OBSTETRICS

Thromboembolism incidence and prophylaxis during vaginal delivery hospitalizations

Alexander M. Friedman, MD; Cande V. Ananth, PhD, MPH; Eri Prendergast, MA; Suneet P. Chauhan, MD; Mary E. D'Alton, MD; Jason D. Wright, MD

OBJECTIVE: Although major international guidelines recommend venous thromboembolism (VTE) prophylaxis during vaginal delivery hospitalization for women with additional risk factors, US guidelines recommend prophylaxis for a very small number of women who are at particularly high risk for an event. The purpose of this study was to characterize practice patterns of VTE prophylaxis in the United States during vaginal delivery hospitalizations and to determine VTE incidence in this population.

STUDY DESIGN: A population-level database was used to analyze VTE incidence and use of VTE prophylaxis during vaginal delivery hospitalizations in the United States between 2006 and 2012 (n = 2,673,986). We evaluated whether patients received either pharmacologic or mechanical prophylaxis. Hospital-level factors and patient characteristics were included in multivariable regression analysis that evaluated prophylaxis administration.

RESULTS: We identified 2,673,986 women who underwent vaginal delivery. Incidence of VTE increased during the study period from 15.6-29.8 events per 100,000 delivery hospitalizations. Within the cohort, 2.6% of patients (n = 68,835) received VTE prophylaxis. Pharmacologic prophylaxis was rare; <1% of women received unfractionated or low-molecular-weight heparin. Although patients with thrombophilia or a previous VTE event were likely to receive prophylaxis (60.8% and 72.8%, respectively), patients with risk factors for VTE such as obesity, smoking, and heart disease were unlikely to receive prophylaxis (rates of 5.9%, 3.3%, and 6.2%, respectively).

CONCLUSION: Our findings demonstrate that the administration of VTE prophylaxis outside a small group of women at extremely high risk for VTE is rare during vaginal delivery hospitalization. Given that VTE incidence is rising in this population, further research to determine whether broadening prophylaxis for VTE may reduce severe maternal morbidity and death is indicated.

Key words: obstetric thromboembolism, risk assessment, severe maternal morbidity

Cite this article as: Friedman AM, Ananth CV, Prendergast E, et al. Thromboembolism incidence and prophylaxis during vaginal delivery hospitalizations. Am J Obstet Gynecol 2015;212:221.e1-12.

Venous thromboembolism (VTE) is a leading cause of maternal death. A systematic review of maternal deaths that was performed by the World Health Organization implicated embolism in 14.9% of maternal deaths in developed countries[1]; the Centers for Disease Control and Prevention estimates that thrombotic pulmonary embolism accounted for 9.4% of pregnancy-related deaths from 2006-2009.[2] In the United States, strategies to reduce VTE have focused primarily on perioperative cesarean prophylaxis and prenatal risk assessment of women who are at particularly high risk for events.[3-7] Despite these efforts that included increasing use of mechanical prophylaxis during cesarean delivery,[8] obstetric thromboembolism has increased 72% during delivery hospitalizations from 1998-2009 according to data from the Nationwide Inpatient Sample.[9,10]

Recommendations for thromboprophylaxis during vaginal delivery in the United States have focused on women at the highest risk for VTE: women with acquired or hereditary thrombophilia and/or previous thromboembolic events.[4,7] VTE is twice as common after cesarean delivery compared with vaginal deliveries[9]; because more women deliver vaginally, many events occur among women who do not undergo cesarean delivery. The prevalence of risk factors for VTE is rising,[9] with obesity, advanced maternal age, and major medical comorbidities becoming increasingly common.[3,11-13] In the United Kingdom, national guidelines recommend postpartum pharmacologic prophylaxis for women with previous VTE events or thrombophilias. Additionally, these guidelines recommend prophylaxis for other common risk factors that include obesity, maternal age ≥35 years, smoking, preeclampsia,

From the Department of Obstetrics and Gynecology, College of Physicians and Surgeons (Drs Friedman, Ananth, D'Alton, and Wright and Ms Prendergast), and Department of Epidemiology, Joseph L. Mailman School of Public Health (Dr Ananth), Columbia University, New York, NY, and Division of Maternal-Fetal Medicine, Department of Obstetrics, Gynecology, and Reproductive Sciences, UT Health Science Center, Houston, TX (Dr Chauhan).

Received May 19, 2014; revised Aug. 3, 2014; accepted Sept. 15, 2014.

The authors report no conflict of interest.

Corresponding author: Alexander Friedman, MD. Alexander.Friedman@gmail.com

0002-9378/$36.00 • © 2015 Elsevier Inc. All rights reserved. • http://dx.doi.org/10.1016/j.ajog.2014.09.017

postpartum hemorrhage, and prolonged labor (Table 1).[14,15] In the setting of a comprehensive strategy to reduce VTE, death from this cause in the United Kingdom decreased by more than one-half, from 1.94 maternal deaths per 100,000 deliveries from 2003-2005 to 0.79 maternal deaths per 100,000 from 2006-2008.[14]

The objectives of this study were to (1) characterize contemporary practice patterns for thromboembolism prophylaxis during vaginal-delivery hospitalizations in the United States, (2) characterize the incidence of thromboembolism, and (3) to determine whether potential opportunities to reduce risk in this clinical setting are being missed.

TABLE 1
Royal College of Obstetricians and Gynaecologists recommendations for postpartum venous thromboembolism prophylaxis

Variable	Recommendation
Major risk factors	At least 7 days of postnatal prophylactic low-molecular-weight heparin is recommended if any 1 risk factor is present
Any previous venous thromboembolism[a]	
Anyone requiring antenatal low-molecular-weight heparin [a]	
Cesarean delivery in labor	
Asymptomatic thrombophilia (inherited or acquired)	
Obesity (body mass index, >40 kg/m^2)[b]	
Prolonged hospital admission	
Medical comorbidities (eg, heart or lung disease, systemic lupus erythematosus, cancer, inflammatory conditions, sickle cell disease, intravenous drug user)	
Minor risk factors	At least 7 days of postnatal prophylactic low-molecular-weight heparin is recommended if ≥2 risk factors are present
Age >35 y	
Obesity (body mass index, >30 kg/m^2)	
Parity ≥ 3	
Smoker	
Elective cesarean delivery	
Any surgical procedure in the puerperium	
Gross varicose veins[c]	
Current systemic infection	
Immobility (eg, paraplegia, symphysis pubis dysfunction with reduced mobility, long distance travel[d])	
Preeclampsia	
Midcavity rotational operative delivery	
Prolonged labor (>24 hr)	
Postpartum hemorrhage >1 L or blood transfusion	

Adapted from Royal College of Obstetricians and Gynaecologists.[15]

[a] At least 6 weeks postnatal prophylaxis required; [b] Based on earliest documented weight during prenatal care; [c] Symptomatic, above the knee or associated with phlebitis/edema, skin changes; [d] >4 hours.

Friedman. Vaginal delivery and thromboprophylaxis. Am J Obstet Gynecol 2015.

METHODS

The Perspective (Premier, Charlotte, NC) was used for the analysis. This voluntary, fee-supported database captures hospitalization data from >600 acute care hospitals in the United States. Patient demographic information, disease and procedure codes, and hospital and provider characteristics are included. The database also contains all billed services such as medications, devices, laboratory tests, and radiologic imaging. Data undergo a quality control process that includes 95 separate quality assurance and data validation checks that confirm accuracy before being used for research.[16] For each individual hospital that is included in the dataset, 100% of discharge data is included. Perspective has been used in numerous outcomes studies[17,18] that include evaluations of postsurgical thromboprophylaxis.[8,19-21] In 2006, approximately 15% of all hospitalizations within the United States (almost 5.5 million hospital discharges) were captured in Perspective.[17] All data were deidentified, and the analysis was approved by the Columbia University institutional review board.

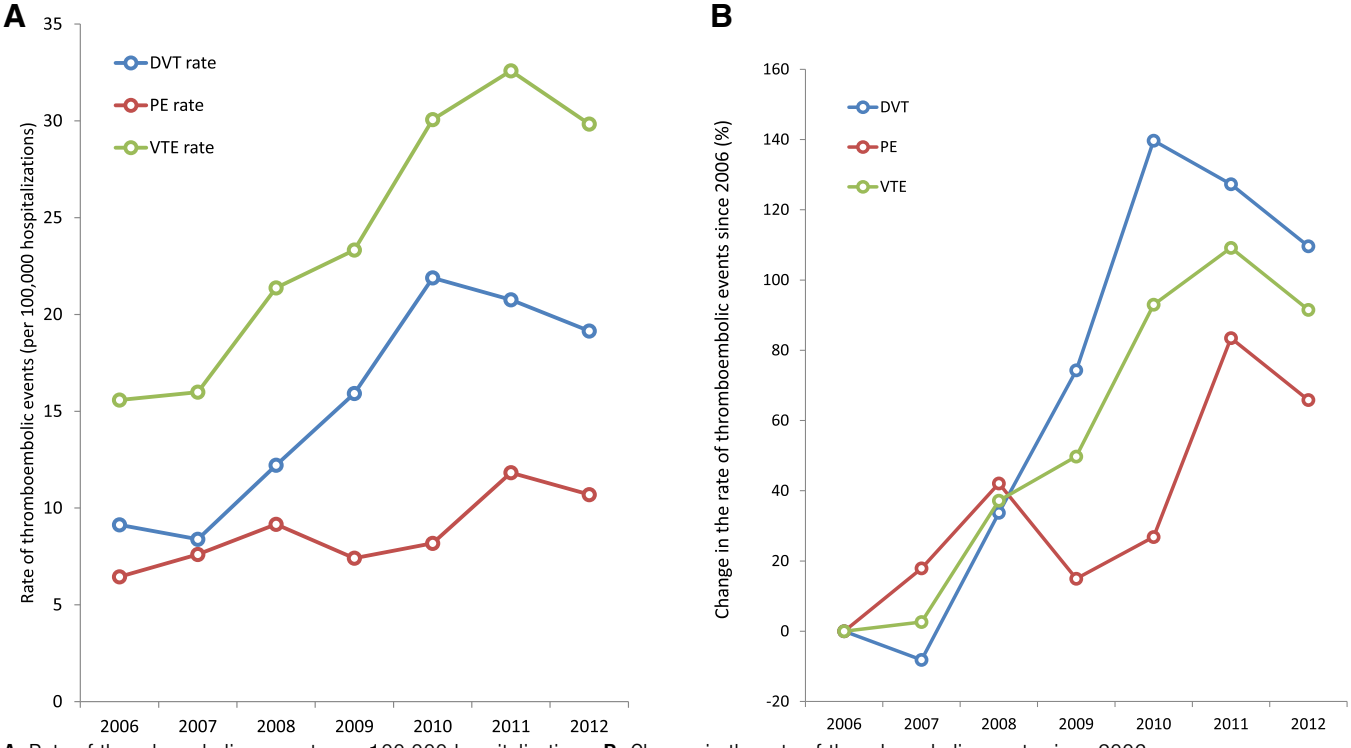
We analyzed the cases of women who underwent vaginal delivery from 2006-2012. Patients were identified with the use of an enhanced method to capture delivery hospitalization based on *International Classification of Diseases—9th Revision* (ICD-9) billing codes V27 and 650 and diagnosis-related group codes 370-375.[22] Patients were excluded if they underwent cesarean delivery with a previously described method.[8] The primary outcome of interest was the use of any VTE prophylaxis during the delivery hospitalization. VTE prophylaxis was classified as mechanical, pharmacologic, or combination pharmacologic/mechanical. Cases that received either graduated compression

stockings or intermittent pneumatic compression were coded as receiving mechanical prophylaxis. Patients who received unfractionated heparin, low-molecular-weight heparin (including enoxaparin sodium, tinzaparin sodium, or dalteparin sodium), or fondaparinux sodium were classified as having received pharmacologic prophylaxis. Patients were classified as having received mechanical prophylaxis if they received an appropriate device during any hospital day. Women were classified as having received pharmacologic prophylaxis if they received an appropriate drug during any hospital day.

Epidemiologic literature was reviewed to identify relevant medical, surgical, and obstetric risk factors that were associated with obstetric thromboembolism.[11,13,23-33] Through an iterative process, clinical risk factors that were demonstrated to be associated with increased postpartum thromboembolism risk in large observational and population-based cohorts were chosen for inclusion in the analysis. Hospital characteristics included location (urban vs rural), teaching status (teaching vs nonteaching), annualized vaginal delivery volume (by quartile), geographic region (Midwest, Northeast, South, West), and hospital size based on the number of beds (<400, 400-600, or >600 beds). Patient demographics included age, race, year of hospitalization, and marital status. Comorbidity was estimated with the Elixhauser index that combines comorbid conditions based on ICD coding into an overall measure of medical comorbidity that is used in large administrative data.[34] Comorbidity was also estimated with an index that was designed specifically for use in obstetric patient populations. This index uses demographic and medical risk factors (such as congenital heart disease, advanced maternal age, diabetes mellitus) that are predictive of maternal death and end-organ injury (acute renal failure, pulmonary edema, stroke) to provide a simple measure for summarizing the burden of maternal illness in an obstetric population.[35]

The association between thromboembolism prophylaxis and clinical and demographic variables was compared with the use of χ^2 tests. Rates of deep vein thrombosis, pulmonary embolism, and VTE are reported per 100,000 delivery hospitalizations. *VTE* was defined as the sum of deep vein thrombosis and pulmonary embolism cases. Cases of VTE were identified by ICD-9 codes for pulmonary embolism (415.1, 415.11, 415.12, 415.19, v12.51, 673.20, 673.21, 673.22, 673.24, 673.80, 673.81, 673.82, 673.84) and deep vein thrombosis (451.1, 451.11, 451.19, 451.2, 451.81, 451.9, 453.4, 453.40, 453.41, 453.42, 453.9, 453.8, 671.40, 67.42, 671.44, 997.2, 999.2). To account for the influence of clinical and demographic factors on the use of prophylaxis, we developed mixed effects log-binomial regression

FIGURE 1
Thromboembolism events



A, Rate of thromboembolism events per 100,000 hospitalizations. **B,** Change in the rate of thromboembolic events since 2006.

DVT, deep vein thrombosis; *PE*, pulmonary embolism; *VTE*, venous thromboembolism.

Friedman. Vaginal delivery and thromboprophylaxis. Am J Obstet Gynecol 2015.

TABLE 2
Demographic characteristics: venous thromboembolism prophylaxis for women hospitalized for a vaginal delivery

Characteristic	No prophylaxis		Any prophylaxis		*P* value
	n	%	n	%	
All patients	2,605,151	97.4	68,835	2.6	
Age, y					< .001
<20	282,392	97.8	6334	2.2	
20-24	666,383	97.7	15,400	2.3	
25-29	753,547	97.7	18,092	2.3	
30-34	593,825	97.5	15,499	2.5	
>34	312,629	96.9	9885	3.1	
Race					< .001
White	1,354,569	97.7	32,356	2.3	
Black	346,027	96.6	12,245	3.4	
Hispanic	234,170	97.6	5780	2.4	
Other/Unknown	674,010	97.9	14,829	2.2	
Year of delivery					< .001
2006	366,317	98.4	5950	1.6	
2007	374,851	98.3	6662	1.8	
2008	352,438	97.8	7825	2.2	
2009	354,460	97.3	9884	2.7	
2010	367,470	96.9	11,675	3.1	
2011	402,359	97.1	11,911	2.9	
2012	390,881	97.2	11,303	2.8	
Marital status					< .001
Married	1,262,380	97.8	28,897	2.2	
Single	1,035,563	97.1	31,201	2.9	
Unknown	310,833	98.4	5112	1.6	
Insurance status					< .001
Medicare	14,737	96.0	616	4.0	
Medicaid	1,132,089	97.6	28,381	2.5	
Commercial	1,304,306	97.9	27,826	2.1	
Uninsured	70,279	97.6	1707	2.4	
Unknown	87,365	92.9	6680	7.1	
Elixhauser index					< .001
None	1,907,431	98.0	39,791	2.0	
1	489,590	97.0	15,169	3.0	
2	131,391	95.9	5642	4.1	
>2	80,364	94.6	4608	5.4	
Hospital location					< .001
Rural	277,621	98.0	5745	2.0	
Urban	2,331,155	97.5	59,465	2.5	

Friedman. Vaginal delivery and thromboprophylaxis. Am J Obstet Gynecol 2015. *(continued)*

TABLE 2
Demographic characteristics: venous thromboembolism prophylaxis for women hospitalized for a vaginal delivery *(continued)*

Characteristic	No prophylaxis n	No prophylaxis %	Any prophylaxis n	Any prophylaxis %	*P* value
Hospital teaching status					< .001
Nonteaching	1,654,770	97.7	38,812	2.3	
Teaching	954,006	97.3	26,398	2.7	
Hospital size: beds, n					< .001
<400	1,468,487	97.8	32,571	2.2	
400-600	720,589	97.2	20,465	2.8	
>600	419,700	97.2	12,174	2.8	
Hospital region					< .001
Midwest	506,126	98.2	9132	1.8	
Northeast	410,908	98.4	6763	1.6	
South	1,084,933	97.2	31,028	2.8	
West	606,809	97.1	18,287	2.9	
Hospital delivery volume quartile					< .001
Lowest volume	646,488	97.6	16,170	2.4	
2nd	652,837	97.9	14,122	2.1	
3rd	662,416	98.3	11,308	1.7	
Highest volume	647,035	96.5	23,610	3.5	
Length of hospitalization, d					< .001
<7	2,596,670	97.8	59,770	2.2	
≥7	12,106	69.0	5440	31.0	
Obstetric comorbidity index					< .001
0	1,989,392	98.0	40,325	2.0	
1	401,979	97.1	11,900	2.9	
2	156,034	95.8	6814	4.2	
3	33,401	93.7	2229	6.3	
4	9,489	91.2	911	8.8	
5	13,821	87.0	2069	13.0	
>5	4,660	82.9	962	17.1	

Univariate analysis of hospital-level and demographic covariates. Delivery volume was calculated by dividing deliveries into quartiles by individual hospital volume, with hospitals with the largest individual delivery volumes in the highest volume quartile.

Friedman. Vaginal delivery and thromboprophylaxis. Am J Obstet Gynecol 2015.

models to examine the use of prophylaxis. These models included all the clinical and demographic characteristics and a hospital-specific random intercept-term to account for hospital-level clustering. Results are reported as risk ratios with 95% confidence intervals (95% CI). A probability value of < .05 was considered statistically significant. All analyses were performed with SAS software (version 9.3; SAS Institute Inc, Cary, NC).

Results

A total of 4,076,078 women were identified as having a delivery hospitalization; 1,402,902 of whom were excluded for delivering by cesarean. A total of 2,673,986 women who had been hospitalized for vaginal delivery were identified and included in the analysis. The incidence of both pulmonary embolism and deep vein thrombosis increased over the course of the study period, and VTE incidence nearly doubled between 2006 and 2012 (Figure 1); 414 women were diagnosed with deep vein

TABLE 3
Medical and obstetric risk factors: venous thromboembolism prophylaxis for women hospitalized for a vaginal delivery

	No prophylaxis		Any prophylaxis		
Risk factor	**n**	**%**	**n**	**%**	***P* value**
All patients	2,605,151	97.4	68,835	2.6	
Previous venous thromboembolism					< .001
No	2,607,347	97.7	61,378	2.3	
Yes	1429	27.2	3832	72.8	
Obesity					< .001
No	2,548,640	97.7	61,449	2.4	
Yes	60,136	94.1	3761	5.9	
Smoking					< .001
No	2,472,954	97.6	60,967	2.4	
Yes	135,822	97.0	4243	3.0	
Immobility					< .001
No	2,608,718	97.6	65,177	2.4	
Yes	58	63.7	33	36.3	
Varicose veins					< .001
No	2,605,123	97.6	64,887	2.4	
Yes	3653	91.9	323	8.1	
Multiparity					< .001
No	2,592,719	97.6	64,358	2.4	
Yes	16,057	95.0	852	5.0	
Hyperemesis					< .001
No	2,608,315	97.6	65,175	2.4	
Yes	461	92.9	35	7.0	
Multiple gestation					< .001
No	2,596,226	97.6	64,098	2.4	
Yes	12,550	91.9	1112	8.1	
Assisted reproductive technology					< .001
No	2,606,959	97.6	65,123	2.4	
Yes	1817	95.4	87	4.6	
Preeclampsia					< .001
No	2,466,523	97.8	56,261	2.2	
Yes	142,253	94.1	8949	5.9	
Placental abruption					< .001
No	2,593,104	97.6	63,943	2.4	
Yes	15,671	92.5	1267	7.5	
Endometritis					< .001
No	2,604,788	97.6	64,834	2.4	
Yes	3988	91.4	376	8.6	

Friedman. Vaginal delivery and thromboprophylaxis. Am J Obstet Gynecol 2015.

(continued)

TABLE 3
Medical and obstetric risk factors: venous thromboembolism prophylaxis for women hospitalized for a vaginal delivery *(continued)*

Risk factor	No prophylaxis		Any prophylaxis		*P* value
	n	%	n	%	
Pyelonephritis					< .001
No	2,607,415	97.6	65,097	2.4	
Yes	1361	92.3	113	7.7	
Systemic inflammatory response syndrome					< .001
No	2,608,763	97.6	65,206	2.4	
Yes	13	76.5	4	23.5	
Sepsis					< .001
No	2,608,588	97.6	65,053	2.4	
Yes	188	54.5	157	45.5	
Pneumonia					< .001
No	2,608,297	97.6	64,972	2.4	
Yes	479	66.8	238	33.2	
Influenza					< .001
No	2,608,433	97.6	65,181	2.4	
Yes	343	92.2	29	7.8	
Adult respiratory distress syndrome					< .001
No	2,608,686	97.6	65,115	2.4	
Yes	90	48.7	95	51.4	
Postpartum hemorrhage					< .001
	2,535,267	97.6	61,374	2.4	
	73,509	95.0	3836	5.0	
Transfusion					< .001
	2,597,084	97.6	63,377	2.4	
	11,692	86.5	1833	13.5	
Heart disease					< .001
No	2,593,200	97.6	64,179	2.4	
Yes	15,576	93.8	1031	6.2	
Sickle cell					< .001
No	2,608,214	97.6	65,163	2.4	
Yes	562	92.3	47	7.7	
Systemic lupus erythematosus					< .001
No	2,606,838	97.6	64,876	2.4	
Yes	1938	85.3	334	14.7	
Renal disease					< .001
No	2,608,131	97.6	64,982	2.4	
Yes	645	73.9	228	26.1	

Friedman. Vaginal delivery and thromboprophylaxis. Am J Obstet Gynecol 2015. *(continued)*

TABLE 3
Medical and obstetric risk factors: venous thromboembolism prophylaxis for women hospitalized for a vaginal delivery *(continued)*

Risk factor	No prophylaxis		Any prophylaxis		*P* value
	n	%	n	%	
Hypercoagulability					< .001
No	2,606,331	97.7	61,423	2.3	
Yes	2445	39.2	3787	60.8	
Surgical					< .001
No	2,608,428	97.6	64,808	2.4	
Yes	348	46.4	402	53.6	
Cancer					< .001
No	2,608,509	97.6	65,188	2.4	
Yes	267	92.4	22	7.6	

Friedman. Vaginal delivery and thromboprophylaxis. Am J Obstet Gynecol 2015.

thrombosis, and 236 women were diagnosed with pulmonary embolism. Use of either mechanical or pharmacologic prophylaxis was uncommon. Of the 68,835 women (2.6%) who received prophylaxis, most (67.5%; n = 46,474 women) received mechanical prophylaxis. Less than 1.0% of patients received either unfractionated or low-molecular-weight heparin (0.39% and 0.45%, respectively). Table 2 displays the patient demographics and hospital characteristics of the cohort. Prophylaxis increased with comorbidity and varied significantly based on geography, hospital delivery volume, and race ($P < .001$). The use of prophylaxis increased over the course of the study period from 1.6% in 2006 to 2.8% in 2012 ($P < .001$). This increase was largely due to mechanical prophylaxis increasing from 0.8% in 2006 to 2.1% in 2012.

Analysis of medical and obstetric risk factors for VTE (Table 3) demonstrated that patients with thrombophilia and previous thromboembolism were likely to receive prophylaxis; 60.8% and 72.8%, respectively, of patients with these diagnoses received prophylaxis. Prophylaxis for other risk factors for VTE such as obesity, smoking, and preeclampsia was rare; women who were diagnosed with these conditions received prophylaxis in 5.9%, 3.0%, and 5.9% of cases, respectively. In multivariate regression analysis, the risk ratios for prophylaxis for a history of thromboembolism and hypercoagulability were 10.14 (95% CI, 9.74–10.56) and 9.32 (95% CI, 8.96–9.71), respectively (Table 4). Other medical risk factors for thromboembolism were associated generally with either a marginally increased probability of prophylaxis or no increase at all. For example, the risk ratios for obesity, smoking, and preeclampsia were 1.29 (95% CI, 1.25–1.34), 1.03 (95% CI, 1.00–1.07), and 1.23 (95% CI, 1.19–1.27), respectively. The obstetric comorbidity index demonstrated that a relatively small number of patients in this cohort were at particularly high risk for major maternal morbidity and/or death. Figure 2 shows the number of patients by obstetric comorbidity index score on a logarithmic scale and the rate of prophylaxis by comorbidity score. The logarithmic scale was used to better represent the relatively small number of patients with high obstetric comorbidity index scores.

Comment

Our findings confirm that routine thromboprophylaxis for women who undergo vaginal deliveries in the United States is limited primarily to a small number of patients at particularly high risk for thromboembolic disease. This includes women with previous thromboembolism and women who have been diagnosed with hypercoagulability. This clinical management follows recommendations from the American College of Obstetricians and Gynecologists and the American College of Chest Physicians that supports postpartum prophylaxis for women who have had previous events and/or hypercoagulability.[4,7]

Routine postcesarean delivery thromboprophylaxis has been identified as a means of systematically reducing maternal death based on nonrandomized study findings.[13] Although empiric postcesarean delivery prophylaxis does not appear to have been implemented optimally across care settings,[8] even with theoretically perfect use, the reduction of thromboembolism incidence with this strategy is limited by the fact that most women deliver vaginally. For example, data from the Nationwide Inpatient Sample from 2006-2009 determined that 46.7% of delivery hospitalization VTE events occurred in the setting of vaginal delivery. In the United Kingdom, where cesarean delivery is less common and postcesarean delivery pharmacologic prophylaxis is more frequent, a population-based study found that 70.9% of postpartum VTE

TABLE 4
Multivariable models of factors predictive of venous thromboembolism prophylaxis during a vaginal delivery hospitalization

Covariate	Any prophylaxis, risk ratio (95% confidence interval)
Age, y	
<20	Referent
20-24	1.08 (1.05–1.12)
25-29	1.23 (1.19–1.27)
30-34	1.36 (1.32–1.41)
>34	1.27 (1.23–1.33)
Race	
White	Referent
Black	1.00 (0.98–1.02)
Hispanic	0.94 (0.91–0.97)
Other/Unknown	0.77 (0.75–0.79)
Year of delivery	
2006	Referent
2007	1.15 (1.11–1.19)
2008	1.35 (1.30–1.39)
2009	1.64 (1.59–1.69)
2010	1.88 (1.82–1.94)
2011	1.96 (1.90–2.02)
2012	1.94 (1.88–2.00)
Marital status	
Married	Referent
Single	1.00 (0.98–1.02)
Unknown	1.06 (1.01–1.11)
Insurance status	
Commercial	Referent
Medicaid	1.06 (1.04–1.08)
Medicare	1.11 (1.02–1.21)
Uninsured	0.95 (0.90–1.00)
Unknown	1.25 (1.21–1.29)
Elixhauser index	
0	0.81 (0.80–0.84)
1	Referent
2	1.16 (1.12–1.20)
>2	1.18 (1.13–1.22)

Friedman. Vaginal delivery and thromboprophylaxis. Am J Obstet Gynecol 2015. (continued)

TABLE 4
Multivariable models of factors predictive of venous thromboembolism prophylaxis during a vaginal delivery hospitalization *(continued)*

Covariate	Any prophylaxis, risk ratio (95% confidence interval)
Hospital location	
Metropolitan	Referent
Nonmetropolitan	0.78 (0.62–0.98)
Hospital teaching status	
Teaching	Referent
Nonteaching	1.08 (0.86–1.36)
Hospital size: beds, n	
<400	Referent
400-600	1.26 (0.97–1.62)
>600	1.29 (0.88–1.87)
Hospital region	
Northeastern	Referent
Midwest	1.02 (0.75–1.38)
South	1.46 (1.10–1.94)
Western	0.65 (0.47–0.90)
Hospital volume	
Lowest quartile	Referent
2nd quartile	0.98 (0.78–1.24)
3rd quartile	0.87 (0.65–1.15)
Highest quartile	1.26 (0.88–1.81)
Obstetric comorbidity index	
0	Reference
1	1.25 (1.21–1.28)
2	1.49 (1.44–1.54)
3	1.64 (1.56–1.73)
4	1.83 (1.69–1.97)
5	2.53 (2.39–2.68)
>5	2.15 (1.98–2.34)
Length of hospital stay, d	
<7	Referent
≥7	6.23 (6.07–6.47)

Friedman. Vaginal delivery and thromboprophylaxis. Am J Obstet Gynecol 2015. (continued)

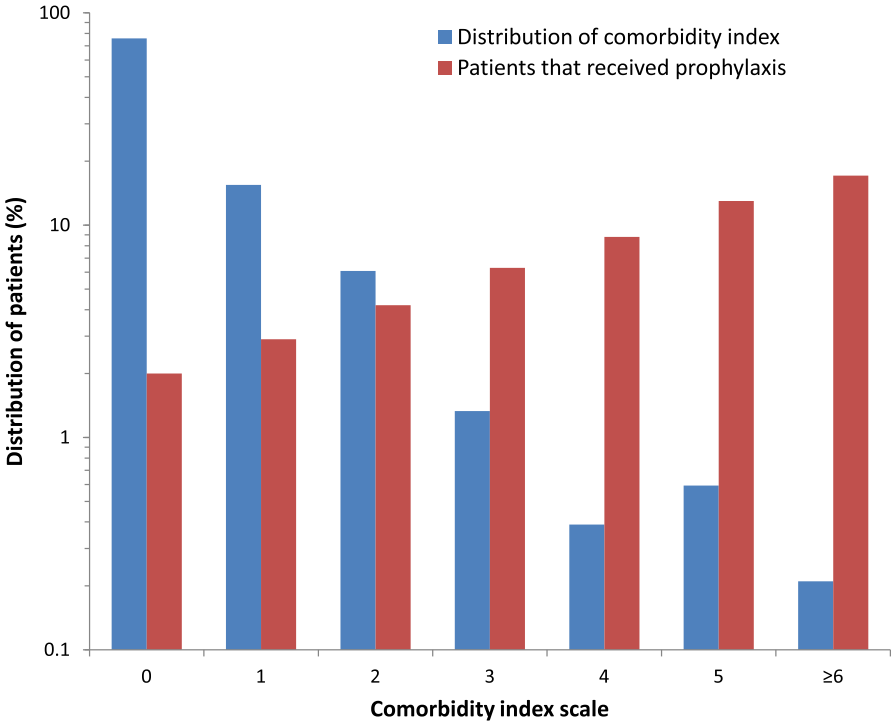
TABLE 4
Multivariable models of factors predictive of venous thromboembolism prophylaxis during a vaginal delivery hospitalization *(continued)*

Covariate	Any prophylaxis, risk ratio (95% confidence interval)
History of thromboembolism	10.14 (9.74–10.56)
Obesity	1.29 (1.25–1.34)
Smoking	1.03 (1.00–1.07)
Immobility	5.71 (4.03–8.07)
Varicose veins	3.23 (2.89–3.60)
Multiparity	1.17 (1.09–1.25)
Hyperemesis	1.88 (1.34–2.60)
Multiple gestation	1.48 (1.39–1.59)
Assisted reproductive technology	1.04 (0.84–1.28)
Preeclampsia	1.23 (1.19–1.27)
Placental abruption	1.62 (1.53–1.72)
Endometritis	1.15 (1.04–1.28)
Pneumonia	1.32 (1.15–1.51)
Pyelonephritis	1.50 (1.24–1.80)
Influenza	0.83 (0.57–1.20)
Adult respiratory distress syndrome	1.59 (1.28–1.97)
Postpartum hemorrhage	1.50 (1.45–1.56)
Transfusion	1.66 (1.57–1.75)
Heart disease	1.02 (0.95–1.08)
Sickle cell disease	0.99 (0.74–1.33)
Systemic lupus erythematosus	1.32 (1.18–1.48)
Renal disease	0.91 (0.79–1.05)
Hypercoagulable state	9.32 (8.96–9.71)
Surgical procedure	2.75 (2.45–3.08)
Cancer	1.87 (1.23–2.86)

All of the variables in the table were included in the multivariate analysis. Risk ratios for each of the demographic and hospital level variables are reported in relation to a referent. Medical and obstetric variable risk ratios are reported with absence of the condition as the referent.

Friedman. Vaginal delivery and thromboprophylaxis. Am J Obstet Gynecol 2015.

FIGURE 2
Incidence of prophylaxis based on comorbidity score



Distribution of patients by comorbidity score as a percentage of all patients is indicated by the *blue bars* in the bar graph. For each comorbidity score group, incidence of prophylaxis as a percentage of all patients is indicated by the *red bars*.

Friedman. Vaginal delivery and thromboprophylaxis. Am J Obstet Gynecol 2015.

events occurred after vaginal delivery and that 29.1% of events occurred after cesarean delivery.[13]

Data from US population-based research, including ours, demonstrates that thromboembolism risk during delivery hospitalizations has not been reduced and may be increasing.[9,10] Callaghan et al[10] analyzed data from the Nationwide Inpatient Sample and found that thrombotic embolism increased 72% from 1998-2009 for women who were hospitalized for delivery. Lack of reduction of VTE may be due to the high prevalence of comorbid risk factors. A population-based study from the United Kingdom of 376,154 pregnancies demonstrated that, in an adjusted model (accounting for mode of delivery), obesity, multiparity, and hemorrhage were associated with increased risk for VTE with incidence risk ratios of 3.45 (95% CI, 2.54−4.69), 1.92 (95% CI, 1.22−2.99), and 2.53 (95% CI, 1.34−4.79) respectively. Comparatively, cesarean delivery was associated with an incidence risk ratio of 1.88 (95% CI, 1.44−2.45).

Many risk factors that are associated with increased VTE risk are increasingly common in the obstetric population. The 2009-2010 National Health and Nutrition Examination Survey found that 31.9% of women 20-39 years old had a body mass index of $\geq$30 kg/m^2, which is a dramatic increase compared with 3 decades ago.[36] From 1990-2012 birth rates for women 35-39 and 40-44 years old have risen steadily in the setting of overall declining fertility.[37] Using data from the Nationwide Inpatient Sample, Ghaji et al[9] found that from 1994-1997 to 2006-2009, medical and obstetric conditions such as diabetes mellitus, heart disease, hypertension, obesity, blood transfusion, hemorrhage, preeclampsia, and postnatal infection were each significantly more likely to be present during delivery hospitalizations during which VTE occurred.

Providing prophylaxis to women who undergo vaginal delivery hospitalization and who have multiple risk factors for VTE may represent a means of systemically reducing VTE incidence. However, currently, there are no large-scale, cost-effective, validated strategies that have been demonstrated to reduce VTE incidence in this population. Although the most recent UK "Saving Mothers' Lives" report demonstrated decreased overall maternal death from thromboembolism in the setting of a comprehensive prophylaxis strategy, it is unclear to what degree targeting high-risk patients who undergo vaginal delivery for prophylaxis reduced overall risk.[14] Given the burden that is posed by maternal thromboembolic disease, further clinical, cost-effectiveness, and decision analysis research is needed urgently to determine the optimal prophylaxis treatment for these patients. Although a large randomized study that would evaluate prophylaxis would be particularly useful in the determination of optimal management strategies, such a trial would be large, lengthy, and very expensive.

Although our study has several notable strengths that include a large cohort of patients in diverse geographic and hospital settings, we recognize important limitations. First, the primary purpose of claims data is billing, and we are unable exclude the possibility of prophylaxis misclassification in some patients, including those who may have been receiving heparin for VTE treatment. This number is likely small given that (1) the Perspective database has been validated in numerous studies that examine drug and device use that includes a study of thromboembolism prophylaxis in an obstetric population[8,38-40] and (2) the number of VTE events is very small relative to the number of patients included in the study. Second, although we are able to estimate the number of patients who received prophylaxis, it is not possible to examine the quality of prophylaxis. Compliance with mechanical

prophylaxis among obstetric patients may be suboptimal given poor appropriate-use rates demonstrated in research in other specialties.[41,42] Third, reported use of pharmacologic prophylaxis does not ensure that the proper dose of the drug was administered throughout the hospitalization. Fourth, because administrative data do not allow for direct determination of patient attributes such as body mass index, it is highly likely that the prevalence of some clinical risk factors are underestimated. Although under-coding likely biased our findings towards overestimation of prophylaxis for risk factors like obesity, we retained these variables in the model, given that rates of prophylaxis were still very low and likely representative of clinical practice. A more concerning issue regarding this type of data model is that, although coding for high acuity conditions such as pulmonary embolism is likely to be more accurate than lower acuity comorbid risk factors, without chart review it is not possible to further validate VTE diagnoses and determine whether VTE incidence is over- or underestimated.[43,44] Fifth, given the large sample size, statistically significant values are highly likely to be noted across comparison groups and may not represent clinically significant differences. Sixth, one of the covariates in the model, hospital length of stay, may represent an outcome (or complication of) prophylaxis as well as risk factor. However, given that, in most circumstances, prolonged hospital stay is a risk factor and is a criteria for prophylaxis based on Royal College of Obstetricians and Gynaecologists recommendations, it was retained in the model. Finally, as with any observational study, we are unable to capture individual patient and physician preferences that likely influence prophylaxis.

In conclusion, our study found that thromboprophylaxis during vaginal delivery hospitalizations was very rare, with the exception of a small group of patients at particularly high risk for an event. Under current prophylaxis strategies, our data demonstrate increased VTE incidence during vaginal delivery hospitalizations. Prophylaxis for women with multiple risk factors may represent an opportunity to reduce severe maternal morbidity and death. Further care quality, comparative effectiveness, and clinical research is needed to better characterize the patient population and drug and device regimens that would benefit from thromboembolism prophylaxis during vaginal delivery hospitalizations. In particular, cost-effectiveness and decision-analysis work that evaluates prophylaxis in women who undergo vaginal deliveries and have additional risk factors may be useful in the determination of potential benefits and strategies for optimal prophylaxis. ■

REFERENCES

1. 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.
2. Centers for Disease Control and Prevention. Pregnancy Mortality Surveillance System. [cited 2014 August 1]; Available at: http://www.cdc.gov/reproductivehealth/MaternalInfantHealth/PMSS.html. Accessed Oct. 6, 2014.
3. Clark SL, Belfort MA, Dildy GA, Herbst MA, Meyers JA, Hankins GD. Maternal death in the 21st century: causes, prevention, and relationship to cesarean delivery. Am J Obstet Gynecol 2008;199:36.e1-5; discussion 91-2.e7-11.
4. James A; Committee on Practice Bulletins—Obstetrics. Thromboembolism in pregnancy. Practice bulletin no. 123. Obstet Gynecol 2011;118:718-29.
5. Quinones JN, James DN, Stamilio DM, Cleary KL, Macones GA. Thromboprophylaxis after cesarean delivery: a decision analysis. Obstet Gynecol 2005;106:733-40.
6. Casele H, Grobman WA. Cost-effectiveness of thromboprophylaxis with intermittent pneumatic compression at cesarean delivery. Obstet Gynecol 2006;108:535-40.
7. Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(suppl):e691S-736S.
8. Friedman AM, Ananth CV, Lu YS, D'Alton ME, Wright JD. Underuse of postcesarean thromboembolism prophylaxis. Obstet Gynecol 2013;122:1197-204.
9. Ghaji N, Boulet SL, Tepper N, Hooper WC. Trends in venous thromboembolism among pregnancy-related hospitalizations, United States, 1994-2009. Am J Obstet Gynecol 2013;209:433.e1-8.
10. Callaghan WM, Creanga AA, Kuklina EV. Severe maternal morbidity among delivery and postpartum hospitalizations in the United States. Obstet Gynecol 2012;120:1029-36.
11. Jacobsen AF, Skjeldestad FE, Sandset PM. Incidence and risk patterns of venous thromboembolism in pregnancy and puerperium: a register-based case-control study. Am J Obstet Gynecol 2008;198:233.e1-7.
12. James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. Am J Obstet Gynecol 2006;194:1311-5.
13. Sultan AA, et al. Risk factors for first venous thromboembolism around pregnancy: a population-based cohort study from the United Kingdom. Blood 2013;121:3953-61.
14. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG 2011;118(suppl 1):1-203.
15. Royal College of Obstetricians and Gynaecologists. Thrombosis and embolism during pregnancy and the puerperium, reducing the risk (Green-Top Guideline no. 37a). London: Royal College of Obstetricians and Gynaecologists; 2009.
16. Stulberg JJ, Delaney CP, Neuhauser DV, Aron DC, Fu P, Koroukian SM. Adherence to surgical care improvement project measures and the association with postoperative infections. JAMA 2010;303:2479-85.
17. Lindenauer PK, Pekow PS, Lahti MC, Lee Y, Benjamin EM, Rothberg MB. Association of corticosteroid dose and route of administration with risk of treatment failure in acute exacerbation of chronic obstructive pulmonary disease. JAMA 2010;303:2359-67.
18. 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.
19. Fang MC, Maselli J, Lurie JD, Lindenauer PK, Pekow PS, Auerbach AD. Use and outcomes of venous thromboembolism prophylaxis after spinal fusion surgery. J Thromb Haemost 2011;9:1318-25.
20. Ritch JM, Kim JH, Lewin SN, et al. Venous thromboembolism and use of prophylaxis among women undergoing laparoscopic hysterectomy. Obstet Gynecol 2011;117:1367-74.
21. Wright JD, Lewin SN, Shah M, et al. Quality of venous thromboembolism prophylaxis in patients undergoing oncologic surgery. Ann Surg 2011;253:1140-6.
22. Kuklina EV, Whiteman MK, Hillis SD, et al. An enhanced method for identifying obstetric deliveries: implications for estimating maternal morbidity. Matern Child Health J 2008;12:469-77.
23. Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J, American College of Chest P. Venous thromboembolism, thrombophilia,

antithrombotic therapy, and pregnancy: American College of Chest Physicians evidence-based clinical practice guidelines (8th ed). Chest 2008;133(suppl):844S-86S.
24. Chan WS. The "ART" of thrombosis: a review of arterial and venous thrombosis in assisted reproductive technology. Curr Opin Obstet Gynecol 2009;21:207-18.
25. Danilenko-Dixon DR, Heit JA, Silverstein MD, et al. Risk factors for deep vein thrombosis and pulmonary embolism during pregnancy or post partum: a population-based, case-control study. Am J Obstet Gynecol 2001;184:104-10.
26. Dargaud Y, Rugeri L, Vergnes MC, et al. A risk score for the management of pregnant women with increased risk of venous thromboembolism: a multicentre prospective study. Br J Haematol 2009;145:825-35.
27. Goldhaber SZ. Risk factors for venous thromboembolism. J Am Coll Cardiol 2010;56:1-7.
28. James AH. Thromboembolism in pregnancy: recurrence risks, prevention and management. Curr Opin Obstet Gynecol 2008;20:550-6.
29. Larsen TB, Sorensen HT, Gislum M, Johnsen SP. Maternal smoking, obesity, and risk of venous thromboembolism during pregnancy and the puerperium: a population-based nested case-control study. Thromb Res 2007;120:505-9.
30. Lindqvist PG, Torsson J, Almqvist A, Bjorgell O. Postpartum thromboembolism: severe events might be preventable using a new risk score model. Vasc Health Risk Manag 2008;4:1081-7.
31. Lussana F, Coppens M, Cattaneo M, Middeldorp S. Pregnancy-related venous thromboembolism: risk and the effect of thromboprophylaxis. Thromb Res 2012;129:673-80.
32. Sultan AA, West J, Tata LJ, Fleming KM, Nelson-Piercy C, Grainge MJ. Risk of first venous thromboembolism in and around pregnancy: a population-based cohort study. Br J Haematol 2012;156:366-73.
33. Tooher R, Gates S, Dowswell T, Davis LJ. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. Cochrane Database Syst Rev 2010:CD001689.
34. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care 1998;36:8-27.
35. Bateman BT, Mhyre JM, Hernandez-Diaz S, et al. Development of a comorbidity index for use in obstetric patients. Obstet Gynecol 2013;122:957-65.
36. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA 2012;307:491-7.
37. Hamilton BE, Martin JA, Ventura SJ. Births: preliminary data for 2012. Natl Vital Stat Rep 2013;62:1-20.
38. Amin AN, Stemkowski S, Lin J, Yang G. Preventing venous thromboembolism in US hospitals: are surgical patients receiving appropriate prophylaxis? Thromb Haemost 2008;99:796-7.
39. Amin AN, Stemkowski S, Lin J, Yang G. Inpatient thromboprophylaxis use in U.S. hospitals: adherence to the seventh American College of Chest Physician's recommendations for at-risk medical and surgical patients. J Hosp Med 2009;4:E15-21.
40. Lindenauer PK, Pekow P, Gao S, Crawford AS, Gutierrez B, Benjamin EM. Quality of care for patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 2006;144:894-903.
41. Bockheim HM, McAllen KJ, Baker R, Barletta JF. Mechanical prophylaxis to prevent venous thromboembolism in surgical patients: a prospective trial evaluating compliance. J Crit Care 2009;24:192-6.
42. Macatangay C, Todd SR, Tyroch AH. Thromboembolic prophylaxis with intermittent pneumatic compression devices in trauma patients: a false sense of security? J Trauma Nurs 2008;15:12-5.
43. White RH, Brickner LA, Scannell KA. ICD-9-CM codes poorly indentified venous thromboembolism during pregnancy. J Clin Epidemiol 2004;57:985-8.
44. White RH, Garcia M, Sadeghi B, et al. Evaluation of the predictive value of ICD-9-CM coded administrative data for venous thromboembolism in the United States. Thromb Res 2010;126:61-7.