

Use of Antihypertensive Medications and Uterotonics During Delivery Hospitalizations in Women With Asthma

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OBJECTIVE: To estimate whether the diagnosis of asthma is associated with the use of specific uterotonic and antihypertensive medications during delivery hospitalizations.

METHODS: We used Perspective, an administrative database, to determine whether women hospitalized for delivery complicated by postpartum hemorrhage or preeclampsia received uterotonics and antihypertensive medications differentially based on the absence or presence of asthma from 2006 to 2015. Given that carboprost and intravenous (IV) labetalol may be associated with asthma exacerbation, adjusted models for receipt of these medications were created with adjusted risk ratios with 95% CIs as measures of effect. Risk for status asthmaticus based on receipt of carboprost and IV labetalol was analyzed.

RESULTS: Over the study period, a total of 5,691,178 women were analyzed, of whom 239,915 (4.2%) had preeclampsia and 139,841 postpartum hemorrhage (2.5%). Carboprost was used less frequently in patients with asthma compared with patients with no asthma (11.4% vs 18.0%) in comparison with IV labetalol, which was used more commonly when a diagnosis of asthma was present (18.5% vs 16.7%). In unadjusted analysis, the presence of asthma was associated with a 37% decrease in likelihood of carboprost use and an 11% increase in likelihood of labetalol use. In adjusted analysis, the presence of asthma was associated with a 32% decrease in likelihood of carboprost use (adjusted risk ratio 0.68, 95% CI 0.62–0.74) compared with a 7% decrease in labetalol use (adjusted risk ratio 0.93, 95% CI 0.90–0.97). Risk for status asthmaticus was significantly increased with use of IV labetalol compared with other antihypertensive medications (6.5 vs 1.7/1,000 delivery hospitalizations, $P < .01$).

CONCLUSION: There may be an opportunity to reduce use of β -blockers and carboprost among patients with asthma. Given their association with status asthmaticus, these drugs should be used cautiously in women with asthma.

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Asthma is a common medical condition encountered during 4–8% of pregnancies. In addition to optimizing long-term medical management of asthma, maternal risk may be reduced by avoiding agents that precipitate bronchospasm when other effective treatment options are available.¹ Many commonly used medications in obstetrics may increase the risk for bronchospasm, including carboprost (15-methyl prostaglandin $F_{2\alpha}$), ergot derivatives, indomethacin, and β -blockers.^{1–3} For patients with asthma, the benefits of administration of these medications must be weighed against risks.



Contraindications to uterotonics and antihypertensive medications may complicate clinical decision-making for patients with asthma in the context of recent major efforts to reduce severe maternal morbidity and mortality by improving management of severe range hypertension and obstetric hemorrhage.^{4–8} Although labetalol is a first-line antihypertensive⁴ and a drug of choice for treating hypertension in pregnancy,⁹ both the 2013 American College of Obstetricians and Gynecologists' (ACOG) Task Force on Hypertension in Pregnancy and the National Partnership for Maternal Safety bundle on severe hypertension recommend avoiding labetalol for patients with asthma because of bronchoconstriction risk.^{4,8} For management of hemorrhage, the ACOG Practice Bulletin on asthma in pregnancy, among other sources, notes carboprost may precipitate bronchospasm.^{1–3,10}

Data on bronchospasm risk related to antihypertensive medications and uterotonics among obstetric patients with asthma are limited,^{11–13} and it is unclear to what degree clinical recommendations affect practice. Given that data on outcomes and practice patterns may be important for optimizing care for patients with asthma in regard to management of hemorrhage and hypertension, the two primary objectives of this study were 1) to evaluate practice patterns in use of antihypertensive medications and uterotonics among patients with asthma during delivery hospitalizations and 2) to evaluate risk for status asthmaticus in this population.

MATERIALS AND METHODS

This analysis used the Perspective database. The Perspective database, maintained by Premier Incorporated, includes data on patient demographics, hospital characteristics, and discharge diagnosis codes as well as medications and devices received during acute care hospitalizations. Perspective reports on 100% of hospitalizations for individual hospitals. The data undergo 95 quality assurance and validation checks before being used for research.¹⁴ Perspective is routinely used for research that evaluates outcomes related to medications and medical devices.^{15–17} Discharges included in the Perspective database represent approximately 15% of inpatient hospital stays annually. Because all data were deidentified, the Columbia University institutional review board deemed the study exempt.

Inclusion criteria for this analysis included delivery hospitalization from January 2006 through March 2015 for women 15–54 years of age. Delivery hospitalizations were identified based on billing and

procedure codes using an approach that ascertains more than 95% of deliveries.¹⁸ Two cohorts of women undergoing delivery hospitalizations were analyzed: those with a diagnosis of preeclampsia and those with a diagnosis of postpartum hemorrhage. Patients with preeclampsia were identified based on International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 642.4x, 642.5x, and 642.7x. Patients with postpartum hemorrhage were identified based on ICD-9-CM codes 666.0x, 666.1x, and 666.2x. In the preeclampsia group, we analyzed whether patients received the following antihypertensive medications: oral labetalol, intravenous (IV) labetalol, nifedipine, and hydralazine. In the postpartum hemorrhage cohort, we identified patients who received the following uterotonic medications: misoprostol, methylergonovine, and carboprost. Because a lower dose of misoprostol is used as a labor induction agent, we used an algorithm developed by Bateman et al¹⁹ to differentiate between induction and uterotonic-dose misoprostol use. The presence of asthma was identified based on ICD-9-CM codes (493, 493.0x, 493.1x, 493.2x, 493.8x, 493.9x).

We evaluated whether the presence of asthma was associated with receipt of 1) labetalol among patients with preeclampsia and 2) carboprost among patients with postpartum hemorrhage. Univariate associations between clinical, hospital, and demographic variables and receipt of intravenous labetalol and carboprost were evaluated using the χ^2 test. Patient demographic characteristics included maternal age, race (white, black, other), marital status, year of discharge, and payer status. Hospital characteristics included teaching status, bed size, geographic region, and urban or rural location. Adjusted risk ratios (RRs) for receipt of IV labetalol and carboprost with 95% CI as measures of effect accounting for demographic, hospital, and asthma diagnosis were derived from fitting log-linear regression models based on the methods of generalized estimating equations that account for hospital clustering effects. This methodologic approach allows for estimation of RRs, which may be more clinically interpretable than odds ratios associated with logistic regression analysis. To account for the possibility of confounding by indication (ie, a diagnosis of asthma itself being related to a higher probability of treatment for severe range hypertension), we performed a sensitivity analysis and repeated the adjusted model with the same covariates evaluating receipt of IV labetalol restricted to patients with preeclampsia requiring treatment with antihypertensive medications. We performed a similar sensitivity analysis for receipt of carboprost restricted to patients with



hemorrhage receiving uterotonics to account for a possible relationship between severity of hemorrhage and asthma diagnosis. Specific preeclampsia diagnosis (severe, superimposed, or mild or unspecified) was included in the models for preeclampsia.

Risk for status asthmaticus (ICD-9-CM 493.01, 493.11, 493.21, 493.91) associated with receipt of antihypertensive medications (IV labetalol, oral labetalol, nifedipine, and hydralazine) and uterotonics (carboprost, misoprostol, methylergonovine) was evaluated. Because patients could receive one or more antihypertensive medications or uterotonic agents, comparisons for each medication were based on receipt of any combination of medications including the specified drug. Because of concerns regarding disclosure of personal health information, categorical data with cell sizes of less than 10 are not presented. All analyses were performed with SAS 9.4.

RESULTS

Of 5,691,178 delivery hospitalizations, 4.2% were complicated by preeclampsia (n=239,915) and 2.5% by postpartum hemorrhage (n=139,841). Overall, 5.2% of women with preeclampsia (n=12,486) and 4.0% of women with postpartum hemorrhage had asthma (n=5,633). Of patients with preeclampsia and asthma, 46.8% (n=5,846) received one or more antihypertensive medications. Uterotonics were administered to 64.5% of women with postpartum hemorrhage and an asthma diagnosis (n=3,639).

Women with preeclampsia and asthma were younger; more likely to be black; have Medicaid insurance; deliver at a hospital in an urban location, a teaching hospital, and in the Northeast and Midwest compared with the South and West; and have severe or superimposed preeclampsia than women without asthma. Women with postpartum hemorrhage with asthma were also more likely to be younger and have Medicaid insurance and deliver in a teaching hospital and in the Northeast and Midwest compared with the South and West than women without asthma (Appendix 1, available online at <http://links.lww.com/AOG/B103>).

Women with preeclampsia and asthma received IV labetalol 1.8% more often, oral labetalol 1.6% more often, nifedipine 2.8% more often, and hydralazine 1.7% more often than those without asthma (absolute percent rate differences). Women with asthma were also 3.8% more likely to receive at least one type of antihypertensive medication. In contrast, although women with asthma who experienced postpartum hemorrhage were 1.0% more likely to receive misoprostol than women without asthma, 6.6% fewer

received carboprost and 3.1% fewer received methylergonovine and were overall 2.9% less likely to receive more than one medication (absolute percent rate differences; Table 1).

In the adjusted model, likelihood of receipt of IV labetalol was 7% lower among women with asthma (adjusted RR 0.93, 95% CI 0.90–0.97) (Table 2). In comparison, likelihood of receipt of carboprost was 32% lower with a diagnosis of asthma (adjusted RR 0.68, 95% CI 0.62–0.74) (Table 2). Other important factors associated with administration of IV labetalol included severe and superimposed preeclampsia in comparison with mild preeclampsia (adjusted RR 3.55, 95% CI 3.34–3.77 and adjusted RR 3.39, 95% CI 3.18–3.61, respectively), study year with labetalol use increasingly likely over the study, and black compared with white race (adjusted RR 1.52, 95% CI 1.46–1.57) (Table 3). Factors associated with increased use of carboprost included hospitals in the South compared with the Northeast (adjusted RR 1.39, 95% CI 1.15–1.67).

The sensitivity analyses for IV labetalol and carboprost receipt are demonstrated in Appendices 2 and 3, available online at <http://links.lww.com/AOG/B103>. Asthma was associated with a 5% lower likelihood of IV labetalol (adjusted RR 0.95, 95% CI 0.92–0.98) and a 27% lower likelihood of carboprost (adjusted RR 0.73, 95% CI 0.67–0.79). Other significant factors in the sensitivity analysis for labetalol included study year with likelihood of labetalol increasing over

Table 1. Medication Receipt

	With Asthma	Without Asthma
Preeclampsia		
All preeclamptics	12,486 (100)	227,429 (100)
Labetalol, IV	2,305 (18.5)	37,911 (16.7)
Labetalol, oral	3,565 (28.6)	61,281 (27.0)
Nifedipine	2,346 (18.7)	36,161 (15.9)
Hydralazine	2,076 (16.6)	33,937 (14.9)
Greater than one medication	2,989 (23.9)	47,670 (20.1)
Postpartum hemorrhage		
All postpartum hemorrhage	5,633 (100)	134,208 (100)
Misoprostol	2,140 (38.0)	49,686 (37.0)
Methylergonovine	2,315 (41.1)	59,255 (44.2)
Carboprost	642 (11.4)	24,150 (18.0)
Greater than one medication	1,286 (22.8)	34,471 (25.7)

IV, intravenous.
Data are n (%).
The table demonstrates whether patients received each of the individual medications alone or in combination with other medications.



Table 2. Unadjusted and Adjusted Models for Receipt of Carboprost

	Unadjusted Model		Adjusted Model	
	RR	95% CI	Adjusted RR	95% CI
Asthma	0.63	0.59–0.69	0.68	0.62–0.74
Year				
2007	0.96	0.91–1.02	0.98	0.92–1.04
2008	0.94	0.89–1.00	0.94	0.88–1.01
2009	0.96	0.91–1.02	0.93	0.86–1.01
2010	0.96	0.91–1.01	0.93	0.86–1.00
2011	1.00	0.95–1.06	0.96	0.88–1.05
2012	0.97	0.92–1.02	0.97	0.88–1.06
2013	0.99	0.94–1.04	0.97	0.88–1.07
2014	1.02	0.96–1.07	0.99	0.90–1.09
2015 (1st quintile)	1.06	0.98–1.16	1.03	0.92–1.16
Hospital bed size				
Small	1.00	Reference	1.00	Reference
Medium	0.99	0.96–1.02	0.97	0.84–1.13
Large	1.14	1.11–1.18	0.98	0.83–1.17
Maternal age (y)				
15–17	1.11	1.03–1.19	0.92	0.86–0.97
18–24	1.00	Reference	1.00	Reference
25–34	0.96	0.93–0.98	0.90	0.84–0.96
35 or older	1.05	1.01–1.09	0.99	0.92–1.06
Insurance status				
Medicare	0.89	0.77–1.03	1.03	0.91–1.15
Medicaid	1.03	1.01–1.06	0.96	0.93–0.99
Private	1.00	Reference	1.00	Reference
Other	1.20	1.12–1.28	0.98	0.91–1.06
Uninsured	1.12	1.04–1.21	1.01	0.93–1.10
Race				
White	1.00	Reference	1.00	Reference
Black	1.04	1.00–1.08	1.02	0.97–1.06
Other	0.98	0.95–1.01	1.00	0.96–1.03
Unknown	0.56	0.30–1.04	0.72	0.41–1.27
Rural hospital	1.05	1.01–1.09	1.14	0.99–1.31
Marital status				
Married	1.00	Reference	1.00	Reference
Unmarried	1.02	0.99–1.04	1.00	0.98–1.03
Unknown	1.02	0.98–1.07	0.99	0.91–1.06
Hospital region				
Northeast	1.00	Reference	1.00	Reference
Midwest	1.16	1.11–1.21	1.07	0.86–1.34
South	1.57	1.51–1.63	1.39	1.15–1.67
West	1.11	1.07–1.17	1.04	0.84–1.29
Teaching hospital	0.95	0.93–0.98	1.05	0.92–1.20

RR, risk ratio.

The adjusted model includes all of the factors in the table. The references for asthma, year, rural hospital location, and hospital teaching status are absence of asthma, 2006, urban location, and nonteaching hospitals, respectively.

the study period and a diagnosis of severe or superimposed preeclampsia compared with mild preeclampsia. In the sensitivity analysis for carboprost, there was a decreased likelihood of drug administration as the study period progressed, and the use of the medication in the South no longer differed significantly compared with the Northeast.

Comparing risk for status asthmaticus among patients receiving labetalol and carboprost, 6.5 per

1,000 deliveries where women with asthma received IV labetalol were complicated by status asthmaticus compared with 1.7 per 1,000 deliveries with other antihypertensive medications ($P<.01$) (Table 4). Overall, 71.4% of status asthmaticus cases occurred among women receiving IV labetalol. In comparison, patients receiving carboprost were not significantly more likely to experience status asthmaticus than patients receiving other uterotonic medications (3.1/1,000 deliveries with



Table 3. Unadjusted and Adjusted Models for Receipt of Intravenous Labetalol

	Unadjusted Model		Adjusted Model	
	RR	95% CI	Adjusted RR	95% CI
Asthma	1.11	1.06–1.16	0.93	0.90–0.97
Year				
2007	1.05	1.00–1.10	1.06	1.00–1.12
2008	1.09	1.03–1.14	1.07	0.99–1.16
2009	1.14	1.08–1.20	1.13	1.04–1.23
2010	1.17	1.12–1.23	1.16	1.05–1.28
2011	1.21	1.15–1.27	1.17	1.07–1.28
2012	1.32	1.27–1.39	1.29	1.16–1.43
2013	1.43	1.37–1.50	1.37	1.24–1.52
2014	1.62	1.55–1.69	1.50	1.35–1.68
2015 (1st quintile)	1.80	1.69–1.92	1.61	1.42–1.83
Hospital bed size				
Small	1.00	Reference	1.00	Reference
Medium	1.09	1.06–1.11	0.96	0.78–1.18
Large	1.26	1.23–1.29	1.03	0.80–1.32
Maternal age (y)				
15–17	0.93	0.88–0.99	0.94	0.89–0.98
18–24	1.00	Reference	1.00	Reference
25–34	1.00	0.97–1.02	1.03	1.00–1.05
35 or older	1.23	1.19–1.26	1.16	1.13–1.20
Insurance status				
Medicare	1.48	1.36–1.61	1.13	1.05–1.22
Medicaid	1.28	1.25–1.31	1.09	1.07–1.12
Private	1.00	Reference	1.00	Reference
Other	1.11	1.05–1.17	1.01	0.94–1.09
Uninsured	1.23	1.15–1.32	1.16	1.07–1.25
Race				
White	1.00	Reference	1.00	Reference
Black	1.78	1.74–1.83	1.52	1.46–1.57
Other	1.21	1.18–1.24	1.18	1.14–1.22
Unknown	1.48	0.97–2.25	1.02	0.73–1.42
Rural hospital	0.62	0.59–0.65	0.85	0.73–0.98
Marital status				
Married	1.00	Reference	1.00	Reference
Unmarried	1.27	1.25–1.30	1.09	1.07–1.12
Unknown	0.95	0.92–0.99	0.91	0.80–1.03
Hospital region				
Northeast	1.00	Reference	1.00	Reference
Midwest	1.05	1.02–1.09	1.00	0.82–1.22
South	1.10	1.07–1.13	0.90	0.74–1.10
West	1.09	1.06–1.13	1.17	0.85–1.61
Teaching	1.37	1.34–1.40	1.20	0.96–1.51
Preeclampsia				
Severe	3.84	3.75–3.93	3.55	3.34–3.77
Mild	1.00	Reference	1.00	Reference
Superimposed	3.99	3.88–4.11	3.39	3.18–3.61

RR, risk ratio.

The adjusted model includes all of the factors in the table. The references for asthma, rural hospital location, and hospital teaching status are absence of asthma, urban location, and nonteaching hospitals, respectively.

carboprost vs 1.0/1,000 deliveries with other uterotonic, $P=.56$). Risk for status asthmaticus was not different based on receipt of other antihypertensive medications (Appendix 4, available online at <http://links.lww.com/AOG/B103>).

DISCUSSION

In our analysis, patients with asthma were more than one third less likely to receive carboprost than those without the diagnosis. Use of methylergonovine maleate, which also may be associated with



Table 4. Risk for Status Asthmaticus for Patients Receiving Intravenous Labetalol and Carboprost

	Status Asthmaticus		
	Per 1,000 Deliveries (95% CI)	Present (n)	Absent (n)
Preeclampsia			
1 or more antihypertensive medications			
Received IV labetalol	6.5 (3.9–10.7)	15	2,290
No IV labetalol*	1.7 (0.8–3.7)	6	3,535
Postpartum hemorrhage			
1 or more uterotonics			
Received carboprost	3.1 (0.9–11.3)	2	642
No carboprost [†]	1.0 (0.3–2.9)	3	2,997

IV, intravenous.

The table demonstrates risk for status asthmaticus/1,000 delivery hospitalizations among patients with asthma receiving uterotonic and antihypertensive medications.

* $P < .01$ for comparison between patients receiving one or greater antihypertensive based on whether IV labetalol was administered.

[†] Comparisons of one or greater uterotonics based on the presence of carboprost were not significant with $P = .56$.

bronchospasm, was similarly administered less frequently among patients with asthma.^{1–3,10} In contrast, administration of IV labetalol was actually likelier in patients with asthma. Our studies suggest that clinical use of labetalol appears to differ from obstetric research protocols that frequently exclude patients with asthma from receiving β -blockers.^{20,21} Major nonobstetric guidelines recommend against administration of β -blockers to patients with asthma,²² and meta-analysis has demonstrated increased risk even when selective β -blockers are used.²³ In other medical specialties, risk and benefits of β -blocker administration with reactive airway disease are balanced depending on the specific clinical scenario.^{24–26} The 2013 ACOG Task Force on Hypertension in Pregnancy and the National Partnership for maternal safety specifically recommend avoiding labetalol because of bronchoconstriction risk.^{4,8}

Given similar theoretical risks, why a differential exists in uterotonic but not antihypertensive management is unclear. An important factor may be that although risks among nonpregnant patients with asthma from β -blockers are well characterized,²² risk for obstetric patients is not well documented. In comparison, there are numerous case reports of life-threatening bronchospasm associated with carboprost.^{12,13} Although case reports can be important in highlighting risk for rare but serious outcomes, they are not representative of specific risks in large populations and, in fact, in this analysis, more cases of status asthmaticus were present among women who received IV labetalol. Although all antihypertensive medications recommended for treatment of obstetric patients may have side effects,^{27–29} and use of a specific agent requires weighing risks and benefits for an individual patient, our finding of an association

between status asthmaticus and IV labetalol further supports caution in using this medication in this population. In addition to research evidence, graduate medical education and society leadership likely play major roles in perceived risk, and future studies are warranted to determine whether ACOG Task Force and National Partnership recommendations are being adopted into practice.

There are several important considerations in interpreting the findings of this study. First, because the database relies on discharge diagnoses, we are unable to determine whether administration of IV labetalol played a causal role in individual cases of status asthmaticus and are limited to demonstrating an association. Second, because of limitations regarding granularity in administrative data and because we do not have access to outpatient records, we cannot assess how asthma severity and control on admission factored into clinical decision-making regarding use of specific uterotonic or antihypertensive medications. Specifically, we cannot determine history of prior events or symptomatology related to asthma diagnosis nor can we account for medical management of asthma before delivery hospitalization admission. Third, because nifedipine can be administered for both severe-range hypertension as well as ongoing blood pressure control, we were not able to determine specific instances when it was used for hypertensive acuity. Fourth, we cannot determine the number of doses or dosage of a uterotonic or antihypertensive medication that a patient received. Fifth, although we found that risk for status asthmaticus was increased with IV labetalol, the number of patients with this condition was small, precluding precise statistical estimates of number needed to harm. Similarly, because of the small number of events, we are unable



to make a precise estimate risk for status asthmaticus associated with carboprost. Sixth, women could have contributed more than one delivery to this data set and this factor could not be reliably controlled for in this data set given that patients cannot be tracked across hospitals. Seventh, we do not have actual clinical documentation as to why specific uterotonic or antihypertensive medications were selected by health care providers. Eighth, we elected not to evaluate asthma exacerbations short of status asthmaticus; given the cross-sectional nature of this administrative data, acute exacerbations short of status asthmaticus could be both an outcome and a marker of disease severity making interpretation problematic. If health care providers were less likely to administer labetalol to patients with asthma presenting with an exacerbation and simultaneously patients were more likely to develop exacerbations short of status asthmaticus as a result of labetalol or carboprost treatment, the model could demonstrate an effect in either direction or no effect at all depending on the relative contributions of the two unmeasurable scenarios. Strengths of this study include a large patient population, a long study period, and diverse clinical settings. Given the rarity of status asthmaticus among obstetric patients, further characterization of risk may require surveillance efforts from large hospital systems or statewide safety initiatives such as the California Maternal Quality Care Collaborative or New York State's Safe Motherhood Initiative.^{6,7,30}

In summary, given that current clinical practice involves high rates of β -blocker use among patients with preeclampsia and asthma, and that multiple other effective agents not associated with bronchospasm are available for both acute and longer term blood pressure control, an opportunity exists to reduce use of labetalol and potential risk in this population. That an association was noted with status asthmaticus further supports that β -blockers should be used with caution in this population.

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