

OBSTETRICS

Obstetric complications among US women with asthma

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OBJECTIVE: We sought to characterize complications of pregnancy, labor, and delivery associated with maternal asthma in a contemporary US cohort.

STUDY DESIGN: We studied a retrospective cohort based on electronic medical record data from 223,512 singleton deliveries from 12 clinical centers across the United States from 2002 through 2008.

RESULTS: Women with asthma had higher odds of preeclampsia (adjusted odds ratio [aOR], 1.14; 95% confidence interval [CI], 1.06–1.22), superimposed preeclampsia (aOR, 1.34; 95% CI, 1.15–1.56), gestational diabetes (aOR, 1.11; 95% CI, 1.03–1.19), placental abruption (aOR, 1.22; 95% CI, 1.09–1.36), and placenta previa (aOR, 1.30; 95% CI, 1.08–1.56). Asthmatic women had a

higher odds of preterm birth overall (aOR, 1.17; 95% CI, 1.12–1.23) and of medically indicated preterm delivery (aOR, 1.14; 95% CI, 1.01–1.29). Asthmatics were less likely to have spontaneous labor (aOR, 0.87; 95% CI, 0.84–0.90) and vaginal delivery (aOR, 0.84; 95% CI, 0.80–0.87). Risks were higher for breech presentation (aOR, 1.13; 95% CI, 1.05–1.22), hemorrhage (aOR, 1.09; 95% CI, 1.03–1.16), pulmonary embolism (aOR, 1.71; 95% CI, 1.05–2.79), and maternal intensive care unit admission (aOR, 1.34; 95% CI, 1.04–1.72).

CONCLUSION: Maternal asthma increased risk for nearly all outcomes studied in a general obstetric population.

Key words: asthma, cesarean delivery, pregnancy complication, preterm birth

Cite this article as: Mendola P, Laughon SK, Männistö TI, et al. Obstetric complications among US women with asthma. *Am J Obstet Gynecol* 2013;208:127.e1-8.

Asthma is the most common chronic disease in pregnancy, complicating 4–8% of pregnancies nearly 10 years ago¹ and the rate of asthma continues to increase. Approximately 10% of US women of reproductive age had active asthma in 2008 through 2010² and 4.2% used a bronchodilator medication at least once during the past month during 2005 through 2008.³ In the National Hospital Discharge Survey, the rate of asthma reported during labor and deliv-

ery nearly doubled from 1993 through 1997 and from 2001 through 2005.⁴

A recent metaanalysis⁵ concluded that maternal asthma increased the risk of low-birthweight and small-for-gestational-age infants, preterm delivery, and preeclampsia. Other conditions, such as gestational diabetes and serious obstetric complications (eg, hemorrhage, placental abruption, and placenta previa), are not consistently associated with maternal asthma, possibly due to underlying

differences in patient populations, methodologic inadequacies (particularly for early studies), and relatively small numbers of women with asthma studied.⁶ Studies generally find that outcomes are more adverse when asthma is poorly controlled⁷ or when asthma is more severe,^{8,9} but few studies are large enough to examine specific risks for less common complications of pregnancy, labor, and delivery. The objectives of this study were to use a large, recent cohort of women in the United States to examine specific risks for complications of pregnancy, labor, and delivery including less frequent adverse outcomes and to explore the reasons for the increased risk of preterm delivery in women with asthma.

MATERIALS AND METHODS

The Consortium on Safe Labor included 12 clinical centers (with 19 hospitals) across 9 American Congress of Obstetricians and Gynecologists (ACOG) US districts. Details of the study and data collection procedures are described elsewhere.¹⁰ Briefly, centers provided electronic medical records and *International Classification of Diseases, Ninth Revision (ICD-9)* discharge codes from the intrapartum admission for 228,562 pregnancies among 208,695 women from 2002

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Received Aug. 6, 2012; revised Oct. 2, 2012; accepted Nov. 12, 2012.

This research was supported by the Intramural Research Program of the National Institutes of Health (NIH), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). The data included in this paper were obtained from the Consortium on Safe Labor, supported by the Intramural Research Program of the NIH, NICHD, through contract number HHSN267200603425C.

The authors report no conflict of interest.

Presented, in part, at the 23rd annual meeting of the International Society for Environmental Epidemiology, Barcelona, Spain, Sept. 13–16, 2011, with an updated analysis presented at the annual meeting of the American College of Epidemiology, Chicago, IL, Sept. 8–11, 2012.

Reprints not available from the authors.

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TABLE 1**ICD-9 diagnoses used to define asthma, chronic disease, and outcomes in Consortium on Safe Labor**

Definition in current study	Collected ICD-9 codes	Definition
Asthma	493-493.9	Asthma
Other chronic diseases		
Diabetes	250-250.9	Diabetes mellitus
	648.0	Other current conditions in mothers classifiable elsewhere but complicating pregnancy, childbirth, or puerperium—diabetes mellitus
Hypertension	401	Essential hypertension
	402	Hypertensive heart disease
	403	Hypertensive renal disease
	404	Hypertensive heart and renal disease
	405	Secondary hypertension
	642.0	Benign essential hypertension complicating pregnancy, childbirth, and puerperium
	642.1	Hypertension secondary to renal disease complicating pregnancy childbirth and puerperium
	642.2	Other preexisting hypertension complicating pregnancy, childbirth, and puerperium
Thyroid diseases	193	Malignant neoplasm of thyroid gland
	226	Benign neoplasm of thyroid glands
	240-240.9	Simple and unspecified goiter
	241-241.9	Nontoxic nodular goiter
	242-242.9	Thyrotoxicosis with or without goiter
	243	Congenital hypothyroidism
	244.0-244.9	Acquired hypothyroidism
	245-245.9	Thyroiditis
	246-246.9	Other disorders of thyroid
	648.1	Other current conditions in mothers classifiable elsewhere but complicating pregnancy, childbirth, or puerperium—thyroid dysfunction
HIV	42	HIV disease
Outcomes		
Gestational diabetes	648.8	Other current conditions in mothers classifiable elsewhere but complicating pregnancy, childbirth, or puerperium—abnormal glucose tolerance
Gestational hypertension	642.3	Transient hypertension of pregnancy
Preeclampsia	642.4	Mild or unspecified preeclampsia
	642.5	Severe preeclampsia
Superimposed preeclampsia	642.7	Preeclampsia or eclampsia superimposed on preexisting hypertension
Placental abruption	641.2	Premature separation of placenta

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(continued)

through 2008. The majority of the cohort (87%) delivered from 2005 through 2007. This analysis is restricted to singleton pregnancies ($n = 223,512$) among 204,180 women. Most women ($n = 185,785$; 83.1%) contributed only 1 pregnancy. Institutional review board approval was obtained by all participating institutions.

Most complications of pregnancy, labor, and delivery as well as the diagnosis of asthma were derived from medical record data supplemented with ICD-9 codes where available (Table 1). The source of case ascertainment (medical record or ICD-9 codes) varied by site. Overall, only 10.7% of asthma cases were reported in ICD-9 discharge codes alone while the remaining cases were noted in the medical record or both sources. We examined various obstetric outcomes including gestational hypertension, preeclampsia, superimposed preeclampsia, maternal seizure (with or without mention of hypertension), gestational diabetes, chorioamnionitis, placenta previa, placental abruption, hemorrhage, pulmonary embolism, postpartum fever, premature rupture of membranes (PROM), preterm PROM (PPROM) (defined as PROM <37 gestational weeks), and breech presentation.

Outcomes derived solely from medical records include prelabor cesarean delivery (defined as a cesarean delivery without any indication of labor and <2 vaginal examinations after admission to hospital), induction, spontaneous labor, route of delivery (vaginal or cesarean), preterm birth (<37 gestational weeks), low birthweight (<2500 g), intrauterine fetal death, maternal intensive care unit (ICU) admission, and maternal death.

Pregnancy was the unit of analysis for all statistical testing. Descriptive statistics were calculated for all study variables and significance testing was based on either linear or logistic regression using generalized estimating equations (GEE) to account for correlations between pregnancies contributed by the same woman. Odds ratios (ORs) and 95% confidence limits were calculated using logistic regression with GEE using a first-order autoregressive covariance structure. Pregnancies among women without asthma were the reference group in

all analyses. All reported odds are adjusted for site and fully adjusted models included site, maternal age, race/ethnicity, marital status, prepregnancy body mass index (weight in kg/height in m²), insurance status, smoking and alcohol use during pregnancy, presence of chronic disease (preexisting diabetes, chronic hypertension, thyroid disease, or human immunodeficiency virus), and parity. Women with chronic hypertension were excluded from the analyses of gestational hypertension and preeclampsia. Women with preexisting diabetes were excluded from the analyses of gestational diabetes. In the analyses of superimposed preeclampsia, women with chronic hypertension were not categorized as having a chronic disease unless they had another chronic condition. Analyses regarding labor and route of delivery were also adjusted for prior cesarean delivery.

Multiple sensitivity analyses were conducted, first 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 as these women may be more likely to have active asthma (as opposed to a history); 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; and finally, restriction to patients with no missing data. Results from these logistic regression with GEE analyses yielded similar findings, so only the full sample analysis is presented. We also ran 2 subgroup analyses: (1) restricted to nulliparas to explore the potential for residual confounding by history of preterm delivery, cesarean delivery, or other prior complications in multiparas, and (2) restricted to preterm deliveries to determine if the precursors of preterm delivery were different for women with asthma.

All statistical analyses were performed using PROC GENMOD in SAS software (version 9.2; SAS Institute Inc, Cary, NC).

RESULTS

Maternal asthma complicated 7.6% of singleton pregnancies. Mothers with

TABLE 1

ICD-9 diagnoses used to define asthma, chronic disease, and outcomes in Consortium on Safe Labor (continued)

Definition in current study	Collected ICD-9 codes	Definition
Placenta previa	641.0	Placenta previa without hemorrhage
	641.1	Hemorrhage from placenta previa
Pulmonary embolism	415.1	Pulmonary embolism and infarction
	673	Obstetrical pulmonary embolism
Hemorrhage	666-666.3	Postpartum hemorrhage
Chorioamnionitis	658.4	Infection of amniotic cavity
	762.7	Chorioamnionitis
Preterm rupture of membranes	658.1	Premature rupture of membranes
Breech presentation	652.2	Breech presentation without mention of version
Fever	672	Pyrexia of unknown origin during puerperium

HIV, human immunodeficiency virus; ICD-9, International Classification of Diseases, Ninth Revision.

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asthma were younger (26.2 vs 27.5 years, $P < .0001$) and more likely to be non-Hispanic black, be unmarried, and have public insurance than their counterparts without asthma (Table 2). Women with asthma were more likely to be obese prior to pregnancy and more likely to have smoking (12.2% vs 6.2%, $P < .0001$) or alcohol use (3.1% vs 1.7%, $P < .0001$) during pregnancy recorded in their medical records. Pregnancies complicated by asthma had a significantly greater burden of other chronic diseases as well (8.2% vs 6.2%, $P < .0001$). Parity was similar among pregnancies with and without asthma but among multiparas, women with asthma had more prior cesarean deliveries (15.3% vs 14.0%, $P < .0001$).

Analyses of the complications of pregnancy, labor, and delivery encountered by women with and without asthma (Table 3) demonstrate a general pattern of increased risk for asthmatic pregnancies.

Hypertensive disorders of pregnancy and maternal seizure

Fully adjusted models indicate increased odds of superimposed preeclampsia (adjusted OR [aOR], 1.34; 95% confidence interval [CI], 1.15–1.56) and preeclampsia (aOR, 1.14; 95% CI, 1.06–1.22). Ec-

lampsia was significantly associated with maternal asthma in site-adjusted models (OR, 1.61; 95% CI, 1.10–2.36) but the risk was attenuated after full adjustment (aOR, 1.41; 95% CI, 0.96–2.07). After observing a significant relationship between asthma and maternal seizure, we stratified seizures by hypertension status and found the increased risk of maternal seizure was primarily in the hypertensive group (aOR, 2.37; 95% CI, 1.40–4.02), suggesting that eclampsia may not have been fully captured in our dataset. Gestational hypertension was elevated in site-adjusted models but not significant after further adjustment.

Other pregnancy complications

Gestational diabetes (aOR, 1.11; 95% CI, 1.03–1.19) and placenta previa (aOR, 1.30; 95% CI, 1.08–1.56) were both increased, but chorioamnionitis was similar in pregnancies with and without asthma.

Complications of labor and delivery

Asthmatic pregnancies had an increased likelihood of being scheduled for prelabor cesarean delivery (aOR, 1.16; 95% CI, 1.09–1.23) or of being induced (aOR, 1.10; 95% CI, 1.06–1.14) compared to pregnancies without asthma. Asthmatic women were more likely to

TABLE 2

Characteristics of mothers with and without asthma

Maternal characteristics	No asthma n = 206,468	Asthma n = 17,044	Site-adjusted P value ^a
Demographic factors			
Maternal age, y mean (SD)	27.5 (6.2)	26.6 (6.2)	< .0001
Race, n (%)			
Non-Hispanic white	102,447 (49.6)	8156 (47.9)	< .0001
Non-Hispanic black	44,840 (21.7)	5444 (31.9)	
Hispanic	36,543 (17.7)	2288 (13.4)	
Asian	8970 (4.3)	211 (1.2)	
Other	4966 (2.4)	265 (1.6)	
Missing	8702 (4.2)	680 (4.0)	
Marital status, n (%)			
Not married	76,248 (36.9)	8765 (51.4)	< .0001
Married	123,800 (60.0)	7461 (43.8)	
Missing	6420 (3.1)	818 (4.8)	
Insurance, n (%)			
Private	116,084 (56.2)	8883 (52.1)	< .0001
Public	65,097 (31.5)	7105 (41.7)	
Other	2774 (1.3)	208 (1.2)	
Missing	22,513 (10.9)	848 (5.0)	
Pregnancies per woman, n (%)			
1	172,355 (91.2)	14,074 (90.7)	
2	15,878 (8.4)	1355 (8.7)	
3	724 (0.4)	80 (0.5)	
4	45 (0.02)	5 (0.03)	
5	1 (< .01)	0 (0.0)	
Clinical factors			
Prepregnancy BMI, kg/m², n (%)			
Underweight, <18.5	7517 (3.6)	463 (2.7)	< .0001
Normal weight, 18.5–<25	74,442 (36.1)	4641 (27.2)	
Overweight, 25–<30	30,909 (15.0)	2614 (15.3)	
Obese, 30–<35	14,212 (6.9)	1530 (9.0)	
Severely obese, ≥35	10,553 (5.1)	1605 (9.4)	
Unknown	68,835 (33.3)	6191 (36.3)	
Smoking during pregnancy, n (%)	12,858 (6.2)	2075 (12.2)	< .0001
Alcohol during pregnancy, n (%)	3559 (1.7)	532 (3.1)	< .0001
Preexisting diabetes, n (%)	2931 (1.4)	381 (2.2)	< .0001
Chronic hypertension, n (%)	3733 (1.8)	480 (2.8)	< .0001

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(continued)

PROM was similar in pregnancies with and without asthma (7.1% vs 7.0%, $P = .98$) but PPRM was higher in asthmatics (3.0% vs 2.2%, $P < .0001$). Fetal presentation also varied by asthma status with more breech presentations among pregnancies complicated by asthma (aOR, 1.13; 95% CI, 1.05–1.22).

With regard to severe complications, the odds of placental abruption (aOR, 1.22; 95% CI, 1.09–1.36), hemorrhage (aOR, 1.09; 95% CI, 1.03–1.16), pulmonary embolism (aOR, 1.71; 95% CI, 1.05–2.79), and maternal ICU admission (aOR, 1.34; 95% CI, 1.04–1.72) were all significantly increased in pregnancies with asthma but there was no difference in postpartum fever and maternal death.

As anticipated, both low birthweight (aOR, 1.16; 95% CI, 1.10–1.23) and preterm delivery (aOR, 1.17; 95% CI, 1.12–1.23) were increased in pregnancies with asthma but the odds of intrauterine fetal death were not significantly higher compared to pregnancies without asthma. Restricting these analyses to nulliparas yielded similar findings (data not shown).

With respect to preterm delivery (Table 4), we found no significant differences in prelabor cesarean deliveries (aOR, 1.06; 95% CI, 0.95–1.19), spontaneous labor (aOR, 0.93; 95% CI, 0.85–1.01), or induction (aOR, 1.04; 95% CI, 0.94–1.15) and women with asthma were no more likely than those without to have a cesarean delivery. However, further examination of the precursors of preterm delivery demonstrated that women with asthma had more medically indicated preterm deliveries (aOR, 1.14; 95% CI, 1.01–1.29) and were less likely to deliver preterm after a spontaneous process (labor or PPRM) (aOR, 0.89; 95% CI, 0.81–0.97).

COMMENT

Women with asthma begin pregnancy with a less favorable profile of demographic, lifestyle, and clinical risk factors including increased obesity, increased smoking, and a higher burden of other chronic diseases. Even after adjustment for these and other risk factors, asthma

have a cesarean delivery than women without asthma regardless of whether they present in spontaneous labor (10.3 vs 9.1%, $P = .0003$) or undergo labor

induction (8.1% vs 7.1%, $P < .0001$). As a result, pregnancies with maternal asthma had a lower odds overall of vaginal delivery (aOR, 0.84; 95% CI, 0.80–0.87).

was independently associated with higher odds for nearly all complications of pregnancy, labor, and delivery under study. Notably, asthmatic women experienced more serious complications including preeclampsia, preterm birth, cesarean delivery, placenta previa, placental abruption, hemorrhage, and pulmonary embolism, with a 34% increased odds of ICU admission. Neonates born to women with asthma were also more likely to be low birthweight.

Our findings are consistent with the recent review and metaanalysis by Murphy et al⁵ that concluded risks were increased for preeclampsia, low birthweight, and preterm delivery in women with asthma. The literature on other complications of pregnancy is less consistent, although several studies reviewed by Dombrowski⁶ have reported increased risk for cesarean delivery and maternal hemorrhage.

An observational cohort conducted by the Maternal-Fetal Medicine Units Network found increased risk for cesarean delivery but only observed increased risks for gestational diabetes and preterm delivery in women with severe asthma (but the number of cases with severe asthma was small: 8 for gestational diabetes mellitus and 16 for preterm delivery).⁸ In contrast, in our fully adjusted models that have substantially more cases with asthma (927 with gestational diabetes mellitus and 2526 preterm pregnancies) but no information on severity, we observed an 11% increase in the odds of gestational diabetes and 17% increase in preterm birth compared to pregnancies without asthma.

Results from prior large retrospective cohorts that examined obstetric complications have also provided conflicting results. Increased risk of miscarriage, hemorrhage, cesarean delivery, and anemia were reported in United Kingdom primary care health system records for pregnancies with asthma from 1988 through 2004¹¹ but risk for placental abruption, placenta previa, hypertensive disorders, diabetes, and other chronic disease with the exception of depression were not elevated. Approximately 35% of women in the study contributed >1

TABLE 2
Characteristics of mothers with and without asthma (continued)

Maternal characteristics	No asthma n = 206,468	Asthma n = 17,044	Site-adjusted P value ^a
Thyroid disease, n (%)	6043 (2.9)	568 (3.3)	.003
HIV/AIDS, n (%)	778 (0.4)	107 (0.6)	< .0001
Any chronic disease (diabetes, hypertension, thyroid, HIV), n (%)	12,722 (6.2)	1404 (8.2)	< .0001
Parity, n (%)			
Nulliparous	82,417 (39.9)	6824 (40.0)	.84
Multiparous	124,051 (60.1)	10,220 (60.0)	
Prior cesarean section, n (%)			
Nullipara	82,417 (39.9)	6824 (40.0)	< .0001
Multipara—no	95,123 (46.1)	7608 (44.6)	
Multipara—yes	28,928 (14.0)	2612 (15.3)	

Analyses are based on singleton pregnancies from the Consortium on Safe Labor, 2002–2008.

AIDS, acquired immunodeficiency syndrome; BMI, body mass index; HIV, human immunodeficiency virus.

^a P values are based on generalized estimating equations that account for multiple pregnancies to same woman.

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pregnancy but the statistical modeling did not control for correlation between pregnancies to the same women and the rates of complications observed were generally lower than our findings. In contrast, a Medicaid-based study in Tennessee covering births from 1995 through 2003 observed higher risk for hypertensive disorders, hemorrhage, gestational diabetes, cesarean section, and low birthweight but not for preterm delivery.⁷ Again, it was unclear how the authors controlled for multiple deliveries to the same women. Failing to control for the correlated pregnancies within women would likely overestimate the risks observed in these populations, but curiously, this was one of the few studies not to report a risk for preterm delivery.⁵

To our knowledge, no prior studies have examined risk for pulmonary embolism in relation to maternal asthma. Pulmonary embolism remains a leading cause of maternal mortality¹² and we observed twice as many cases in pregnancies complicated by asthma compared to those without asthma (12/10,000 vs 6/10,000 deliveries, respectively). It may be that this risk was secondary to the higher rate of cesarean delivery or thrombosis associated with preeclampsia but since the number of cases in our

study was relatively small (n = 20 among women with asthma), the cause remains unknown. As embolism represents another vascular endpoint with serious consequences found to be associated with asthma, further research is needed to confirm this novel finding.

Asthma is a complex chronic disease and the underlying immune dysfunction may increase the likelihood of poor placentation, resulting in both increases in gestational hypertensive disorders and placenta previa or abruption. Mothers with asthma have high-risk profiles, so their low likelihood of spontaneous labor (with more induction and prelabor cesarean section) may be expected but even when women with asthma labored, they were significantly less likely to have a vaginal delivery than their nonasthmatic counterparts. Perhaps the increased risk of pregnancy complications observed with asthma (eg, preeclampsia) also contributed to unsuccessful attempted vaginal delivery. Physician-diagnosed asthma increased risk for idiopathic preterm labor in a small case-control study from Quebec, Canada,¹³ but the authors did not observe effects associated with methacholine challenge suggesting nonatopic, noncholinergic mechanisms. Our data suggest an in-

TABLE 3

Singleton pregnancy complications among US women with asthma

Outcomes	No asthma n = 206,468 n (%)	Asthma n = 17,044 n (%)	Site-adjusted P value ^a	Site-adjusted odds ratio (95% CI) ^a	Fully adjusted odds ratio (95% CI) ^{a,b}
Hypertensive disorders of pregnancy					
Superimposed preeclampsia	1680 (0.8)	213 (1.3)	< .0001	1.54 (1.33–1.79)	1.34 (1.15–1.56)
Eclampsia	207 (0.1)	33 (0.2)	.01	1.61 (1.10–2.36)	1.41 (0.96–2.07)
Preeclampsia	9628 (4.7)	924 (5.4)	< .0001	1.24 (1.16–1.33)	1.14 (1.06–1.22)
Gestational hypertension	5523 (2.7)	557 (3.3)	.0003	1.18 (1.08–1.30)	1.08 (0.98–1.19)
Maternal seizure					
All maternal seizures	176 (0.1)	33 (0.2)	.0008	1.93 (1.32–2.83)	1.79 (1.21–2.63)
Maternal seizure without hypertension noted	93 (0.05)	14 (0.09)	.19	1.45 (0.83–2.55)	1.35 (0.77–2.37)
Maternal seizure with hypertension noted	83 (0.05)	19 (0.12)	.0006	2.51 (1.48–4.25)	2.37 (1.40–4.02)
Other pregnancy complications					
Gestational diabetes	10,420 (5.1)	927 (5.4)	.06	1.07 (1.00–1.15)	1.11 (1.03–1.19)
Chorioamnionitis	6415 (3.1)	504 (3.0)	.32	1.05 (0.95–1.16)	1.06 (0.96–1.17)
Placenta previa	1444 (0.7)	141 (0.8)	.06	1.19 (0.99–1.42)	1.30 (1.08–1.56)
Complications of labor and delivery					
Prelabor cesarean delivery	23,688 (11.5)	2193 (12.9)	< .0001	1.15 (1.10–1.21)	1.16 (1.09–1.23)
Spontaneous labor	111,523 (54.0)	8921 (52.3)	< .0001	0.86 (0.84–0.89)	0.87 (0.84–0.90)
Cesarean delivery after spontaneous labor	18,835 (9.1)	1749 (10.3)	.0003	1.10 (1.05–1.16)	1.06 (1.00–1.12)
Induction	71,257 (34.5)	5930 (34.8)	< .0001	1.10 (1.06–1.13)	1.10 (1.06–1.14)
Cesarean delivery after induction	14,746 (7.1)	1381 (8.1)	< .0001	1.22 (1.15–1.29)	1.17 (1.10–1.24)
All vaginal delivery	149,199 (72.3)	11,721 (68.8)	< .0001	0.84 (0.81–0.87)	0.84 (0.80–0.87)
PPROM	4596 (2.2)	516 (3.0)	< .0001	1.23 (1.12–1.36)	1.18 (1.07–1.30)
PROM	14,379 (7.0)	1212 (7.1)	.98	1.00 (0.94–1.07)	0.99 (0.93–1.05)
Breech presentation	8785 (4.3)	811 (4.8)	.01	1.10 (1.02–1.19)	1.13 (1.05–1.22)
Placental abruption	3242 (1.6)	380 (2.2)	< .0001	1.27 (1.14–1.42)	1.22 (1.09–1.36)
Maternal hemorrhage	13,423 (6.5)	1292 (7.6)	.001	1.11 (1.04–1.18)	1.09 (1.03–1.16)
Maternal pulmonary embolism	114 (0.06)	20 (0.12)	.008	1.90 (1.18–3.07)	1.71 (1.05–2.79)
Maternal postpartum fever	5531 (2.7)	532 (3.1)	.35	1.05 (0.95–1.15)	0.99 (0.90–1.09)
Maternal ICU admission	902 (0.6)	73 (0.6)	.01	1.38 (1.08–1.76)	1.34 (1.04–1.72)
Maternal death	18 (0.01)	1 (0.01)	.70	Not calculated	Not calculated
Low birthweight, <2500 g	16,551 (8.1)	1815 (10.7)	< .0001	1.26 (1.19–1.33)	1.16 (1.10–1.23)
Preterm birth, <37 wk	23,618 (11.4)	2526 (14.8)	< .0001	1.25 (1.19–1.31)	1.17 (1.12–1.23)
Intrauterine fetal death	1148 (0.6)	110 (0.7)	.26	1.12 (0.92–1.38)	1.07 (0.87–1.32)

Women with and without asthma had following rates of missing data: 5.9% and 6.9% on vertex presentation, 24.0% and 21.3% on ICU admission, 8.5% and 11.0% on seizures, and 0.8% and 1.1% on birthweight, respectively. Analyses are based on singleton pregnancies from the Consortium on Safe Labor, 2002–2008.

CI, confidence interval; ICU, intensive care unit; PPRM, preterm premature rupture of membranes; PROM, premature rupture of membranes.

^a All P values are based on generalized estimating equations that account for multiple pregnancies to the same woman. All P values are adjusted for site; ^b Adjusted for site; maternal age; maternal race; marital status; insurance; prepregnancy body mass index; smoking during pregnancy; alcohol use during pregnancy; history of diabetes (except for gestational diabetes), human immunodeficiency virus, chronic hypertension (except for gestational hypertension, preeclampsia, eclampsia, or maternal seizure with hypertension), or thyroid disease; and parity (spontaneous labor, induction, cesarean delivery, and vaginal delivery adjusted for prior cesarean delivery instead of parity alone).

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TABLE 4

Precursors for preterm deliveries among US women with asthma

Variable	No asthma n = 23,618 n (%)	Asthma n = 2526 n (%)	Site-adjusted P value ^a	Site-adjusted odds ratio (95% CI) ^a	Fully adjusted odds ratio (95% CI) ^{a,b}
Prelabor cesarean delivery	4625 (19.6)	511 (20.2)	.22	1.07 (0.96–1.19)	1.06 (0.95–1.19)
Spontaneous labor	12,726 (53.9)	1345 (53.3)	.08	0.93 (0.85–1.01)	0.93 (0.85–1.01)
Cesarean delivery after spontaneous labor	3172 (13.4)	359 (14.2)	.22	1.08 (0.96–1.22)	1.07 (0.94–1.21)
Induction	6267 (26.5)	670 (26.5)	.42	1.04 (0.95–1.15)	1.04 (0.94–1.15)
Cesarean delivery after induction	1606 (6.8)	176 (7.0)	.39	1.07 (0.91–1.27)	1.02 (0.86–1.21)
PPROM	4596 (19.5)	516 (20.4)	.86	1.01 (0.91–1.12)	1.02 (0.92–1.13)
Spontaneous process (labor or PPRM)	15,359 (65.0)	1609 (63.7)	.009	0.89 (0.81–0.97)	0.89 (0.81–0.97)
Indicated	3297 (14.0)	404 (16.0)	.06	1.13 (1.00–1.27)	1.14 (1.01–1.29)
Elective or no recorded indication	8824 (37.4)	913 (36.1)	.98	1.00 (0.92–1.09)	1.00 (0.91–1.09)

Preterm delivery includes all singletons delivered <37 completed weeks from the Consortium on Safe Labor, 2002–2008.
CI, confidence interval; PPRM, preterm premature rupture of membranes.

^a P values are based on generalized estimating equations that account for multiple pregnancies to same woman—all P values are adjusted for site; ^b Adjusted for site; maternal age; maternal race; marital status; insurance; prepregnancy body mass index; smoking during pregnancy; alcohol use during pregnancy; history of diabetes, human immunodeficiency virus, chronic hypertension, or thyroid disease; and parity/prior cesarean section.

Mendola. Obstetric complications among US women with asthma. *Am J Obstet Gynecol* 2013.

creased risk of eclampsia, significant in a site-adjusted model, and given the high risk for maternal seizure when hypertensive disorders were noted in the medical record, cases of eclampsia likely were miscoded. This assumption is supported by the fact that very few women had epilepsy or other seizure disorders, so our finding that risk of maternal seizure or eclampsia is increased in women with asthma may be another indication of the confluence of factors leading from poor immunologic adaptation to pregnancy to preeclampsia/eclampsia.¹⁴

The strengths of this analysis include having clinical data from a large, contemporary US population. The number of women with asthma in the obstetric population continues to increase and as management of asthma continues to improve,^{15,16} more recent data are valuable to examine the impact of maternal asthma on obstetric outcomes. The electronic medical records and discharge summaries provide a wealth of rich clinical data and the large sample size allows for rigorous analysis of less common, but more serious obstetric complications. With >17,000 pregnancies with asthma, we have one of the largest study populations to date. We are, however, limited by the data captured in the intrapartum records and discharge summaries. Not

all clinical centers provided comparable data, but an intensive chart review of key variables compared to the electronic records found very good agreement¹⁰ and we conducted a series of sensitivity analyses to test the robustness of our findings (restricted to sites with lower variability in asthma prevalence, sites with complete data, patients with complete data, and only pregnancies with ICD-9-confirmed asthma) and found similar results.

The major limitation of our study is the lack of information on asthma control, exacerbations, and treatment. Several studies have shown that adverse outcomes are more common (or only occur) in pregnancies with poor asthma control.^{7,9,17} Presumably, the asthma cases in our study represent a mix of severity and treatment and we cannot evaluate how well our findings apply to the subgroup of women with well-controlled asthma. It is possible that records could be biased and more likely to include the diagnosis of asthma when complications arise, 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

Our findings confirm that women with asthma have an increased risk of

preeclampsia, preterm birth, and low birthweight.⁵ Since chronic inflammation is a hallmark of asthma and increases in proinflammatory cytokines are known to play an important role in triggering the spontaneous onset of labor,¹⁸ we considered the potential for spontaneous pathways leading to preterm delivery among women with asthma. However, when we examined the precursors of preterm delivery in our data, medically indicated delivery was more common in asthmatic pregnancies and women with asthma were less likely to deliver as a result of a spontaneous process (labor or PPRM). This suggests that the increased risk of preterm birth among women with asthma is not driven by spontaneous preterm labor but rather is due to their compromised medical condition. Inflammation related to asthma does not seem to be triggering preterm labor at the population level.

We also found that asthma increased the risk of other serious obstetric complications including placental abruption, hemorrhage, pulmonary embolism, and maternal ICU admission as well as increasing risk for gestational diabetes, breech presentation, and cesarean delivery. The National Asthma Education and Prevention Program and ACOG have

published guidelines for evaluation and treatment of asthma in pregnancy^{15,16} and clinical strategies to manage women with asthma and improve outcomes have been well described.¹⁹ Monitoring peak flow as an estimate of forced expiratory volume in 1 second (FEV₁) is recommended and good control of asthma symptoms has been associated with improved outcomes, particularly for preterm birth. For example, >21% of women with poor spirometry across pregnancy (FEV₁ <80% of expected) delivered preterm in the Maternal-Fetal Medicine Units Network study, compared to 15% when FEV₁ was more favorable ($\geq$ 80% of expected).⁹ Asthma should be actively managed during pregnancy including objective assessment of symptoms and lung function, avoidance of asthma triggers, patient education, and step therapy to adjust the number and frequency of medications needed to control symptoms.¹⁹ The importance of good asthma control for the well-being of the baby should be clearly communicated to the patient, particularly for those who may resist taking needed medication due to concern about the impact of pharmaceuticals on the fetus.

Given that asthma is the most common chronic condition in pregnancy and the proportion of women of reproductive age with asthma is likely to increase for the foreseeable future, our findings are concerning. We observed a pattern of increased risk for nearly all outcomes studied in the general obstetric population, which likely included women with mild asthma and good asthma control. Since both asthma severity and control contribute to morbidity during pregnancy, more research is needed to determine factors that predict poor obstetric outcomes and determine if certain vulnerable women can benefit

from targeted intervention to ameliorate their obstetric risks. Our data from a large, contemporary, nationwide US cohort suggest that we still have a long way to go to improve obstetric outcomes for women with asthma. ■

ACKNOWLEDGMENTS

Institutions involved in the Consortium on Safe Labor include, in alphabetical order: Baystate Medical Center, Springfield, MA; Cedars-Sinai Medical Center Burnes Allen Research Center, Los Angeles, CA; Christiana Care Health System, Newark, DE; EMMES Corp, Rockville, MD (Data Coordinating Center); Georgetown University Hospital, MedStar Health, Washington, DC; Indiana University Clarian Health, Indianapolis, IN; Intermountain Healthcare and the University of Utah, Salt Lake City, UT; Maimonides Medical Center, Brooklyn, NY; MetroHealth Medical Center, Cleveland, OH; Summa Health System, Akron City Hospital, Akron, OH; University of Illinois at Chicago, Chicago, IL; University of Miami, Miami, FL; and University of Texas Health Science Center at Houston, Houston, TX.

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