestational-Age and Preterm Birth and Birth Weight of Term Neonates, by Neonatal Zika Virus Test Results, New York City, 2016

	Neonatal Zika Virus Test Result	
Outcome	Positive (n=20)	Negative (n=182)
SGA neonate	2 (10.0)	21 (11.5)
Preterm neonate	1 (5.0)	13 (7.1)
Birth weight of term neonates (g)*	3,149±556	3,282±468

SGA, small for gestational age.
Data are n (%) or mean±SD.
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 antenatal Zika virus infection, 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 of gestation only. Positive neonatal Zika virus test result, n=19; negative neonatal Zika virus test result, n=169.

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, because a high proportion of New York City 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 New York City, or not tested at all. Next, because 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 (eg, 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 CIs 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 comorbidities 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, because the self-reported variables used for the birth certificate are usually documented at the first obstetric visit, most women would have provided these data before 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 serologic 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 New York City 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.

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PEER REVIEW HISTORY

Received April 30, 2019. Received in revised form August 19, 2019. Accepted August 29, 2019. Peer reviews and author correspondence are available at http://links.lww.com/AOG/B625.