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RESEARCH ARTICLE

Utilization of venous thromboembolism prophylaxis in American hospitalized pregnant women undergoing cesarean section

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Abstract

Background Pregnancy-related venous thromboembolism (VTE) is a leading preventable cause of maternal mortality in the United States; however, American guidelines for pharmacologic VTE prophylaxis remain less aggressive than other developed countries. The Safe Motherhood Initiative (SMI) combines aspects of American and international guidelines to increase utilization of prophylaxis and thereby decrease incidence of pregnancy-related VTE. *Objectives* To evaluate the prescribing and administration rates of pharmacologic VTE prophylaxis for women undergoing cesarean section (c-section) when retrospectively applying the SMI recommendations. *Setting* Large academic medical center in Sacramento, California, USA. *Method* This was a single-center retrospective cohort study of pregnant women undergoing c-section who would have met criteria for pharmacologic prophylaxis according to the SMI. *Main outcome measures* Prescribing and administration rates of mechanical and pharmacologic VTE prophylaxis. Secondary outcomes included incidence of thromboembolism within 6 weeks after c-section and thromboembolic associated mortality. *Results* A total of 616 charts were analyzed. When applying the SMI guidelines for VTE prophylaxis, the prescribing rates for mechanical and pharmacologic prophylaxis were 94.3% and 4.71% of patients, respectively, and 94.9% of ordered pharmacologic prophylaxis doses were administered. The incidence of 6-week post-partum VTE was 0.49%. There were no cases of VTE-associated mortality. *Conclusion* This study demonstrated that a large population of c-section patients fit the SMI criteria for pharmacologic VTE prophylaxis but did not receive it. We observed a 0.49% rate of VTE, which was slightly higher than the nationally reported average rate of 0.3%. With growing rates of pregnancy-associated VTE in the United States, perhaps a more aggressive guideline is warranted.

Keywords Cesarean section · Maternal morbidity · Obstetric thromboembolism · Venous thromboembolism · Venous thromboembolism prophylaxis · United States

Impacts on practice

- The observed rate of post-partum VTE seems higher than the known national average, which may support a need for more aggressive VTE prophylaxis guidelines in the United States.
- Patients who undergo c-section should be carefully assessed for other comorbidities that can increase the risk of VTE, and pharmacologic prophylaxis should be considered.
- Research is necessary to elucidate the safety of applying a broad, standardized approach to post-c-section pharmacologic VTE prophylaxis and to determine the appropriate dosing strategy for the obese patient population.

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Introduction

Among developed countries, pregnancy-related venous thromboembolism (VTE) is a leading and often preventable cause of maternal mortality, accounting for nearly 15% of all maternal deaths [1]. The risk of VTE is high not only during pregnancy, but also in the postpartum period with the highest risk occurring during the first 6 weeks following delivery [2]. In the United States, maternal mortality has been rising with 26.4 deaths reported to occur per 100,000 births, and approximately 9.3% of these pregnancy-related deaths are attributable to pulmonary embolism [1, 3–6]. Of particular concern is the population of pregnant women who deliver via cesarean section (c-section). Overall, pregnant women have a 4–5 fold increase in VTE risk compared to women who are not pregnant, and the risk of VTE following c-section is fourfold greater than following vaginal delivery. VTE following c-section is reported to occur at an average rate of 0.3% [7–10]. A recent review of pregnancy-related mortality in California identified VTE among the top five causes of pregnancy-related deaths and reported c-section as the documented type of delivery for 14 of the 20 cases of VTE-cause mortality [11].

Post-cesarean pharmacologic prophylaxis remains significantly underutilized in the United States due to less aggressive guidelines [12]. This is in contrast to the United Kingdom, which demonstrated a reduction in VTE-related maternal mortality after it expanded its guidelines to include post-cesarean pharmacologic prophylaxis [13, 14]. Currently, there is a lack of consensus regarding pharmacologic prophylaxis among the guidelines, which include American organizations [American Congress of Obstetricians and Gynecologists (ACOG), American College of Chest Physicians (ACCP), and the American Society of Regional Anesthesia and Pain Medicine (ASRA)] and the United Kingdom's Royal College of Obstetricians and Gynecologists (RCOG) [7, 9, 14–16]. The lack of standardization among guidelines has spurred the creation of several initiatives to implement maternal safety bundles, including VTE prophylaxis bundles; however, specific indications for pharmacologic prophylaxis in c-section patients remain controversial [6, 17, 18].

In an attempt to bridge this gap and decrease pregnancy-related VTE, District II of ACOG in New York integrated all four guidelines to create the Safe Motherhood Initiative (SMI) VTE bundle [17]. Outcome data from the implementation of the SMI VTE bundle has not been published; however, the need to evaluate and standardize pharmacologic prophylaxis is prudent. We used the SMI recommendations as a guideline to identify the number of post-cesarean patients in our institution who would be candidates for pharmacologic prophylaxis and evaluated the prescribing and administration rates of prophylaxis as well as the occurrence of postpartum VTE at a large academic medical center.

Aim of study

The aim of this study was to evaluate the prescribing and administration rates of pharmacologic VTE prophylaxis for women undergoing c-section at a large academic medical center when retrospectively applying the more aggressive SMI guideline.

Ethics approval

This single-center retrospective cohort study was approved by the Institutional Review Board (IRB) of the University of California, Davis Medical Center (IRB ID: 801729-1). The requirement of formal consent was waived owing to its retrospective nature.

Method

This was a single-center retrospective cohort study of pregnant women undergoing c-section from May 1st, 2013, to September 1st, 2015, at the University of California, Davis Medical Center (UCDMC) in Sacramento, California. At UCDMC, the current practice for VTE prophylaxis follows the American College of Obstetrics and Gynecology (ACOG) recommendations to administer mechanical prophylaxis for all c-section patients and pharmacologic prophylaxis for c-section patients meeting one of the following major risk criteria: high risk thrombophilia, history of VTE, or thrombophilia AND history of VTE [9]. The Vizient (formerly University HealthSystems Consortium) database was used to screen and identify pregnant patients using the International Classifications of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) coding for risk factors included in the SMI recommendations, which were consistent with previous studies (Tables 1, 2) [17, 19, 20]. Renal disease, intrauterine growth restriction (IUGR), and assisted reproductive technology (ART) were risk factors not included in previous studies utilizing ICD-9 coding, so these disease states were screened for secondarily during chart review. Data were abstracted via chart review using the hospital's electronic health record.

The study included pregnant women aged 18 and older undergoing c-section who had one additional risk factor for VTE and qualified for pharmacologic prophylaxis according to the SMI (Table 1). Therefore, all patients included in the

Table 1 Safe Motherhood Initiative risk-factor-based recommendation for postpartum prophylaxis [17]

Prophylactic LMWH or UFH until discharge is recommended for the following
At least 1 or more
Already receiving heparin as outpatient
Pre-pregnancy class 3 obesity (BMI ≥ 40 kg/m^2)
Any history of VTE
Thrombophilia and family history of VTE
OR 2 or more risk factors for VTE
Cesarean delivery
Hemorrhage
Hysterectomy
General anesthesia
Postpartum infection
Age > 40 or < 15 years
Pre-pregnancy obesity (BMI ≥ 30 kg/m^2)
Bed rest
Any thrombophilia
Medical or pregnancy complications
Medical conditions: heart disease, lupus renal disease, sickle cell, major infection, other major medical conditions (diabetes, smoking, hypertension, substance abuse)
Pregnancy complications: IUGR, preeclampsia, multiple gestation, ART

LWMH low molecular weight heparin, *UFH* unfractionated heparin, *BMI* body mass index, *VTE* venous thromboembolism, *IUGR* intrauterine growth restriction, *ART* assisted reproductive technology

Table 2 Medical condition and pregnancy complications

Diagnosis/risk factor	ICD-9-CM Code	N (%)
Cesarean delivery	74, 74.0, 74.1, 74.2, 74.3, 74.4, 74.9, 74.91, 74.99	616 (100%)
Hemorrhage	Antepartum: 640.9, 641.1, 641.2, 641.3, 641.8, 641.9,	63 (10.1%)
	Postpartum: 666, 667, 669.1	108 (17.6%)
Postpartum infection	670, 672	23 (3.7%)
Pre-pregnancy obesity (BMI > 30)	278.0	162 (26.3%)
Bed rest		279 (44.8%)
Any thrombophilia (including history of thrombosis and antiphospholipid syndrome)	273.8, 286.9, 289.8, V12.51, 286.5, 289.9, 795.79	8 (1.3%)
Medical conditions		
Heart disease	390–399, 412–417, 420–429	31 (5%)
Lupus	695.4, 710	2 (0.32%)
Renal disease (CrCl < 60)		2 (0.32%)
Major infection	See postpartum infection	See postpartum infection
Other major medical conditions		
Hypertension	401–405	273 (44.3%)
Diabetes	648, 250	150 (24.3%)
Smoking	305.1, V15.82	65 (10.6%)
Substance abuse	305.2, 305.3, 305.4, 305.5, 305.6, 305.7	34 (5.5%)
Pregnancy complications		
Intrauterine growth restriction		23 (3.7%)
Preeclampsia	642	113 (18.3%)
Multiple gestation	651	102 (16.6%)
Assisted reproductive technology		16 (2.6%)

ICD-9-CM International Classification of Diseases, Ninth Revision, Clinical Modification; *BMI* body mass index, *CrCl* creatinine clearance

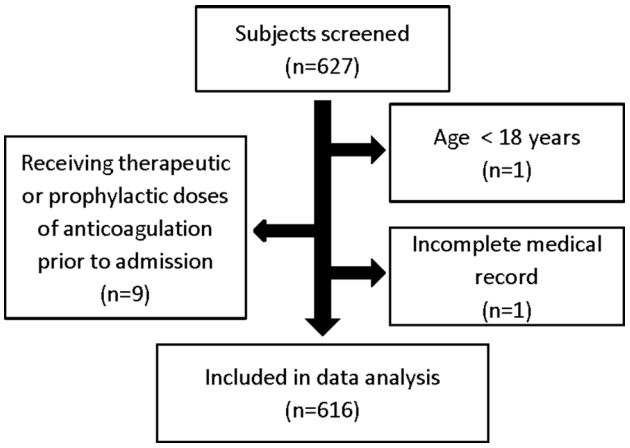

Fig. 1 Patient selection process

study had at minimum two risk factors for VTE and would have qualified for pharmacologic prophylaxis according to the SMI recommendations. Patients receiving prophylactic or therapeutic doses of anticoagulation prior to admission and those with incomplete medical records were excluded.

Primary endpoints were prescribing rates of mechanical or pharmacologic prophylaxis. Secondary endpoints included incidence of VTE within 6 weeks following a c-section and VTE-associated mortality. Descriptive statistics were used for analysis. Continuous variables were tested using the *t* test or Kruskal–Wallis test. Categorical variables were tested using Chi Square or Fisher's Exact. Test selection was based on the validity of the normal assumption.

Results

A total of 627 patients were identified for screening in the Vizient database, and 616 patients were included in the final analysis. Eleven patients were excluded: 9 patients received therapeutic or prophylactic anticoagulation prior to admission, one patient was under 18 years of age at the time of c-section, and one patient had an incomplete medical record (Fig. 1).

The mean age at the time of delivery was 32 ± 6.35 years, mean pre-pregnancy body mass index (BMI) was 30.5 ± 11.6 kg/m^2; and hemoglobin and platelet counts were within normal limits on admission (Table 3). After c-section, bed rest was the most common risk factor for VTE (45.3%) and was defined as an antepartum bed rest order lasting at least 7 days, which is consistent with the RCOG definition [14]. Other common risk factors included hemorrhage (antepartum 10.2%, postpartum 17.5%), anemia (36%), pre-pregnancy obesity (defined as BMI ≥ 30, 26.3%), diabetes (24.3%), smoking (10.5%), hypertension (44.3%), preeclampsia (18.3%), and multiple gestation (16.6%).

Table 3 Baseline characteristics

Variable	Mean ± SD
Age (years)	32 ± 6.35
BMI (kg/m^2)	30.6 ± 11.6
Hemoglobin on admission (mg/dL)	11.8 ± 1.3
Hemoglobin post c-section (mg/dL)	9.7 ± 1.6
Platelet count on admission (k/mm^3)	215 ± 62.2
Platelet count post c-section (mg/dL)	182.8 ± 58
Serum creatinine (mg/dL)	0.69 ± 0.31

BMI body mass index, *c-section* cesarean section

Table 4 Primary and secondary endpoint measures

	N (%)
Primary endpoints	
Mechanical prophylaxis prescribed	581 (94.3%)
Pharmacologic prophylaxis prescribed	29 (4.71%)
Pharmacologic prophylaxis administered	262/276 (94.9%)
Secondary endpoints	
Postpartum VTE within 6 weeks of c-section	3 (0.49%)
VTE-associated mortality	0

VTE venous thromboembolism, *c-section* cesarean section

Table 5 Risk factors from patients who experienced postpartum venous thromboembolism

Patient A	Patient B	Patient C
C-section	C-section	C-section
Hypertension/preeclampsia	Obesity	Obesity
Heart disease	Hypertension	History of VTE
	Bedrest	Substance abuse

c-section cesarean section, *VTE* venous thromboembolism

Five hundred eighty-one (94.3%) patients had orders for mechanical prophylaxis and 29 (4.71%) had orders for pharmacologic prophylaxis (Table 4). All 29 patients receiving pharmacologic prophylaxis received at least one dose, and overall, 94.9% of ordered doses were administered. Six patients were not provided any prophylaxis during their admission.

Three patients experienced VTE within the 6 week period following the c-section (0.49%); no VTE-related mortality was identified. Pre-pregnancy obesity (BMI > 40 kg/m^2) was a common risk factor between patient B and C, and hypertension was common between patient A and B. Other risk factors included preeclampsia, immobility, history of VTE, heart disease, and substance abuse (Table 5).

Patient A underwent an emergent c-section for severe preeclampsia. Postpartum, she was diagnosed with peripartum cardiomyopathy and had limited mobility secondary to

tachycardia with ambulation. The patient received mechanical prophylaxis throughout the hospital stay but no pharmacologic prophylaxis. The patient developed an apical thrombus within 1 week postpartum.

Patient B, with a pre-pregnancy BMI 55 kg/m^2 and gestational hypertension, had a c-section for failed induction of labor. Pharmacologic prophylaxis was initiated post-operatively with enoxaparin 40 mg subcutaneously once daily, but was not continued on discharge. The patient developed a lower extremity DVT within 2 weeks following delivery.

Patient C, with history of DVT (details unknown), substance abuse (active marijuana, history of methamphetamines), and morbid obesity (pre-pregnancy BMI 44 kg/m^2), underwent elective c-section. The patient was initiated on mechanical VTE prophylaxis, but not pharmacologic prophylaxis during admission. The patient was diagnosed with lower extremity DVT approximately 4 weeks postpartum.

Discussion

When applying the SMI criteria, we identified that pharmacologic VTE prophylaxis for at risk women undergoing c-section is severely underutilized at UCDMC. This is likely attributed to differing recommendations from the various professional organizations. Current prescribing practices for VTE prophylaxis in pregnant women undergoing c-section at UCDMC follows the more conservative ACOG guidelines, according to which a relatively small population of patients with VTE risk factors are candidates for pharmacologic prophylaxis.

In a cohort study of 293 patients who underwent c-section at a similar tertiary hospital, 85%, 34.8%, and 1% of patients would fulfill RCOG, ACCP, and ACOG criteria for pharmacologic prophylaxis, respectively, which highlights the gap in prophylaxis practices [16]. Our study specifically looked at the SMI guideline which has only been implemented in one district in the United States (New York). We thought it would be a reasonable approach to utilize the SMI in our study as a compromise between the most aggressive guideline from RCOG and the more conservative guideline from ACOG (Table 6) [9, 14]. We also targeted a patient sample that was representative of a "general" cesarean population in terms of post-partum VTE risk.

Each patient in our study who experienced post-partum thrombosis had at least three risk factors for VTE, but only one received pharmacologic prophylaxis. Although Patient C did not have a true VTE, the thrombotic event may have still been prevented with appropriate pharmacologic VTE prophylaxis measures. This highlights a potential need to reconsider the effectiveness of the ACOG guidelines in terms of identifying appropriate candidates for pharmacologic prophylaxis, and statewide initiatives such as the California Maternal Quality Care Collaborative (CMQCC) have begun promoting toolkits that recommend more aggressive pharmacologic prophylaxis in c-section patients [18]. However, it remains unclear what constitutes true best practice, and the difficulty in identifying this for the purpose of guideline creation is multifactorial.

First, the lack of consensus among the different guidelines is likely due to the lack of high quality data demonstrating effectiveness. Because VTE is a relatively rare event, most data identifying risk factors and evaluating therapy are observational and retrospective.

Second, the identified risk factors among the different guidelines are also inconsistent. The ACCP guideline attributes a baseline risk value of greater than 3% for patients with one minor risk factor and emergent cesarean section or patients with one major risk factor for post-partum VTE [7]. Most patients in our study met the former criteria for this baseline risk (c-section plus one minor risk factor); however, our study demonstrated a much lower event rate than 3%. This may be due to the fact that nearly all patients received mechanical prophylaxis, or the disparity may be due to the difficulty in accurately assigning values for the long list of VTE risk factors because these are largely identified in retrospective analyses with varying odds ratios [2, 10, 20–24]. This may explain why other guidelines do not provide this value. There is a long list of risk factors for VTE, but the relative significance of each one remains unclear. The only risk factors consistent among all the guidelines are previous history of VTE and diagnosed thrombophilia. James and colleagues used an univariate analysis for various medical conditions considered to be risk factors for pregnancy related thrombosis, which is the basis for risk factor inclusion in the RCOG and SMI guidelines [20]. Several risk factors were identified, but with varying odds ratios. For example, the odds ratio for obesity was 4.4 (3.4–5.7), whereas the odds ratio for preeclampsia was 0.9 (0.7–1.0), yet both conditions are equally weighted risk factors in the SMI. Thus, it is still difficult to discern which risk factors are of greater significance. Considering these results, the patients experiencing VTE in our study all had risk factors with significant odds ratios as determined by James et al.: obesity [OR 4.4 (3.4–5.7)], heart disease [OR 7.1 (6.2–8.3)], hypertension [OR 1.8 (1.4–2.3)], and history of VTE [OR 24.8 (17.1–36.0)].

Third, with rising obesity nationwide, there are no specific guidelines for adjusting prophylactic doses of anticoagulation for obese patients; however, pre-pregnancy morbid obesity with a BMI > 40 kg/m^2 is considered a major risk factor for VTE per RCOG [14, 25]. Both obese patients in our study met this criterion. Patient B did appropriately receive post-partum prophylactic enoxaparin until discharge, but received standard dosing (40 mg subcutaneously daily) and subsequently developed a lower extremity DVT. Studies

Table 6 Existing guidelines for post-partum VTE prophylaxis [7, 9, 14, 17]

RCOG (2015)	SMI (2013)	ACCP (2012)	ACOG (2011)
2 or more risk factors	*At least 1 major risk factor*	*C-section with at least 1 major risk factor*	*At least 1 major risk factor*
Age > 35	Any history of VTE	Immobility (strict bed rest for ≥ 1 week in the antepartum period)	High-risk thrombophilia
Obesity (BMI ≥ 30)	Pre-pregnancy obesity (BMI ≥ 40)	Postpartum hemorrhage ≥ 1 L with surgery	History of VTE
Parity ≥ 3	Thrombophilia AND family history of VTE	Previous VTE	Thrombophilia AND family history of VTE
Smoker		Preeclampsia AND fetal growth restriction	
Elective c-section	*OR 2 or more minor risk factors*	Thrombophilia (antithrombin deficiency, factor V Leiden [homozygous or heterozygous], Prothrombin G20210a [homozygous or heterozygous])	
Family history of VTE	C-section	Medical conditions (lupus, heart disease, sickle cell disease)	
Low-risk thrombophilia (heterozygous for factor V Leiden or prothrombin G20210A mutations)	Hemorrhage (if stable after 12–24 h)	Blood transfusion	
Gross varicose veins	Hysterectomy	Postpartum infection	
Current systemic infection	General anesthesia		
Immobility (e.g. paraplegia, pelvic girdle pain, long-distance travel)	Postpartum infection	*OR C-section with at least 2 minor risk factors*	
Current pre-eclampsia	Age > 40 or < 15 years	BMI > 30	
Multiple pregnancy	Pre-pregnancy obesity (BMI ≥ 30)	Multiple pregnancy	
Preterm delivery in this pregnancy (< 37 weeks)	Bed rest	Postpartum hemorrhage > 1 L	
Stillbirth during this pregnancy	Any thrombophilia	Smoking > 10 cigarettes/day	
Mid-cavity rotational or operative delivery	Medical or pregnancy complications (heart disease, lupus, renal disease, sickle cell, major infection, other major medical conditions, IUGR, preeclampsia, multiple gestation, ART)	Fetal growth restriction (gestational age + sex-adjusted birth weight < 25th percentile)	
Prolonged labour (> 24 h)		Thrombophilia (Protein C or S deficiency)	
Post-partum hemorrhage > 1 L OR blood transfusion		Pre-eclampsia	

RCOG Royal College of Obstetricians and Gynaecologists, *SMI* Safe Motherhood Initiative, *ACCP* American College of Chest Physicians, *ACOG* American College of Obstetricians and Gynecologists, *VTE* venous thromboembolism, *BMI* body mass index, *c-section* cesarean section, *IUGR* intrauterine growth restriction, *ART* assisted reproductive technology

of non-pregnant obese patients suggest increased dosing may be necessary to achieve appropriate levels of prophylaxis and laboratory monitoring may be required [26, 27]. One study specifically recommended unfractionated heparin (UFH) dosed at 7500 units TID or enoxaparin at 40 mg BID for patients with BMI > 40 kg/m^2 [27]. These doses have not been validated in the pregnant population; however, it is a possibility that the patient in our study was underdosed. Monitoring of anti-factor Xa levels may have also been a strategy to assess this patient's level of anticoagulation, but this practice has not been studied for prophylactic doses in pregnant patients.

In addition to potentially subtherapeutic dosing in obesity, Patient B may have also benefited from continuing pharmacologic prophylaxis after discharge. Little is known about the appropriate duration of pharmacologic prophylaxis; however, RCOG does provide guidance based on risk score [14]. Per this risk assessment scoring system, Patient B would have qualified for at least 10 days of pharmacologic prophylaxis.

Lastly, using a more aggressive approach following a c-section may concern some clinicians due to the presumed risk of bleeding associated with the use of anticoagulant agents in the presence of neuraxial anesthesia. However, a recent systematic review of 10 studies, including a total of 296 patients receiving neuraxial anesthesia in the setting of either low molecular weight heparin (LMWH) or unfractionated heparin (UFH) thromboprophylaxis, revealed no cases of spinal epidural hematoma, thus suggesting the utilization of anticoagulation in prophylactic doses may be safe [28]. To minimize the risk of spinal hematoma, prophylactic LMWH should be discontinued 10–12 h prior to catheter placement [15].

Additionally, in our study, 10% and 17% of patients experienced antepartum and postpartum hemorrhage, respectively. Although these types of bleeding are common for c-section delivery, they remain risk factors for post-partum VTE; however, it may seem counterintuitive to some to order an anticoagulant agent post hemorrhage despite the likely low risk for bleeding with prophylactic doses of anticoagulation. Roshani and colleagues found that patients on therapeutic doses of LMWH during pregnancy did not have higher incidences of post-partum hemorrhage [29]. Although post-partum prophylactic doses have not been studied, we may be able to infer safety with these doses given less exposure to drug.

Limitations of this study stem from its retrospective design. All data, including incidence of post-partum VTE, were collected via chart review. UCDMC is a major referral center for high risk pregnancies and premature neonatal care. For this reason, follow-up after discharge is limited as many women return to their community hospitals and offices for postpartum care. Thus, although our VTE rate is consistent with nationally reported rates, the rate of post c-section VTE is likely underestimated. Additionally, given the low rate of pharmacologic prophylaxis administered, we are not able to comment on the safety of medication administration in terms of major bleeding.

Conclusion

Although the majority of patients received mechanical prophylaxis, very few received pharmacologic prophylaxis despite having relevant risk factors identified in the SMI guideline. A 0.49% rate of VTE was observed, which was slightly higher than the nationally reported average rate of 0.3%. Although we cannot determine whether or not this may be due to the use of a less aggressive guideline, the current study demonstrates potential gaps in evidence and recommendations regarding the correct approach to post-partum pharmacologic VTE prophylaxis in patients undergoing c-section. With growing rates of pregnancy-associated VTE complications in the United States, perhaps a more aggressive guideline is warranted.

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