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Patterns of Second-Line Uterotonic Use in a Large Sample of Hospitalizations for Childbirth in the United States: 2007 - 2011

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Abstract

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Introduction—The incidence of postpartum hemorrhage due to uterine atony has increased significantly in the United States during the past decade. For patients with refractory uterine atony after oxytocin administration, second-line uterotonics including methylergonovine maleate, carboprost, and misoprostol are recommended. In this study we describe hospital-level patterns of second-line uterotonic use in a large, nationwide sample of admissions for childbirth in the United States.

Methods—The Premier Research Database was used to define a cohort of 2,180,916 patients hospitalized for delivery at 1 of 367 hospitals from 2007 to 2011. Mixed-effects logistic regression models were used to estimate the hospital-specific frequency of second-line uterotonic use adjusting for measured patient-level and hospital-level characteristics that might be risk factors for uterine atony.

Results—The median hospital-level frequency of second-line uterotonic use was 7.1% (interquartile range 5.2% to 10.8%). In the fully adjusted model, the mean (SE) predicted probability of second-line uterotonic use was 7.02% (0.26%), with 95% of the hospitals having a predicted (SE) probability between 1.69% (0.12%) and 24.96% (1.28%).

Conclusions—We observed wide interhospital variation in the use of second-line uterotonics that was not explained by patient-level or hospital-level characteristics. Studies aimed at defining the optimal pharmacologic strategies for the management of uterine atony are needed, particularly in light of the increasing incidence of atonic postpartum hemorrhage in the United States and other developed countries.

Introduction

Postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality.¹⁻⁴ In the developed world, the incidence of PPH overall, and that of severe cases resulting in transfusion and hysterectomy, have increased significantly over the past decade.^{1,5-8} These increases appear to be directly linked to a concomitant increase in the incidence of uterine atony.^{1,6}

For prophylaxis against uterine atony, oxytocin is routinely used during the third stage of labor.^{9,10} If the uterus fails to adequately contract in response to oxytocin administration, second-line uterotonics including methylergonovine maleate, carboprost, and misoprostol are recommended.⁹ While commonly used, these drugs have important side effects and complications including (depending on the drug) hypertension, nausea/vomiting, bronchospasm, pyrexia, and gastrointestinal disturbance.¹¹ Few data are available to guide clinicians regarding the circumstances under which these drugs should be administered, how to balance their risks and benefits, or which drug has an optimal safety and efficacy profile.

Despite being endorsed by the American College of Obstetricians and Gynecologists for the second-line treatment of uterine atony,⁹ there are surprisingly few data about the use of these drugs in current clinical practice. Determining whether there is between-hospital variability in the use of these medications and the extent to which variability can be explained by differences in patient- and hospital-level characteristics are important steps to establishing clinical and research priorities in this area of obstetric practice.

The objective of this study was to describe the hospital-level patterns of use of second-line uterotonics in the treatment of uterine atony in a large, nationwide sample of delivery admissions in the United States.

Methods

Data source

Data for the study were obtained from the Premier Research Database between the fourth quarter of 2007 and the third quarter of 2011. Premier is a hospital-based health care utilization database that contains administrative codes for discharge diagnoses based on the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9 CM). Premier also contains detailed information on all charges for procedures, medications, blood products, and laboratory and radiologic diagnostic tests performed during inpatient hospitalizations. The database has been used extensively in prior studies to evaluate the patterns of use and safety of inpatient medications.¹²⁻¹⁷ The use of this database for research was approved by the Partners IRB (Boston, MA).

Cohort

Using a modified version of the algorithm described by Kuklina et al.¹⁸ that uses diagnosis and procedure codes from the ICD-9 CM, we identified inpatient admissions with diagnosis or procedure codes indicating delivery (Supplemental Digital Content 1). We excluded hospitalizations with any codes indicating abortion, ectopic pregnancy, hydatidiform mole, or other abnormal products of conception. Because we were specifically interested in hospital-level rates of second-line uterotonic administration, we restricted our analysis to hospitals with more than 100 deliveries in the database (because smaller numbers of deliveries would yield unstable estimates of second-line uterotonic use) and with at least 1 patient charged for a second-line uterotonic (to exclude hospitals in which uterotonic administration may not be reliably coded). This resulted in the exclusion of 14 and 12 hospitals, respectively. The final cohort included 367 hospitals.

Exposure

The Premier database contains charge codes that can be used to identify drugs administered during a hospital admission. In our study, these charge codes were used to identify second-line uterotonics (methylergonovine maleate, carboprost, or misoprostol) that were used during the hospitalization for delivery. Because misoprostol at low doses (i.e., oral 50 µg or intravaginal 25 µg to a cumulative dose < 250 µg) can also be used as an induction drug,¹⁹ we considered misoprostol as a second-line uterotonic only if the total dose was in excess of 400 µg and if the patient did not have an ICD-9 CM procedure code indicating medical induction of labor.

Covariates

We considered 5 groups of covariates which might act as risk factors for uterine atony and thus account for variation in the use of second-line uterotonics: (1) patient demographics, (2) year of delivery, (3) mode of delivery, (4) medical and obstetrical conditions, and (5) hospital characteristics. We assessed the following patient demographics: maternal age

(categorized as <20, 20-24, 25-29, 30-34, 35-39, 40-44, 45-55 years; categorized to avoid the assumption of monotonicity between age and model logits) and race/ethnicity (categorized as non-Hispanic Caucasian, non-Hispanic African-American, Hispanic, and other/unknown). Mode of delivery was defined as vaginal versus cesarean and induced or noninduced, both of which were defined by ICD-9 CM procedure codes (Supplemental Digital Content 2). Medical and obstetrical conditions which might act as risk factors for atony were defined based on the presence of ICD-9 CM diagnosis codes during the delivery hospitalization and included preexisting hypertension, gestational hypertension, preeclampsia/eclampsia, preexisting diabetes, gestational diabetes, preterm delivery, obesity, polyhydramnios, abnormal placentation including placenta previa, placental abruption, previous cesarean delivery, stillbirth, multiple gestations, and chorioamnionitis (Supplemental Digital Content 2). We assessed the following delivery hospital characteristics (recorded directly in the database): teaching status, urban (versus rural) location, geographic region (categorized as Midwest, Northeast, South, and West), and annual delivery volume tertile (which divides the hospitals into 3 equally sized groups, based on delivery volume, categorized as low, medium, or high, which corresponds to thresholds of <814 deliveries, 814-1892 deliveries, and >1892 deliveries, respectively).

Statistical analysis

The proportion of patients admitted for delivery who received methylergonovine maleate, carboprost, or misoprostol was determined for each hospital. The mean, median, and interquartile range for overall use of second-line uterotonic and individual second-line uterotonic use were reported. Hospitals were divided into quartiles based on the overall proportion of patients who received 1 or more second-line uterotonics. Baseline patient and hospital characteristics that were likely to influence the use of second-line uterotonics were described,^{1,16,20-22} stratified by hospital quartile, and compared with a chi-square test.

Mixed-effects logistic regression models were used to estimate the hospital-specific frequency of second-line uterotonic use adjusting for the case mix of patients and hospital characteristics, accounting for random variation. In these models, a variable identifying each hospital was included as a normally distributed random intercept, and demographic, obstetric, and hospital-level covariates were modeled as fixed effects. The hospital-specific intercept represents the hospital-specific frequency for second-line uterotonic use after adjusting for patient and hospital characteristics.

We used sequential mixed effects models to assess the relative influence of different patient and hospital characteristics for between-hospital variation in second-line uterotonic use. We constructed sequential models with increasing levels of adjustment to account for the following sets of covariates: (Model 1) patient demographics, (Model 2) demographics and year of delivery, (Model 3) demographics, year of delivery, and method/mode of delivery, (Model 4) demographics, year of delivery, method/mode of delivery, and medical/obstetrical conditions, and (Model 5) demographics, year of delivery, method/mode of delivery, medical/obstetrical conditions, and hospital characteristics. After adjusting for all of these patient- and hospital-level characteristics, the hospital-specific intercepts represent the

“intrinsic” hospital-level tendency to use second-line uterotonics independent of measured patient- and hospital-level factors.

Due to the large number of patient and hospital level factors, we used propensity scores as a data reduction technique at each stage of sequential adjustment.²³ For each of the 5 sequential models, a separate propensity score was estimated to predict exposure to a second-line uterotonic. The propensity score was centered on the mean such that the random intercept for each hospital represents the probability that an average patient (defined as patient with a propensity score at the mean) would be treated with a second-line uterotonic in a given hospital. Additional details regarding the models are available in the Supplemental Digital Content 3.

Results

The cohort included 2,180,916 patients hospitalized for delivery at 1 of 367 hospitals. The median hospital level frequency of second-line uterotonic use was 7.1% (interquartile range (IQR) 5.2% to 10.8%). The median hospital level frequency of methylergonovine maleate use was 5.2%, carboprost 1.0%, and misoprostol 1.2% (Table 1).

We stratified hospitals into quartiles based on the proportion of patients treated with 1 or more second-line uterotonics (Table 2). There were significant differences among hospital quartiles in all of the covariates assessed ($p < 0.01$), with the exception of stillbirth ($p = 0.55$) and gestational diabetes ($p = 0.09$).

The results of the 5 sequential mixed-effects logistic regression models with demographic, medical, obstetric, and hospital-level covariates added at each step are shown in Table 3 (beta coefficients and p-values for each of the propensity score models and measures of model calibration shown in Supplemental Digital Content Tables 1 and 2). The between-hospital variance in the use of second-line uterotonics is described by σ_b^2 . The mean predicted probability of exposure to a second-line uterotonic and the 2.5th to 97.5th percentile is also displayed. If the between-hospital variation in second-line uterotonic use is fully explained by the covariates in the model, σ_b^2 would be expected to approach zero and all hospitals would be predicted to have the same probability of second-line uterotonic use. In the unadjusted model, the σ_b^2 (SE) was 0.61 (0.05); the mean (SE) probability of exposure to second-line uterotonics was 7.30% (0.28%) and 95% of the hospitals had a predicted probability between 1.69% (0.12%) and 26.58% (1.37%). These estimates remove random variation compared with the crude estimates, but do not account for potential between-hospital differences in patient and hospital characteristics. In the fully adjusted model (Model 5), the σ_b^2 decreased slightly to 0.57 (0.04). The mean predicted probability was 7.02% (0.26%), with 95% of the hospitals having a predicted probability between 1.69% (0.12%) and 24.96% (1.28%). The predicted probabilities of second-line uterotonic use for each hospital in rank-order in the unadjusted and fully adjusted models are presented in Figure 1. We observed little attenuation of the variation in use of these drugs when accounting for a broad range of patient and hospital characteristics.

Discussion

In this large, nationwide sample of delivery admissions in the United States, we observed significant variability in the frequency of second-line uterotonic use. Adjustment for patient demographics, mode of delivery, medical and obstetrical conditions, year of delivery, and hospital characteristics did little to explain this variation in practice, with the frequency of second-line uterotonic use ranging from 1.7% to 25% in the fully adjusted model. These findings suggest that the frequency of second-line uterotonic use is largely based on non-medical and institution-specific factors, such as individual physician preferences, uterotonic drug availability, drug cost and local hospital culture.

There has been a substantial increase in the incidence of atonic hemorrhage, including severe atonic hemorrhage requiring transfusion and/or hysterectomy, in a number of developed countries.^{1,5-8} In addition, hemorrhage remains a leading cause of maternal morbidity²⁴ and mortality² in the United States. As a consequence, there is a need to optimize preventive and therapeutic clinical practices in order to reduce rates of atonic PPH. We observed wide variability in the rates of second-line uterotonic use, which may be related to the limited data regarding the relative effectiveness or timing of administration of these drugs. Studies to address these evidence gaps are needed to ascertain optimal pharmacologic approaches for managing patients with uterine atony. This research should be made an important priority within the field of obstetrics, especially as rates of uterine atonic PPH are increasing.

Our study is subject to certain limitations inherent in its design. We were not able to examine the association between uterotonic drug use and postpartum blood loss or the time to achievement of adequate uterine tone; these data are not available in the Premier database. Future prospective studies are needed to evaluate and define the indications for second-line uterotonic use and to determine if their dose or timing is associated with less hemorrhage-related morbidity due to uterine atony. Because the database does not include the indications for which a medication was administered, we made the assumption that misoprostol was not being used as a treatment for uterine atony if administered at low doses or in patients with procedure codes indicating induction of labor; this may have led to an underestimation of the frequency of misoprostol use as a second-line uterotonic. We do not have information on the dose or timing of prophylactic oxytocin given before second-line uterotonic use, nor do we have information about the use of supplemental oxytocin. Identification of patient comorbidities and obstetric conditions that may be potential explanatory variables was based on ICD-9 CM codes. For some conditions, such as obesity, the sensitivity of the ICD-9 CM codes is limited and some potentially relevant risk factors for PPH (e.g., history of PPH, birth weight) do not have corresponding codes. While these limitations may lead us to underestimate the extent to which patient- and hospital-level covariates explain the variation in second-line uterotonic use, it is very unlikely to fully explain the significant interhospital differences that we report.

In summary, using a nationwide dataset, we observed wide interhospital variation in second-line uterotonic use that was not explained by patient- or hospital-level characteristics. With rates of atonic PPH steadily increasing in the United States, greater emphasis should be

placed on defining optimal pharmacologic strategies for the management of uterine atony and on investigating hospital- and provider-level factors to explain the wide variation in second-line uterotonic use.

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References

1. Bateman BT, Berman MF, Riley LE, Leffert LR. The epidemiology of postpartum hemorrhage in a large, nationwide sample of deliveries. *Anesth Analg*. 2010; 110:1368–73. [PubMed: 20237047]
2. Berg CJ, Callaghan WM, Syverson C, Henderson Z. Pregnancy-related mortality in the United States, 1998 to 2005. *Obstetrics and gynecology*. 2010; 116:1302–9. [PubMed: 21099595]
3. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. *Lancet*. 2006; 367:1066–74. [PubMed: 16581405]
4. King JF, Slaytor EK, Sullivan EA. Maternal deaths in Australia, 1997-1999. *Med J Aust*. 2004; 181:413–4. [PubMed: 15487953]
5. Bateman BT, Mhyre JM, Callaghan WM, Kuklina EV. Peripartum hysterectomy in the United States: nationwide 14 year experience. *Am J Obstet Gynecol*. 2012; 206:63. e1-8. [PubMed: 21982025]
6. Callaghan WM, Kuklina EV, Berg CJ. Trends in postpartum hemorrhage: United States, 1994-2006. *Am J Obstet Gynecol*. 2010; 202:353. e1-6. [PubMed: 20350642]
7. Knight M, Callaghan WM, Berg C, Alexander S, Bouvier-Colle MH, Ford JB, Joseph KS, Lewis G, Liston RM, Roberts CL, Oats J, Walker J. Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group. *BMC Pregnancy Childbirth*. 2009; 9:55. [PubMed: 19943928]
8. Kramer MS, Berg C, Abenhaim H, Dahhou M, Rouleau J, Mehrabadi A, Joseph KS. Incidence, risk factors, and temporal trends in severe postpartum hemorrhage. *Am J Obstet Gynecol*. 2013; 209:449. e1-7. [PubMed: 23871950]
9. American College of Obstetricians and Gynecologists: ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists Number 76, October 2006: Postpartum hemorrhage. *Obstet Gynecol*. 2006; 108:1039–47. [PubMed: 17012482]
10. Westhoff G, Cotter AM, Tolosa JE. Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage. *Cochrane Database Syst Rev*. 2013; 10:CD001808. [PubMed: 24173606]
11. Breathnach F, Geary M. Uterine atony: definition, prevention, nonsurgical management, and uterine tamponade. *Semin Perinatol*. 2009; 33:82–7. [PubMed: 19324236]
12. Lindenauer PK, Pekow P, Wang K, Gutierrez B, Benjamin EM. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. *JAMA*. 2004; 291:2092–9. [PubMed: 15126437]
13. Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med*. 2005; 353:349–61. [PubMed: 16049209]
14. Rothberg MB, Pekow PS, Lahti M, Brody O, Skiest DJ, Lindenauer PK. Antibiotic therapy and treatment failure in patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease. *JAMA*. 2010; 303:2035–42. [PubMed: 20501925]
15. Schneeweiss S, Seeger JD, Landon J, Walker AM. Aprotinin during coronary-artery bypass grafting and risk of death. *N Engl J Med*. 2008; 358:771–83. [PubMed: 18287600]

16. Bateman BT, Bykov K, Choudhry NK, Schneeweiss S, Gagne JJ, Polinski JM, Franklin JM, Doherty M, Fischer MA, Rassen JA. Type of stress ulcer prophylaxis and risk of nosocomial pneumonia in cardiac surgical patients: cohort study. *BMJ*. 2013; 347:f5416. [PubMed: 24052582]
17. Bateman BT, Huybrechts KF, Hernandez-Diaz S, Liu J, Ecker JL, Avorn J. Methylergonovine maleate and the risk of myocardial ischemia and infarction. *Am J Obstet Gynecol*. 2013; 209:459.e1-e13. [PubMed: 23850529]
18. Kuklina EV, Whiteman MK, Hillis SD, Jamieson DJ, Meikle SF, Posner SF, Marchbanks PA. An enhanced method for identifying obstetric deliveries: implications for estimating maternal morbidity. *Matern Child Health J*. 2008; 12:469–77. [PubMed: 17690963]
19. Rahman H, Pradhan A, Kharka L, Renjhen P, Kar S, Dutta S. Comparative evaluation of 50 microgram oral misoprostol and 25 microgram intravaginal misoprostol for induction of labour at term: a randomized trial. *J Obstet Gynaecol Can*. 2013; 35:408–16. [PubMed: 23756271]
20. Combs CA, Murphy EL, Laros RK Jr. Factors associated with postpartum hemorrhage with vaginal birth. *Obstet Gynecol*. 1991; 77:69–76. [PubMed: 1984230]
21. Combs CA, Murphy EL, Laros RK Jr. Factors associated with hemorrhage in cesarean deliveries. *Obstet Gynecol*. 1991; 77:77–82. [PubMed: 1984231]
22. Kramer MS, Dahhou M, Vallerand D, Liston R, Joseph KS. Risk factors for postpartum hemorrhage: can we explain the recent temporal increase? *J Obstet Gynaecol Can*. 2011; 33:810–9. [PubMed: 21846436]
23. Huybrechts KF, Rothman KJ, Brookhart MA, Silliman RA, Crystal S, Gerhard T, Schneeweiss S. Variation in antipsychotic treatment choice across US nursing homes. *J Clin Psychopharmacol*. 2012; 32:11–7. [PubMed: 22198446]
24. Wanderer JP, Leffert LR, Mhyre JM, Kuklina EV, Callaghan WM, Bateman BT. Epidemiology of obstetric-related ICU admissions in Maryland: 1999-2008*. *Crit Care Med*. 2013; 41:1844–52. [PubMed: 23648568]

Figure 1.

Estimated hospital-level uterotonic use rate by hospital rank of use: unadjusted model (blue diamonds) and fully adjusted model (red squares).

Table 1

Hospital-Level Frequencies of Second-Line Uterotonic Administration Among Delivery Admissions

	Mean (%)	Median (%)	Lower Quartile (%)	Upper Quartile (%)
Any Uterotonic	9.0	7.1	5.2	10.8
Methylergonovine maleate	6.3	5.2	3.1	7.5
Carboprost	1.5	1.0	0.5	1.6
Misoprostol	2.4	1.2	0.4	3.0

Data presented as percentages.

Any uterotonic refers to the use of at least 1 of the following uterotonic drugs: methylergonovine maleate, carboprost, misoprostol,

Table 2

Patient- and Facility-Level Characteristics According to Quartile of Uterotonic Administration.

	N (%) of Patients			
	1st quartile	2nd quartile	3rd quartile	4th quartile
Number of hospitals	91	92	92	92
Number of patients	420,117	669,952	502,484	588,363
Demographic characteristics				
Age group, years				
12-19	35133(8.4)	62608(9.3)	48494(9.7)	58792(10.0)
20-24	91045(21.7)	153396(22.9)	119029(23.7)	148597(25.3)
25-29	115440(27.5)	191375(28.6)	144067(28.7)	168221(28.6)
30-34	108003(25.7)	164167(24.5)	120811(24.0)	132415(22.5)
35-39	56619(13.5)	79910(11.9)	57067(11.4)	64777(11.0)
40-44	12973(3.1)	17463(2.6)	12308(2.4)	14589(2.5)
45-55	904(0.2)	1033(0.2)	708(0.1)	972(0.2)
Race/ethnicity				
African-American	52284(12.4)	101504(15.2)	72194(14.4)	70830(12.0)
Hispanic	48553(11.6)	76355(11.4)	50056(10.0)	70874(12.0)
Caucasian	213465(50.8)	361630(54.0)	260771(51.9)	278628(47.4)
Unknown	105815(25.2)	130463(19.5)	119463(23.8)	168031(28.6)
Method/Mode of delivery				
Cesarean delivery	152450(36.3)	238083(35.5)	162136(32.3)	193995(33.0)
Induction of labor	84692(20.2)	133070(19.9)	101722(20.2)	105904(18.0)
Medical/obstetrical conditions				
Preexisting hypertension	8753(2.1)	14965(2.2)	10402(2.1)	11606(2.0)
Gestational hypertension	14252(3.4)	25113(3.7)	18204(3.6)	19901(3.4)
Preeclampsia/Eclampsia	18669(4.4)	27911(4.2)	21459(4.3)	22851(3.9)
Preexisting diabetes	3458(0.8)	6373(1.0)	4348(0.9)	5471(0.9)
Gestational diabetes	23487(5.6)	37479(5.6)	27890(5.6)	33299(5.7)
Preterm delivery	29513(7.0)	51885(7.7)	35363(7.0)	44255(7.5)
Obesity	14061(3.3)	25295(3.8)	19612(3.9)	24367(4.1)
Polyhydramnios	4112(1.0)	4852(0.7)	4334(0.9)	5048(0.9)
Abnormal placentation (including previa)	4897(1.2)	7705(1.2)	6940(1.4)	7116(1.2)
Placental abruption	4179(1.0)	6892(1.0)	5584(1.1)	6347(1.1)
Previous cesarean delivery	70759(16.8)	113467(16.9)	78549(15.6)	94150(16.0)
Stillbirth	2557(0.6)	4134(0.6)	2998(0.6)	3555(0.6)

	<u>N (%) of Patients</u>			
	1 st quartile	2 nd quartile	3 rd quartile	4 th quartile
Multiple gestation	8783(2.1)	13264(2.0)	9147(1.8)	10539(1.8)
Chorioamnionitis	6148(1.5)	9270(1.4)	10461(2.1)	8689(1.5)
Hospital characteristics				
Teaching hospital(vs nonteaching)	182849(43.5)	291313(43.5)	175655(35.0)	143564(24.4)
Region				
Midwest	60584(14.4)	94635(14.1)	126140(25.1)	82176(14.0)
Northeast	146600(34.9)	104786(15.6)	52401(10.4)	47064(8.0)
South	180791(43.0)	323322(48.3)	206391(41.1)	250875(42.6)
West	32142(7.7)	147209(22.0)	117552(23.4)	208248(35.4)
Urban(vs rural)	367379(87.4)	633329(94.5)	454875(90.5)	520939(88.5)
Delivery volume tertile (annual delivery volume)				
<814	49878(11.9)	28862(4.3)	40380(8.0)	57114(9.7)
814-1892	153213(36.5)	125458(18.7)	165389(32.9)	109914(18.7)
>1892	217026(51.7)	515632(77.0)	296715(59.0)	421335(71.6)

Data presented as n (%)

Table 3

Estimated Hospital-level Uterotonic Usage Rate Based on Mixed-effects Models with Increasing Levels of Adjustment for Patient- and Hospital-level Factors.

Models	β_0 (SE)	σ_b^2 (SE) ^a	Uterotonic Usage Rate (%)		
			Average hospital (SE) ^b	Range ^c	
				2.5 %ile (SE)	97.5 %ile (SE)
Unadjusted	-2.54 (0.04)	0.61 (0.05)	7.30 (0.28)	1.69 (0.12)	26.58 (1.37)
Adjusted for:					
Demographics (Model 1)	-2.54 (0.04)	0.60 (0.05)	7.29 (0.28)	1.69 (0.12)	26.44 (1.36)
Demographics, Year of delivery (Model 2)	-2.55 (0.04)	0.60 (0.05)	7.27 (0.28)	1.69 (0.12)	26.38 (1.36)
Demographics, Year of delivery, Method/Mode of delivery (Model 3)	-2.55 (0.04)	0.60 (0.05)	7.27 (0.28)	1.69 (0.12)	26.33 (1.36)
Demographics, Year of delivery, Method/Mode of delivery, Medical/obstetrical conditions (Model 4)	-2.57 (0.04)	0.61 (0.05)	7.13 (0.27)	1.63 (0.12)	26.22 (1.37)
Demographics, Year of delivery, Method/Mode of delivery, Medical/obstetrical conditions, Hospital characteristics (Model 5)	-2.58 (0.04)	0.57 (0.04)	7.02 (0.26)	1.69 (0.12)	24.96 (1.28)

Estimate of the between-hospital variation. The random intercept b_j is assumed to be normally distributed with mean 0 and variance σ_b^2 . σ_b^2 represents the hospital-specific deviation from β_0 , the marginal (averaged across hospitals) probability of using a second-line uterotonic for a patient with the mean propensity score. With increasing levels of adjustment, there is less unexplained variation and σ_b^2 is expected to decrease.

^b Prescribing proportion for the "average" patient, defined as a patient with a mean propensity score. The average differs slightly between models since different factors are being adjusted for in the various models; it is estimated as $\exp(\beta_0 + b_j) / [1 + \exp(\beta_0 + b_j)]$.

^c The interval that contains the prescribing probability for the 95% hospitals in the center of the range is given by: $\{\exp(\beta_0 - 1.96\sigma_b) / [1 + \exp(\beta_0 - 1.96\sigma_b)] ; \exp(\beta_0 + 1.96\sigma_b) / [1 + \exp(\beta_0 + 1.96\sigma_b)]\}$ SE=standard error