

Neonatal health of infants born to mothers with asthma

Pauline Mendola, PhD,^a Tuija I. Männistö, MD, PhD,^a Kira Leishear, PhD,^b Uma M. Reddy, MD, MPH,^c Zhen Chen, PhD,^d and S. Katherine Laughon, MD, MS^a Rockville, Md

Background: Maternal asthma is associated with serious pregnancy complications, but newborn morbidity is understudied.

Objective: We wanted to determine whether infants of asthmatic mothers have more neonatal complications.

Methods: The Consortium on Safe Labor (2002-2008), a retrospective cohort, included 223,512 singleton deliveries at ≥ 23 weeks' gestation. Newborns of mothers with asthma ($n = 17,044$) were compared with newborns of women without asthma by using logistic regression models with generalized estimating equations to calculate adjusted odds ratios (ORs) and 95% CIs. Electronic medical record data included gestational week at delivery, birth weight, resuscitation, neonatal intensive care unit (NICU) admission, NICU length of stay, hyperbilirubinemia, respiratory distress syndrome, apnea, sepsis, anemia, transient tachypnea of the newborn, infective pneumonia, asphyxia, intracerebral hemorrhage, seizure, cardiomyopathy, periventricular or intraventricular hemorrhage, necrotizing enterocolitis, aspiration, retinopathy of prematurity, and perinatal mortality.

Results: Preterm delivery was associated with maternal asthma for each week after 33 completed weeks of gestation and not earlier. Maternal asthma also increased the adjusted odds of small for gestational age (OR = 1.10; 95% CI, 1.05-1.16), NICU admission (OR = 1.12; 95% CI, 1.07-1.17), hyperbilirubinemia (OR = 1.09; 95% CI, 1.04-1.14), respiratory distress syndrome (OR = 1.09; 95% CI, 1.01-1.19), transient tachypnea of the newborn (OR = 1.10; 95% CI, 1.02-1.19), and asphyxia (OR = 1.34; 95% CI, 1.03-1.75). Findings persisted for term infants (≥ 37 weeks) who had additional increased odds of intracerebral hemorrhage (OR = 1.84; 95% CI, 1.11-3.03) and anemia (OR = 1.30; 95% CI, 1.04-1.62).

Conclusions: Maternal asthma was associated with prematurity and small for gestational age. Adverse neonatal outcomes, including respiratory complications, hyperbilirubinemia, and NICU admission, were increased in association with maternal

asthma even among term deliveries. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

Key words: Neonatal health, maternal asthma, respiratory distress syndrome, transient tachypnea of the newborn, neonatal jaundice, preterm birth

Maternal asthma is the most common chronic disease in pregnancy,¹ and the rate of asthma reported during labor and delivery has nearly doubled between 1993-1997 and 2001-2005.² A recent meta-analysis concluded that maternal asthma increased the risk of preeclampsia, low-birth weight, and infants small for gestational age (SGA), as well as preterm delivery.³ In addition, we recently reported that women with asthma in the Consortium on Safe Labor (CSL) also have increased risk of serious obstetric complications, including placental abruption and pulmonary embolism, as well as a higher likelihood of maternal admission to the intensive care unit.⁴ Because pregnancy, labor, and delivery complications are elevated among asthmatic mothers, their neonates may be expected to also have increased risks of complications. Indeed, a recent systematic review and meta-analysis found maternal asthma increased the risk of congenital malformations, perinatal mortality, and neonatal hospitalization.⁵ However, few detailed analyses have been conducted to compare the neonatal health of the offspring of women with asthma with women without asthma, especially for less-frequent adverse perinatal outcomes.

Few population-based studies have examined neonatal risks beyond preterm birth and growth restriction. Two historic population-based cohorts evaluated a small set of neonatal outcomes associated with maternal asthma^{6,7}; however, both had relatively modest numbers of asthmatic women which limited their statistical power. Transient tachypnea of the newborn has been associated with maternal asthma in prior studies with the association reported to be stronger in male and term infants.⁷ An increased risk of hyperbilirubinemia was reported among infants of mothers who took corticosteroids to manage their asthma, but no association was observed for other asthmatic mothers, making it unclear whether this association was due to more severe maternal disease or a drug effect.⁶

The objective of this study was to examine whether the infants of asthmatic mothers experience a greater burden of complications during the newborn hospital admission than infants of nonasthmatic mothers in a recent, large, nationwide US cohort of singleton newborns.

METHODS

The CSL included 12 clinical centers (with 19 hospitals) across 9 American Congress of Obstetricians and Gynecologists US districts. Details of the study and data collection procedures are described elsewhere.⁸ Briefly, electronic medical records and discharge *International Classification of Diseases, Ninth Revision* (ICD-9) codes from both mother and infant hospital records were

From ^athe Epidemiology Branch, ^bthe Division of Epidemiology, Statistics, and Prevention Research (DESPR), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD); ^cthe Pregnancy and Perinatology Branch, NICHD; and ^dthe Bioinformatics and Biostatistics Branch, DESPR, NICHD.

Supported by the Intramural Research Program of the National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development. The Consortium on Safe Labor was supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, through contract no. HHSN267200603425C.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication May 16, 2013; revised June 13, 2013; accepted for publication June 17, 2013.

Corresponding author: Pauline Mendola, PhD, National Institute of Child Health and Human Development, 6100 Executive Blvd, Rm 7B03F, Rockville, MD 20852. E-mail: pauline.mendola@nih.gov.

0091-6749

<http://dx.doi.org/10.1016/j.jaci.2013.06.012>

Abbreviations used

CSL: Consortium on Safe Labor
 ICD-9: *International Classification of Diseases, Ninth Revision*
 LGA: Large for gestational age
 NICU: Neonatal intensive care unit
 OR: Odds ratio
 SGA: Small for gestational age

available for 228,562 deliveries among 208,695 women from 2002 to 2008. This analysis was restricted to singleton infants ($n = 223,512$) among 204,180 women. Most women ($n = 185,785$; 91.0%) contributed only 1 pregnancy. Women with >1 pregnancy could contribute to both the “no asthma” and “asthma” groups if they were diagnosed with asthma between pregnancies. Once an asthma diagnosis was recorded, it was assumed to affect all subsequent pregnancies. No information on asthma treatment was available in the delivery admission medical records. Institutional review board approval was obtained by all participating institutions.

Most neonatal complications, as well as the diagnosis of maternal asthma, were recorded in the medical record and supplemented with ICD-9 codes from discharge summaries (see Table E1 in this article's Online Repository at www.jacionline.org). Neonatal complications studied included perinatal mortality (defined as fetal deaths of >23 weeks' gestation, intrapartum deaths, and neonatal deaths within the first week of life), delivery room resuscitation and the level needed, neonatal intensive care unit (NICU) admission, NICU length of stay, hyperbilirubinemia, respiratory distress syndrome, apnea, sepsis, anemia, transient tachypnea of the newborn, pneumonia, asphyxia, intracerebral hemorrhage, seizure, cardiomyopathy, periventricular or intraventricular hemorrhage, necrotizing enterocolitis, aspiration, and retinopathy of prematurity. Gestational age and birth weight were reported both as continuous and categorized variables. We calculated the average gestational age and conducted fetuses-at-risk models,⁹ comparing the risk of delivery at each gestational week from 23 to 37 weeks (eg, <24 weeks compared with ≥ 24 weeks, <25 weeks compared with ≥ 25 weeks, etc). SGA (lowest 10% of birth weight for age and sex) and large for gestational age (LGA; highest 10% of birth weight for age and sex) were calculated on the basis of the distributions in our data after excluding missing or implausible values ($n = 2649$; 1.2%) and infants with unknown or ambiguous sex ($n = 316$; 0.1%).¹⁰

Covariates selected for inclusion in risk models were based on our prior study of obstetric risks associated with maternal asthma.⁴ In addition, we evaluated mode of delivery and infant sex as potential confounders. Mode of delivery (vaginal or cesarean section) was included in final models, but infant sex was not associated with maternal asthma.

The neonate was the unit of analysis for all statistical testing. Descriptive statistics were calculated for all study variables, and significance testing was based on either logistic or Poisson regression with the use of generalized estimating equations to account for correlations between multiple pregnancies contributed by the same woman. Odds ratios (ORs) and 95% CIs were calculated with a first-order autoregressive covariance structure that compared infants born to women with and without asthma. All reported ORs were adjusted for site, and fully adjusted models included site, maternal age, maternal race/ethnicity, marital status, pre-pregnancy body mass index (weight divided by height; kg/m^2), insurance status, smoking and alcohol use during pregnancy, presence of chronic disease (pre-existing diabetes, chronic hypertension, thyroid disease, or HIV), parity, and mode of delivery.

Additional analyses were stratified by infant sex and restricted to term infants (≥ 37 weeks). Multiple sensitivity analyses were conducted to test the robustness of our findings, given potential bias or error in medical record ascertainment, including restriction to women with ICD-9-coded asthma, removing sites with asthma rates at the tails of the distribution (2 sites each at the high and the low end), restriction to sites with complete data, restriction to infants with no missing data, and, finally, restriction to neonates from nulliparous women. Results from these analyses yielded similar findings, so only the main analysis is presented. All statistical analyses were performed with PROC GENMOD in SAS software version 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

Newborns of mothers with asthma were more likely to be preterm, weighed significantly less, and were more likely to be delivered by cesarean section, particularly after induction or spontaneous labor (Table I). The proportion of male and female infants was similar in both groups.

In fully adjusted models (Table II), we observed the expected differences in outcomes related to fetal growth. Term infants of mothers with asthma were more likely to weigh <2500 g (2.9% vs 2.2%; OR = 1.13; 95% CI, 1.02-1.26) and less likely to weigh ≥ 4000 g (7.2% vs 8.4%; OR = 0.84; 95% CI, 0.79-0.90) than infants of mothers without asthma. Weight for gestational age had a similar pattern, with increased odds of SGA (11.9% vs 9.8%; OR = 1.10; 95% CI, 1.05-1.16) and lower odds of LGA (9.2% vs 10.0%; OR = 0.91; 95% CI, 0.86-0.96).

Newborns whose mothers had asthma were more likely to be admitted to the NICU (15.2% vs 11.9%; OR = 1.12; 95% CI, 1.07-1.17) but had a similar NICU length of stay as infants of nonasthmatic mothers. Hyperbilirubinemia was increased when mothers had asthma (OR = 1.09; 95% CI, 1.04-1.14) as were the odds of respiratory distress syndrome (4.1% vs 3.2%; OR = 1.09; 95% CI, 1.01-1.19), transient tachypnea of the newborn (4.6% vs 3.5%; OR = 1.10; 95% CI, 1.02-1.19), and asphyxia (0.4% vs 0.3%; OR = 1.34; 95% CI, 1.03-1.75). No differences in perinatal mortality, delivery room resuscitation, apnea, sepsis, anemia, pneumonia, intracerebral hemorrhage, seizure, cardiomyopathy, periventricular or intraventricular hemorrhage, necrotizing enterocolitis, aspiration, and retinopathy of prematurity were observed in the adjusted analyses.

Examining the risk of preterm birth at each gestational week found that risks were comparable between women with and without asthma before 33 weeks and became significantly increased at 34, 35, and 36 completed weeks for infants born to mothers with asthma (Fig 1).

No substantive differences were observed when analyses were stratified by infant sex (see Tables E2 and E3 in this article's Online Repository at www.jacionline.org), although these analyses had less precision because of smaller sample sizes. Restricting the analyses to term infants also yielded similar findings (see Table E4 in this article's Online Repository at www.jacionline.org) with additional elevated odds of anemia (OR = 1.30; 95% CI, 1.04-1.62) and intracerebral hemorrhage (OR = 1.84; 95% CI, 1.11-3.03).

DISCUSSION

Asthma is known to increase complications during pregnancy, labor, and delivery,⁴ including increased risk of preeclampsia, preterm delivery, low birth weight, and SGA.³ In this large US cohort study, we also found increased risk of neonatal complications associated with maternal asthma that persisted after adjustment for mode of delivery and maternal clinical and demographic factors. Newborns of mothers with asthma were more likely to be admitted to the NICU, to experience hyperbilirubinemia, and to have higher risk of respiratory complications, including respiratory distress syndrome, transient tachypnea of the newborn, and asphyxia. Among term infants born to mothers with asthma, the risk of these neonatal morbidities were still higher with additional increased risk of intracerebral hemorrhage and anemia compared with term neonates born to mothers without asthma. Our large sample permitted a novel analysis of preterm birth risk at each

TABLE I. Infant characteristics among singleton pregnancies with and without maternal asthma (n = 223,512), CSL, 2002-2008

Infant characteristics	No asthma (n = 206,468)	Asthma (n = 17,044)	P value*
Sex, no. (%)			
Female	100,644 (48.9)	8,353 (49.1)	.62
Male	105,354 (51.1)	8,646 (50.9)	
Unknown	470 (0.2)	45 (0.3)	
Gestational age (wk), mean $\pm$ SD	38.6 $\pm$ 2.3	38.4 $\pm$ 2.5	<.0001
Term (≥ 37 wk), no. (%)	182,850 (88.6)	14,518 (85.2)	<.0001
34-36 wk, no. (%)	15,719 (7.6)	1,653 (9.7)	
29-33 wk, no. (%)	5,194 (2.5)	631 (3.7)	
23-28 wk, no. (%)	2,705 (1.3)	242 (1.4)	
Route of delivery, no. (%)			
Vaginal	149,199 (72.3)	11,721 (68.8)	<.0001
Cesarean section (all)	57,269 (27.7)	5,323 (31.2)	<.0001
Prelabor	23,688 (41.4)	2,193 (41.2)	
After induction	14,746 (25.7)	1,381 (25.9)	
After spontaneous labor	18,835 (32.9)	1,749 (32.9)	
Birth weight (g), mean $\pm$ SD†	3,249.6 $\pm$ 604.4	3,173.5 $\pm$ 629.6	<.0001
Singleton infants per woman, no. (%)			
1	172,355 (91.2)	14,074 (90.7)	.06
2	15,878 (8.4)	1,355 (8.7)	
3	724 (0.4)	80 (0.5)	
4	45 (0.02)	5 (0.03)	
5	1 (<0.01)	0 (0.0)	

*Determined by generalized estimating equations that account for multiple pregnancies to the same woman and adjusted for site.

†Birth weight was missing or implausible for 2,486 infants: 2,347 (1.1%) and 139 (0.8%) for neonates of mothers without and with asthma, respectively.

gestational week from 23 to 37, and we observed that the increase in risk associated with maternal asthma was only significantly elevated after 33 weeks. We also found the anticipated decrements in fetal growth and birth weight among the infants of asthmatic mothers. Given the increasing prevalence of asthma in women of reproductive age, it is reassuring that we did not observe an increased risk of perinatal mortality, apnea, sepsis, pneumonia, seizure, cardiomyopathy, periventricular or intraventricular hemorrhage, necrotizing enterocolitis, aspiration, or retinopathy of prematurity among the newborns of mothers with asthma.

With respect to respiratory complications, our finding for asphyxia appears to be novel with a >30% increased risk among newborns of asthmatic mothers. The risk of asphyxia was also increased >80% in a sensitivity analysis restricted to term infants. Transient tachypnea of the newborn has been previously reported in association with maternal asthma, but studies were either unadjusted for cesarean delivery¹¹ or had relatively small numbers of mothers with asthma.^{7,11,12} We report an independent increase in the risk of transient tachypnea of the newborn, even after controlling for important risk factors such as cesarean delivery, as well as other maternal clinical and demographic characteristics. Both of the historic cohorts evaluated respiratory distress syndrome and reported nonsignificantly elevated point estimates,^{6,7} which is consistent with our finding of a significant increase in risk associated with maternal asthma, given that we have greater statistical power.

The mechanisms underlying the effect of maternal asthma and neonatal respiratory complications are not clear. It is possible that some newborn respiratory complications are due to shared genetic factors with their asthmatic mothers. For example, infants of asthmatic mothers may have variations in surfactant protein A haplotypes that could confer a nonspecific risk of less optimal respiratory function.¹³ Animal studies also suggest potential genetic pathways associated with β -adrenergic hyporesponsiveness,¹⁴

which may interfere with pulmonary fluid resorption and decreased production that normally occurs after birth.¹⁵

In our data, the odds of neonatal jaundice were elevated among infants born to women with asthma, which was not entirely consistent with findings from one other cohort study with 817 asthmatic women from Halifax County in Nova Scotia.⁶ In that study, hyperbilirubinemia was increased but only among the small subgroup of infants of asthmatic mothers (17% of the sample) who took steroids, resulting in 18 cases among 139 infants. Infants whose mothers took no medication (46%) or β -agonists only (37%) had no jaundice risk with OR of 1.0 (95% CI, 0.6-1.6) and 1.0 (95% CI, 0.6-1.7), respectively. The investigators hypothesized that this could have been due to a drug effect, but whether the risk was due to more severe maternal disease was unable to be determined. It is important to note that prior studies have identified neonatal jaundice¹⁶ or treatment for jaundice¹⁷ as a predictor of childhood asthma, but these reports have not taken maternal asthma into account. Perhaps maternal asthma, which increases risk of asthma among offspring,¹⁸ is a common cause for both neonatal jaundice and childhood asthma. This intriguing possibility merits further study.

We conducted several sensitivity analyses to assess the robustness of our findings. Results restricted to term births are reported to lessen any potential bias due to unmeasured confounding, given that preterm birth could operate as a potential mediator of the neonatal effects under study.^{19,20} Although the association between maternal asthma and preterm birth was strong, it is important to note that the infant complications we observed were not primarily a function of prematurity. In general, the odds of adverse outcomes were higher for term infants.

Infant sex has been posited as an influential effect modifier of both maternal and fetal/infant outcomes associated with maternal asthma,²¹ perhaps because of sexually dimorphic placental characteristics²² or a difference in adaptation to pregnancy determined

TABLE II. Infant outcomes for singleton deliveries among US women with and without asthma, CSL, 2002-2008

Outcomes	No asthma (n = 206,468)	Asthma (n = 17,044)	Site-adjusted P value*	Site-adjusted odds ratio (95% CI)*	Fully adjusted odds ratio (95% CI)†
Perinatal mortality, no. (%)‡	1,333 (0.7)	129 (0.8)	.18	1.13 (0.94-1.36)	1.10 (0.92-1.33)
Level of resuscitation in delivery room CPAP or higher, no. (%)§	3,431 (1.7)	354 (2.1)	.17	1.08 (0.97-1.21)	1.02 (0.91-1.14)
Term birth weight, no. (%)					
<2500 g	3,929 (2.2)	412 (2.9)	<.0001	1.26 (1.13-1.39)	1.13 (1.02-1.26)
2500-3999 g (reference)	161,951 (89.5)	12,976 (89.9)			
≥4000 g	15,133 (8.4)	1,041 (7.2)	<.0001	0.84 (0.79-0.90)	0.84 (0.79-0.90)
Size for gestational age, no. (%)¶					
SGA	20,256 (9.8)	2,008 (11.8)	<.0001	1.18 (1.13-1.25)	1.10 (1.05-1.16)
AGA (reference)	163,094 (79.0)	13,315 (78.1)			
LGA	20,616 (10.0)	1,574 (9.2)	.001	0.91 (0.86-0.96)	0.91 (0.86-0.96)
NICU admission, no. (%)	24,656 (11.9)	2,589 (15.2)	<.0001	1.22 (1.17-1.28)	1.12 (1.07-1.17)
NICU length of stay (d), mean ± SD	17.3 ± 27.9	17.0 ± 24.7	.65	0.99 (0.92-1.05)	0.96 (0.90-1.02)
Hyperbilirubinemia, no. (%)	30,252 (14.7)	2,554 (15.0)	.001	1.06 (1.02-1.10)	1.09 (1.04-1.14)
Respiratory distress syndrome, no. (%)	6,641 (3.2)	694 (4.1)	<.0001	1.21 (1.11-1.31)	1.09 (1.01-1.19)
Apnea, no. (%)#	4,272 (2.3)	447 (2.7)	.12	1.08 (0.98-1.20)	1.02 (0.92-1.13)
Sepsis, no. (%)	5,659 (2.7)	570 (3.3)	.007	1.13 (1.03-1.24)	1.02 (0.93-1.12)
Anemia, no. (%)	3,826 (1.9)	381 (2.2)	.07	1.10 (0.99-1.23)	1.02 (0.92-1.14)
Transient tachypnea, no. (%)	7,230 (3.5)	783 (4.6)	<.0001	1.21 (1.12-1.30)	1.10 (1.02-1.19)
Infective pneumonia, no. (%)	1,291 (0.6)	132 (0.8)	.41	1.08 (0.90-1.30)	1.01 (0.84-1.22)
Asphyxia, no. (%)	527 (0.3)	63 (0.4)	.003	1.50 (1.15-1.95)	1.34 (1.03-1.75)
Intracerebral hemorrhage, no. (%)	519 (0.3)	52 (0.3)	.30	1.17 (0.87-1.56)	1.09 (0.81-1.46)
Seizure, no. (%)	419 (0.2)	50 (0.3)	.03	1.38 (1.03-1.87)	1.24 (0.92-1.69)
Cardiomyopathy, no. (%)	188 (0.1)	23 (0.1)	.85	1.04 (0.68-1.61)	0.91 (0.58-1.43)
Periventricular or intraventricular hemorrhage, no. (%)	1,192 (0.6)	119 (0.7)	.49	1.07 (0.88-1.29)	0.97 (0.80-1.18)
Necrotizing enterocolitis, no. (%)	420 (0.2)	35 (0.2)	.87	1.03 (0.72-1.48)	0.86 (0.60-1.23)
Aspiration, no. (%)	1,046 (0.5)	98 (0.6)	.51	1.07 (0.87-1.32)	1.00 (0.81-1.24)
Retinopathy of prematurity, no. (%)	932 (0.5)	77 (0.5)	.93	1.01 (0.80-1.28)	0.93 (0.73-1.18)

AGA, Appropriate for gestational age; CPAP, continuous positive airway pressure.

*Determined by generalized estimating equations that account for multiple pregnancies to the same woman.

†Adjusted for site; maternal age; maternal race/ethnicity; marital status; insurance; pre-pregnancy body mass index; smoking and alcohol use during pregnancy; history of either pre-existing diabetes, HIV, chronic hypertension, or thyroid disease; parity; and cesarean delivery.

‡Perinatal mortality was defined as intrauterine death, intrapartum death, or death during the first 7 days of NICU admission.

§Missing for 498 infants: 476 (0.2%) and 22 (0.1%) of mothers without and with asthma, respectively.

||Birth weight was missing or implausible for 2,486 infants: 2,347 (1.1%) and 139 (0.8%) for neonates of mothers without and with asthma, respectively.

¶SGA was defined as lowest 10% of birth weight for age and sex; LGA was defined as highest 10% of birth weight for age and sex; AGA was the reference category.

#Apnea is missing all observations from 1 study site (20,596 neonates).

by infant sex.²³ We observed similar effects among males and females, although with less precision than in the main analysis. Prior studies that report effect modification by preterm/term status and infant sex generally have elevated point estimates with substantially overlapping CIs, suggesting low statistical power and lack of precision as a likely explanation for the subgroup differences. For example, in a New Jersey cohort with <2300 asthma cases,⁷ maternal asthma increased the risk of transient tachypnea of the newborn for males (OR = 1.91; 95% CI, 1.35-2.71) but not significantly for females (OR = 1.51; 95% CI, 0.94-2.47) where precision was a bit less.

The major limitation of our study was the lack of information on asthma control, exacerbations, and treatment because these characteristics were not recorded in the delivery admission medical records. Several studies have shown that adverse outcomes are more common (or only occur) in pregnancies with poor asthma control.²⁴⁻²⁶ In a study conducted in the Maternal Fetal Medicine Units Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, no difference in perinatal risks were associated with asthma medication with the exception of inhaled corticosteroids that increased risks of preterm and low birth weight, likely a consequence of more severe

asthma. Presumably, the asthma cases in our study represent a mix of severity and treatment methods so we cannot evaluate how well our findings apply to the subgroup of women with well-controlled asthma. If treatment and good control do improve neonatal outcomes, then our findings are a conservative estimate of the effect of maternal asthma on infant health for women with more severe disease. Given that our data come from a nationwide study intended to capture current obstetric practice⁸ and were not selected in any way for asthma or other maternal morbidity, we feel confident that a proportion of the women studied had mild asthma or were well controlled, and yet the population level risks we observed for the infants of asthmatic mothers remained high for several serious neonatal complications. We considered the possibility that the electronic medical records could have been biased and more likely to include the diagnosis of maternal asthma when complications arose, but the overall prevalence of asthma we observed (7.6%) was similar to the general population estimates of 10% for women of reproductive age and of asthma in pregnancy reported in the early 2000s (4%-8%).¹ The lack of reporting bias is further supported by the fact that our findings were similar when analyses were restricted to maternal asthma coded in the discharge summary, in case asthma only noted in the medical

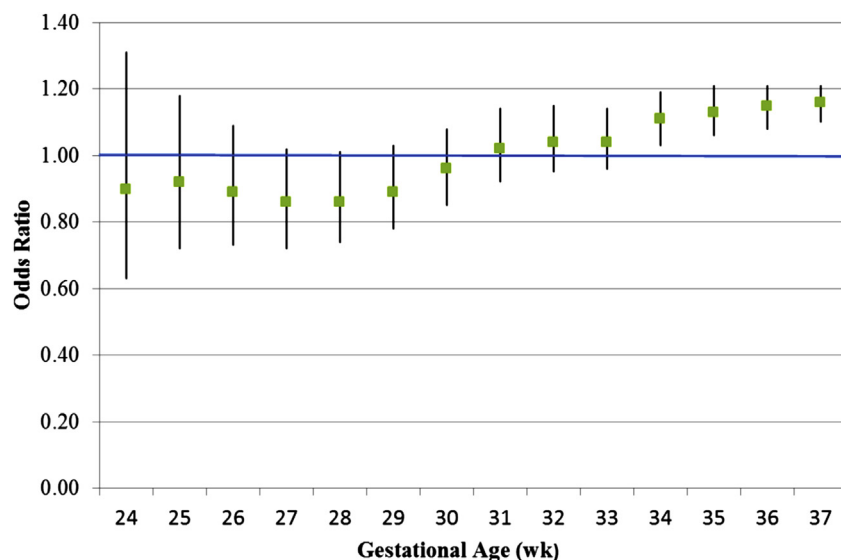


FIG 1. The ORs with 95% CIs of preterm birth for each gestational week for infants born to mothers with asthma compared with infants of mothers without asthma, with a fetuses-at-risk approach whereby each gestational age defines the cutoff of the comparison groups.

record was a childhood history or not active during pregnancy. Our results were also similar when we excluded sites that reported the highest and lowest prevalence of maternal asthma, suggesting that site-specific variations in reporting or true differences in asthma prevalence in the underlying populations did not drive the observed associations.

Our study is the largest to date with detailed clinical information on the effect of maternal asthma and the potential to investigate uncommon neonatal morbidities among >17,000 singleton infants of asthmatic mothers. The guidelines for treatment of asthma in pregnancy²⁷ and clinical strategies to manage asthma²⁸ are well described. Recent reports suggest that medication use is lower during early pregnancy than before pregnancy,^{29,30} which appears to be consistent with active step therapy, although it may also indicate a reluctance of patients to continue medications. To that end, patients should be reassured that continuing asthma medication during pregnancy at the level needed to control the disease is important to improve both maternal and fetal outcomes.³¹ An ongoing clinical trial is investigating enhanced monitoring of lung function during pregnancy as a strategy for improving maternal asthma control which may, in turn, improve obstetric and neonatal outcomes.³² Our findings suggest that more work needs to be done in this area to further reduce neonatal morbidity.

In conclusion, maternal asthma is the most common chronic disease in pregnancy and is known to increase risk of both preterm delivery and infant growth restriction. Our large contemporary US cohort allowed us to examine preterm risk for each gestational week from 23 to 37 and to evaluate serious but less common adverse neonatal outcomes. It is reassuring that earlier preterm birth was not increased among infants of women with asthma, with comparable risks from 23 to 33 weeks' gestation and significant increases appearing at 34, 35, and 36 weeks. Many serious complications were not elevated in newborns of asthmatic mothers despite their mothers' increased risk of pregnancy and obstetric complications.⁴ However, we did find a higher risk of NICU admission, hyperbilirubinemia, and respiratory

complications in neonates of mothers with asthma than in newborns of women without asthma, and these risks were independent of prematurity or the increase in cesarean delivery. In particular, respiratory distress syndrome, asphyxia, and transient tachypnea of the newborn occurred more frequently in infants whose mothers have asthma. Future work should consider the effect of maternal asthma on neonatal health, including whether optimizing maternal asthma control can mitigate newborn risks.

Institutions involved in the Consortium on Safe Labor include, in alphabetical order, Baystate Medical Center, Springfield, Mass; Cedars-Sinai Medical Center Burnes Allen Research Center, Los Angeles, Calif; Christiana Care Health System, Newark, Del; Georgetown University Hospital, MedStar Health, Washington, DC; Indiana University Clarian Health, Indianapolis, Ind; Intermountain Healthcare and the University of Utah, Salt Lake City, Utah; Maimonides Medical Center, Brooklyn, NY; MetroHealth Medical Center, Cleveland, Ohio; Summa Health System, Akron City Hospital, Akron, Ohio; The EMMES Corporation, Rockville Md (Data Coordinating Center); University of Illinois at Chicago, Chicago, Ill; University of Miami, Miami, Fla; and University of Texas Health Science Center at Houston, Houston, Texas.

Clinical implications: Both term and preterm infants of asthmatic mothers experience more newborn complications, including serious morbidity. Additional research is needed on asthma management during pregnancy to attempt to mitigate newborn morbidity.

REFERENCES

1. Kwon HL, Triche EW, Belanger K, Bracken MB. The epidemiology of asthma during pregnancy: prevalence, diagnosis, and symptoms. *Immunol Allergy Clin North Am* 2006;26:29-62.
2. Berg CJ, Mackay AP, Qin C, Callaghan WM. Overview of maternal morbidity during hospitalization for labor and delivery in the United States: 1993-1997 and 2001-2005. *Obstet Gynecol* 2009;113:1075-81.
3. Murphy VE, Namazy JA, Powell H, Schatz M, Chambers C, Attia J, et al. A meta-analysis of adverse perinatal outcomes in women with asthma. *BJOG* 2011;118:1314-23.

4. Mendola P, Laughon SK, Männistö TI, Leishear K, Reddy UM, Chen Z, et al. Obstetric complications among US women with asthma. *Am J Obstet Gynecol* 2013; 208:127-8.
5. Murphy V, Wang G, Namazy J, Powell H, Gibson P, Chambers C, et al. The risk of congenital malformations, perinatal mortality and neonatal hospitalisation among pregnant women with asthma: a systematic review and meta-analysis. *BJOG* 2013;120:812-22.
6. Alexander S, Dodds L, Armson BA. Perinatal outcomes in women with asthma during pregnancy. *Obstet Gynecol* 1998;92:435-40.
7. Demissie K, Marcella SW, Breckenridge MB, Rhoads GG. Maternal asthma and transient tachypnea of the newborn. *Pediatrics* 1998;102:84-90.
8. Zhang J, Troendle J, Reddy UM, Laughon SK, Branch DW, Burkman R, et al. Contemporary cesarean delivery practice in the United States. *Am J Obstet Gynecol* 2010;203:326.
9. Yudkin PL, Wood L, Redman CW. Risk of unexplained stillbirth at different gestational ages. *Lancet* 1987;1:1192-4.
10. Männistö T, Mendola P, Reddy U, Laughon SK. Neonatal outcomes and birth weight in pregnancies complicated by maternal thyroid disease. *Am J Epidemiol* 2013 [Epub ahead of print] DOI: 10.1093/aje/kwt031.
11. Clark JM, Hulme E, Devendrakumar V, Turner MA, Baker PN, Sibley CP, et al. Effect of maternal asthma on birthweight and neonatal outcome in a British inner-city population. *Paediatr Perinat Epidemiol* 2007;21:154-62.
12. Schatz M, Zeiger RS, Hoffman CP, Saunders BS, Harden KM, Forsythe AB. Increased transient tachypnea of the newborn in infants of asthmatic mothers. *Am J Dis Child* 1991;145:156-8.
13. Pettigrew MM, Gent JF, Zhu Y, Triche EW, Belanger KD, Holford TR, et al. Respiratory symptoms among infants at risk for asthma: association with surfactant protein A haplotypes. *BMC Med Genet* 2007;8:15.
14. Barnes PJ. Endogenous catecholamines and asthma. *J Allergy Clin Immunol* 1986; 77:791-5.
15. Wyszogrodski I, Taesch HW Jr, Avery ME. Isoxsuprine-induced alterations of pulmonary pressure-volume relationships in premature rabbits. *Am J Obstet Gynecol* 1974;119:1107-11.
16. Ku MS, Sun HL, Sheu JN, Lee HS, Yang SF, Lue KH. Neonatal jaundice is a risk factor for childhood asthma: a retrospective cohort study. *Pediatr Allergy Immunol* 2012;23:623-8.
17. Aspberg S, Dahlquist G, Kahan T, Kallen B. Confirmed association between neonatal phototherapy or neonatal icterus and risk of childhood asthma. *Pediatr Allergy Immunol* 2010;21:e733-9.
18. Martinez FD. Maternal risk factors in asthma. *Ciba Found Symp* 1997;206:233-9.
19. VanderWeele TJ, Mumford SL, Schisterman EF. Conditioning on intermediates in perinatal epidemiology. *Epidemiology* 2012;23:1-9.
20. Wilcox AJ, Weinberg CR, Basso O. On the pitfalls of adjusting for gestational age at birth. *Am J Epidemiol* 2011;174:1062-8.
21. Clifton VL, Davies M, Moore V, Wright IM, Ali Z, Hodyl NA. Developmental perturbation induced by maternal asthma during pregnancy: the short- and long-term impacts on offspring. *J Pregnancy* 2012;2012:741613.
22. Clifton VL. Sexually dimorphic effects of maternal asthma during pregnancy on placental glucocorticoid metabolism and fetal growth. *Cell Tissue Res* 2005;322: 63-71.
23. Dodds L, Armson BA, Alexander S. Use of asthma drugs is less among women pregnant with boys rather than girls. *BMJ* 1999;318:1011.
24. Enriquez R, Griffin MR, Carroll KN, Wu P, Cooper WO, Gebretsadik T, et al. Effect of maternal asthma and asthma control on pregnancy and perinatal outcomes. *J Allergy Clin Immunol* 2007;120:625-30.
25. Bakhireva LN, Schatz M, Jones KL, Chambers CD. Asthma control during pregnancy and the risk of preterm delivery or impaired fetal growth. *Ann Allergy Asthma Immunol* 2008;101:137-43.
26. Schatz M, Dombrowski MP, Wise R, Momirova V, Landon M, Mabie W, et al. Spirometry is related to perinatal outcomes in pregnant women with asthma. *Am J Obstet Gynecol* 2006;194:120-6.
27. National Asthma Education and Prevention Program. Working Group Report on Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment, Update 2004. Rockville, Md: Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute; 2005.
28. Dombrowski MP, Schatz M. ACOG practice bulletin: clinical management guidelines for obstetrician-gynecologists number 90, February 2008: asthma in pregnancy. *Obstet Gynecol* 2008;111:457-64.
29. Zetstra-van der Woude PA, Vroegop JS, Bos HJ, de Jong-van den Berg LT. A population analysis of prescriptions for asthma medications during pregnancy. *J Allergy Clin Immunol* 2013;131:711-7.
30. Enriquez R, Wu P, Griffin MR, Gebretsadik T, Shintani A, Mitchel E, et al. Cessation of asthma medication in early pregnancy. *Am J Obstet Gynecol* 2006;195: 149-53.
31. Dombrowski MP, Schatz M. Asthma in pregnancy. *Clin Obstet Gynecol* 2010;53: 301-10.
32. Lim A, Stewart K, Abramson MJ, Walker SP, George J. Multidisciplinary approach to management of maternal asthma (MAMMA [copyright]): the PROTOCOL for a randomized controlled trial. *BMC Public Health* 2012;12:1094.

TABLE E1. ICD-9 codes used to identify the neonatal complications in the CSL, 2002-2008

Definition in the present study	Collected ICD-9 codes	Definition
Hyperbilirubinemia	744.6	Unspecified fetal and newborn jaundice
	744.7	Kernicterus of fetus or newborn not due to isoimmunization
Respiratory distress syndrome	769	Respiratory distress syndrome
Intracerebral hemorrhage	767.0	Subdural and cerebral hemorrhage
	772.2	Subarachnoid hemorrhage
Seizure	779.0	Convulsions in the newborn
	780.32	Complex febrile convulsions
	780.39	Other convulsions
Cardiomyopathy	425	Cardiomyopathy
Periventricular or intraventricular hemorrhage	772.10-772.14	Intraventricular hemorrhage of fetus or newborn
Necrotizing enterocolitis	777.5	Necrotizing enterocolitis in newborn
Retinopathy of prematurity	362.21	Retinopathy of prematurity
Sepsis	771.81	Septicemia [sepsis] of newborn
	038	Septicemia
	995.91	Sepsis
	995.92	Severe sepsis
Transient tachypnea	770.6	Transitory tachypnea of newborn
Anemia	776.5	Congenital anemia
	776.6	Anemia of prematurity
Apnea	770.81	Primary apnea of newborn
	770.82	Other apnea of newborn
	786.03	Apnea
Asphyxia	768.5	Severe birth asphyxia
	768.6	Mild or moderate birth asphyxia
	768.9	Unspecified asphyxia in live born infant
Infectious pneumonia	480	Viral pneumonia
	481	Pneumococcal pneumonia
	482	Other bacterial pneumonia
	483	Pneumonia due to other specified organism
	484	Pneumonia in infectious diseases classified elsewhere
	485	Bronchopneumonia, organism unspecified
	486	Pneumonia, organism unspecified
	487.0	Influenza with pneumonia
	770.0	Congenital pneumonia
Aspiration	770.1	Fetal and newborn aspiration
	770.85	Aspiration of postnatal stomach contents without respiratory symptoms
	770.86	Aspiration of postnatal stomach contents with respiratory symptoms

TABLE E2. Female infant outcomes for singleton deliveries among US women with and without asthma, CSL, 2002-2008 (n = 108,997)

Outcomes	No asthma (n = 100,644)	Asthma (n = 8,353)	Site-adjusted P value*	Site-adjusted odds ratio (95% CI)*	Fully adjusted odds ratio (95% CI)†
Perinatal mortality, no. (%)‡	561 (0.6)	46 (0.6)	.92	0.98 (0.73-1.34)	0.96 (0.70-1.30)
Level of resuscitation in delivery room CPAP or higher, no. (%)§	1,533 (1.9)	162 (2.4)	.35	1.08 (0.92-1.28)	0.98 (0.82-1.16)
Term birth weight, no. (%)					
<2500 g	2,355 (2.7)	254 (3.6)	.0001	1.30 (1.14-1.49)	1.17 (1.02-1.34)
2500-3999 g (reference)	80,992 (91.2)	6,500 (91.2)			
≥4000 g	5,426 (6.1)	371 (5.2)	.0005	0.82 (0.74-0.92)	0.81 (0.73-0.91)
Size for gestational age, no. (%)¶					
SGA	9,911 (9.9)	963 (11.5)	<.0001	1.16 (1.08-1.25)	1.07 (0.99-1.15)
AGA (reference)	79,575 (79.1)	6,547 (78.4)			
LGA	10,047 (10.0)	790 (9.5)	.07	0.93 (0.86-1.01)	0.92 (0.85-1.00)
NICU admission, no. (%)	10,824 (10.8)	1,174 (14.1)	<.0001	1.27 (1.18-1.35)	1.15 (1.07-1.23)
NICU length of stay (d), mean ± SD	17.7 ± 28.4	17.1 ± 24.7		0.99 (0.90-1.08)	0.98 (0.89-1.07)
Hyperbilirubinemia, no. (%)	14,438 (14.4)	1,224 (14.7)	.02	1.06 (1.01-1.12)	1.09 (1.02-1.16)
Respiratory distress syndrome	2,780 (2.8)	308 (3.7)	<.0001	1.28 (1.13-1.45)	1.15 (1.01-1.30)
Apnea, no. (%)#	1,945 (2.1)	200 (2.5)	.47	1.06 (0.91-1.23)	0.98 (0.84-1.14)
Sepsis, no. (%)	2,472 (2.5)	266 (3.2)	.003	1.22 (1.07-1.39)	1.10 (0.96-1.26)
Anemia, no. (%)	1,836 (1.8)	183 (2.2)	.14	1.12 (0.96-1.31)	1.03 (0.88-1.20)
Transient tachypnea, no. (%)	2,920 (2.9)	319 (3.8)	.003	1.20 (1.07-1.36)	1.09 (0.96-1.23)
Infective pneumonia, no. (%)	512 (0.5)	54 (0.7)	.39	1.14 (0.85-1.51)	1.06 (0.79-1.42)
Asphyxia, no. (%)	229 (0.2)	28 (0.3)	.04	1.50 (1.01-2.23)	1.34 (0.89-2.00)
Intracerebral hemorrhage, no. (%)	227 (0.2)	29 (0.4)	.03	1.54 (1.04-2.29)	1.43 (0.97-2.13)
Seizure, no. (%)	175 (0.2)	22 (0.3)	.10	1.46 (0.93-2.30)	1.36 (0.86-2.16)
Cardiomyopathy, no. (%)	81 (0.1)	13 (0.2)	.26	1.40 (0.78-2.52)	1.39 (0.76-2.54)
Periventricular or intraventricular hemorrhage, no. (%)	503 (0.5)	57 (0.7)	.14	1.23 (0.93-1.63)	1.10 (0.83-1.45)
Necrotizing enterocolitis, no. (%)	179 (0.2)	15 (0.2)	.77	1.08 (0.63-1.86)	0.89 (0.52-1.52)
Aspiration, no. (%)	480 (0.5)	48 (0.6)	.31	1.17 (0.87-1.58)	1.09 (0.81-1.48)
Retinopathy of prematurity, no. (%)	453 (0.5)	46 (0.6)	.15	1.26 (0.92-1.71)	1.14 (0.83-1.55)

AGA, Appropriate for gestational age; CPAP, continuous positive airway pressure.

*Determined by generalized estimating equations that account for multiple pregnancies to the same woman.

†Adjusted for site; maternal age; maternal race/ethnicity; marital status; insurance; pre-pregnancy body mass index; smoking and alcohol use during pregnancy; history of either pre-existing diabetes, HIV, chronic hypertension, or thyroid disease; parity; and cesarean delivery.

‡Perinatal mortality was defined as intrauterine death, intrapartum death, or death during the first 7 days of NICU admission.

§Missing for 234 infants: 223 (0.2%) and 11 (0.1%) of mothers without and with asthma, respectively.

||Birth weight was missing or implausible for 1,095 infants: 1,044 (1.0%) and 51 (0.6%) for neonates of mothers without and with asthma, respectively.

¶SGA was defined as lowest 10% of birth weight for age and sex; LGA was defined as highest 10% of birth weight for age and sex; AGA was the reference category.

#Apnea is missing all observations from 1 study site (10,115 neonates).

TABLE E3. Male infant outcomes for singleton deliveries among US women with and without asthma, CSL, 2002-2008 (n = 114,000)

Outcomes	No asthma (n = 105,354)	Asthma (n = 8,646)	Site-adjusted P value*	Site-adjusted odds ratio (95% CI)*	Fully adjusted odds ratio (95% CI)†
Perinatal mortality, no. (%)‡	588 (0.6)	63 (0.7)	.06	1.28 (0.99-1.67)	1.24 (0.95-1.62)
Level of resuscitation in delivery room CPAP or higher, no. (%)§	1,873 (2.3)	190 (2.8)	.31	1.08 (0.93-1.26)	0.99 (0.84-1.16)
Term birth weight, no. (%)					
<2500 g	1,559 (1.7)	158 (2.2)	.03	1.20 (1.02-1.42)	1.09 (0.92-1.29)
2500-3999 g (reference)	80,846 (87.8)	6,470 (88.7)			
≥4000 g	9,697 (10.5)	666 (9.1)	<.0001	0.84 (0.78-0.92)	0.86 (0.79-0.93)
Size for gestational age, no. (%)¶					
SGA	10,310 (9.8)	1,040 (12.0)	<.0001	1.21 (1.13-1.30)	1.14 (1.06-1.22)
AGA (reference)	83,304 (79.1)	6,748 (78.1)			
LGA	10,532 (10.0)	780 (9.0)	.005	0.89 (0.83-0.97)	0.89 (0.82-0.96)
NICU admission, no. (%)	13,668 (13.0)	1,393 (16.1)	<.0001	1.18 (1.11-1.25)	1.09 (1.02-1.16)
NICU length of stay (d), mean ± SD	17.0 ± 27.4	16.9 ± 24.7	.74	0.99 (0.90-1.08)	0.95 (0.87-1.03)
Hyperbilirubinemia, no. (%)	15,769 (15.0)	1,328 (15.4)	.02	1.06 (1.01-1.12)	1.10 (1.03-1.17)
Respiratory distress syndrome, no. (%)	3,816 (3.6)	380 (4.4)	.01	1.15 (1.03-1.28)	1.04 (0.93-1.17)
Apnea, no. (%)#	2,313 (2.4)	243 (2.9)	.21	1.09 (0.95-1.25)	1.04 (0.91-1.19)
Sepsis, no. (%)	3,161 (3.0)	301 (3.5)	.35	1.06 (0.94-1.20)	0.96 (0.85-1.09)
Anemia, no. (%)	1,981 (1.9)	197 (2.3)	.28	1.09 (0.93-1.26)	1.02 (0.87-1.18)
Transient tachypnea, no. (%)	4,292 (4.1)	463 (5.4)	.0002	1.21 (1.10-1.34)	1.11 (1.01-1.23)
Infective pneumonia, no. (%)	775 (0.7)	78 (0.9)	.68	1.05 (0.83-1.33)	0.99 (0.78-1.25)
Asphyxia, no. (%)	295 (0.3)	33 (0.4)	.06	1.42 (0.99-2.04)	1.27 (0.88-1.82)
Intracerebral hemorrhage, no. (%)	290 (0.3)	23 (0.3)	.62	0.90 (0.58-1.38)	0.84 (0.54-1.30)
Seizure, no. (%)	244 (0.2)	28 (0.3)	.17	1.32 (0.89-1.97)	1.15 (0.77-1.74)
Cardiomyopathy, no. (%)	107 (0.1)	10 (0.1)	.45	0.78 (0.41-1.49)	0.63 (0.32-1.23)
Periventricular or intraventricular hemorrhage, no. (%)	687 (0.7)	61 (0.7)	.65	0.94 (0.72-1.23)	0.87 (0.66-1.14)
Necrotizing enterocolitis, no. (%)	240 (0.2)	20 (0.2)	.99	1.00 (0.63-1.59)	0.85 (0.53-1.36)
Aspiration, no. (%)	562 (0.5)	49 (0.6)	.89	0.98 (0.73-1.31)	0.93 (0.69-1.25)
Retinopathy of prematurity, no. (%)	479 (0.5)	31 (0.4)	.20	0.78 (0.54-1.14)	0.73 (0.50-1.07)

AGA, Appropriate for gestational age; CPAP, continuous positive airway pressure.

*Determined by generalized estimating equations that account for multiple pregnancies to the same woman.

†Adjusted for site; maternal age; maternal race/ethnicity; marital status; insurance; pre-pregnancy body mass index; smoking and alcohol use during pregnancy; history of either pre-existing diabetes, HIV, chronic hypertension, or thyroid disease; parity; and cesarean delivery.

‡Perinatal mortality was defined as intrauterine death, intrapartum death, or death during the first 7 days of NICU admission.

§Missing for 262 infants: 251 (0.2%) and 11 (0.1%) of mothers without and with asthma, respectively.

||Birth weight was missing or implausible for 1,194 infants: 1,122 (1.1%) and 72 (0.8%) for neonates of mothers without and with asthma, respectively.

¶SGA was defined as lowest 10% of birth weight for age and sex; LGA was defined as highest 10% of birth weight for age and sex; AGA was the reference category.

#Apnea is missing all observations from 1 study site (10,462 neonates).

TABLE E4. Term infant outcomes for singleton deliveries among US women with asthma, CSL, 2002-2008 (n = 197,368)

Outcomes	No asthma (n = 182,850)	Asthma (n = 14,518)	Site-adjusted P value*	Site-adjusted odds ratio (95% CI)*	Fully adjusted odds ratio (95% CI)†
Perinatal mortality, no. (%)‡	300 (0.2)	31 (0.2)	.25	1.24 (0.86-1.80)	1.23 (0.85-1.79)
Level of resuscitation in delivery room CPAP or higher, no. (%)§	1,575 (1.1)	154 (1.3)	.41	1.07 (0.91-1.27)	1.00 (0.84-1.18)
Size for gestational age, no. (%)					
SGA	17,919 (9.8)	1,764 (12.2)	<.0001	1.22 (1.16-1.29)	1.14 (1.08-1.20)
AGA (reference)	144,782 (79.2)	11,348 (78.2)			
LGA	18,290 (10.0)	1,316 (9.1)	.0002	0.89 (0.84-0.95)	0.89 (0.83-0.94)
NICU admission, no. (%)	12,619 (6.9)	1,233 (8.5)	<.0001	1.18 (1.11-1.26)	1.09 (1.02-1.16)
NICU length of stay (d), mean ± SD	6.0 ± 10.8	6.7 ± 12.6	.08	1.11 (0.99-1.26)	1.09 (0.96-1.23)
Hyperbilirubinemia, no. (%)	28,347 (15.5)	2,342 (16.1)	.0003	1.07 (1.03-1.12)	1.10 (1.05-1.15)
Respiratory distress syndrome, no. (%)	1,147 (0.6)	121 (0.8)	.004	1.32 (1.09-1.60)	1.22 (1.00-1.47)
Apnea, no. (%)¶	796 (0.5)	82 (0.6)	.17	1.17 (0.93-1.47)	1.13 (0.90-1.42)
Sepsis, no. (%)	2,255 (1.2)	206 (1.4)	.50	1.05 (0.91-1.22)	0.96 (0.83-1.11)
Anemia, no. (%)	789 (0.4)	90 (0.6)	.01	1.34 (1.07-1.67)	1.30 (1.04-1.62)
Transient tachypnea, no. (%)	4,757 (2.6)	459 (3.2)	.006	1.15 (1.04-1.27)	1.04 (0.94-1.15)
Infective pneumonia, no. (%)	662 (0.4)	63 (0.4)	.92	1.01 (0.78-1.32)	0.96 (0.73-1.25)
Asphyxia, no. (%)	287 (0.16)	35 (0.24)	.007	1.63 (1.14-2.33)	1.45 (1.01-2.07)
Intracerebral hemorrhage, no. (%)	123 (0.07)	20 (0.14)	.01	1.84 (1.13-3.01)	1.84 (1.11-3.03)
Seizure, no. (%)	189 (0.1)	22 (0.2)	.15	1.39 (0.89-2.18)	1.33 (0.84-2.10)
Cardiomyopathy, no. (%)	84 (0.1)	11 (0.1)	.61	1.18 (0.63-2.21)	1.05 (0.54-2.04)
Periventricular or intraventricular hemorrhage, no. (%)	118 (0.06)	18 (0.12)	.04	1.68 (1.02-2.78)	1.56 (0.93-2.61)
Necrotizing enterocolitis, no. (%)	40 (0.02)	2 (0.01)	.62	0.70 (0.17-2.85)	0.58 (0.14-2.42)
Aspiration, no. (%)	899 (0.5)	80 (0.6)	.75	1.04 (0.82-1.31)	0.97 (0.77-1.22)
Retinopathy of prematurity, no. (%)	22 (0.01)	4 (0.03)	.19	2.03 (0.70-5.87)	1.74 (0.57-5.36)

AGA, Appropriate for gestational age; CPAP, continuous positive airway pressure.

*Determined by generalized estimating equations that account for multiple pregnancies to the same woman.

†Adjusted for site; maternal age; maternal race/ethnicity; marital status; insurance; pre-pregnancy body mass index; smoking and alcohol use during pregnancy; history of either pre-existing diabetes, HIV, chronic hypertension, or thyroid disease; parity; and cesarean delivery.

‡Perinatal mortality was defined as intrauterine death, intrapartum death, or death during the first 7 days of NICU admission.

§Missing for 298 infants: 284 (0.2%) and 14 (0.1%) of mothers without and with asthma, respectively.

||SGA was defined as lowest 10% of birth weight for age and sex; LGA was defined as highest 10% of birth weight for age and sex; AGA was the reference category.

¶Apnea is missing all observations from 1 study site (19,250 neonates).