Venous Thromboembolism After Blood Transfusions in Women Undergoing Hysterectomy for Non-Malignant Indications: A Retrospective Cohort Study

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ABSTRACT

Objective: To quantify the effect of blood transfusion on the risk of venous thromboembolism (VTE) among women undergoing hysterectomy for non-malignant indications.

Methods: A retrospective cohort study using the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) was conducted. Women who underwent hysterectomy for non-malignant indications between 2011 and 2016 were identified using the Current Procedural Terminology and Internationally Classification of Diseases codes. The primary outcome was development of VTE. Data on patient demographics and perioperative variables were obtained. Pair-wise comparison using χ^2 tests were performed to compare women with and without VTE. Multivariable logistic regression was performed to adjust for potential confounders and identify independent predictors of VTE.

Results: Between 2011 and 2016, 169 593 women underwent hysterectomy for non-malignant indications. The overall incidence of VTE was 0.32%. Patient characteristics associated with VTE included obesity and higher American Society of Anesthesiologists (ASA) status. Associated operative factors included abdominal surgery, blood transfusion, and prolonged operative time ($P < 0.05$ for all). Following adjustment for potential confounders, abdominal hysterectomy was associated with greater odds of VTE than laparoscopic or vaginal approaches (adjusted odds ratio [aOR] 1.81; 95% CI 1.48–2.21 and aOR 2.31; 95% CI 1.62–3.28, respectively). Greater odds of VTE were also observed with OR time >150 minutes (aOR 1.88; 95% CI 1.46–2.42), ASA class ≥III (aOR 1.53; 95% CI 1.05–2.26), and intra- and postoperative transfusion (aOR 2.65; 95% CI 1.78–3.95 and aOR 2.98; 95% CI 1.95–4.55, respectively).

Conclusion: The risk of VTE is low in women undergoing hysterectomy for non-malignant indications. Blood transfusion was associated with the highest risk of VTE.

Keywords: blood transfusion; hysterectomy; venous thromboembolism

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RÉSUMÉ

Objectif : Quantifier l'effet de la transfusion sanguine sur le risque de thromboembolie veineuse (TEV) chez les femmes qui subissent une hystérectomie pour une indication bénigne.

Méthodologie : Une étude de cohorte rétrospective a été réalisée au moyen de la base de données du programme national d'amélioration de la qualité chirurgicale de l'American College of Surgeons (ACS NSQIP). Les femmes ayant subi une hystérectomie pour une indication bénigne entre 2011 et 2016 ont été recensées à l'aide des codes de la CPT (Current Procedural Terminology) et de la Classification internationale des maladies (CIM). Le critère de jugement principal était l'apparition de la TEV. Les données démographiques des patientes et les variables périopératoires ont été obtenues. Une comparaison par paires a été effectuée à l'aide de tests du χ^2 pour comparer les femmes avec et sans TEV. Une analyse de régression logistique multivariée a été réalisée pour tenir compte des facteurs de confusion potentiels et déterminer les prédicteurs indépendants de la TEV.

Résultats : Entre 2011 et 2016, 169 593 femmes ont subi une hystérectomie pour une indication bénigne. L'incidence globale de la TEV était de 0,32 %. Les caractéristiques des patientes associées à la TEV étaient l'obésité et un score ASA (American Society of Anesthesiologists) élevé. Les facteurs opératoires connexes étaient la laparotomie, la transfusion sanguine et le temps opératoire prolongé ($P < 0,05$ pour tous). Après un ajustement des données pour tenir compte des facteurs de confusion potentiels, l'hystérectomie abdominale était liée à un risque accru de TEV par rapport aux voies d'abord laparoscopiques ou vaginales (rapport de cotes ajusté [RCa] : 1,81; IC à 95 % : 1,48–2,21 et RCa : 2,31; IC à 95 % : 1,62–3,28, respectivement). Un risque accru de TEV a aussi été observé avec un temps opératoire de > 150 minutes (RCa : 1,88; IC à 95 % : 1,46–2,42), un score ASA de ≥ III (RCa : 1,53; IC à 95 % : 1,05–2,26) et la transfusion per- et postopératoire (RCa : 2,65; IC à 95 % : 1,78–3,95 et RCa : 2,98; IC à 95 % : 1,95–4,55, respectivement).

Conclusion : Le risque de TEV est faible chez les femmes qui subissent une hystérectomie pour une indication bénigne. La transfusion sanguine était liée au risque le plus élevé de TEV.

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INTRODUCTION

Hysterectomies are the most common gynaecologic surgery performed in North America, and venous thromboembolism (VTE) is a serious and potentially life-threatening surgical complication with an estimated rate of 0.5% to 2% in hysterectomy patients.[1–6] Patients who are at elevated risk of VTE benefit from postoperative thromboprophylaxis; however, there is no consensus on the role of preoperative thromboprophylaxis, especially for minimally invasive surgery. The identification of risk factors for VTE will help identify patients who may require therapies outside of the usual postoperative care to help prevent VTE development.[7]

For women undergoing hysterectomy, excessive bleeding requiring transfusion is a known complication, occurring in 2.6% to 5.5% of hysterectomies.[3,8] The association between blood transfusion and VTE has been corroborated by studies in other surgical disciplines—including general, colorectal, vascular, and orthopedic surgery—which have found that intraoperative and postoperative transfusions are associated with the development of VTE.[9–13] The association between blood transfusion and VTE at the time of surgery is consistent with Virchow's triad: The increased exposure of phosphotidyleserine on aging red blood cells results in a hypercoagulable state.[13,14] Furthermore, these studies do not differentiate patients who have the expected amount of blood loss and require transfusion from those who encounter unexpected surgical complexity resulting in greater than expected blood loss and consequent transfusion.

Within gynaecology, increased risk of VTE has also been observed in gynaecologic oncology patients who have received blood transfusion.[15] However, because malignancy is a known risk factor for VTE occurrence, it is uncertain whether these findings are generalizable to women who undergo hysterectomy for non-malignant indications.[16] Among women undergoing hysterectomy for non-malignant indications, transfusion has not been studied as a risk factor for VTE. Given the paucity of literature on this topic, our objective was to determine the effect of blood transfusion on the development of VTE among women undergoing hysterectomy for non-malignant conditions.

METHODS

Deidentified data from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) were used to perform a retrospective cohort analysis. The NSQIP database is a highly reliable and risk-adjusted international database in which certified surgical clinical reviewers collect information on preoperative, intraoperative, and 30-day postoperative variables.[17] This study was conducted after obtaining approval from the Ottawa Health Science Network research ethics board (Ottawa, ON; ID 20140342-01H).

NSQIP uses Current Procedural Terminology codes, which are developed and maintained by the American Medical Association and are the preferred system for coding and describing healthcare services and procedures throughout the United States.[18] All women meeting the inclusion criteria who underwent hysterectomy between 2011 and 2016 were included using the Current Procedural Terminology codes 58150, 58152, 58180, 58260, 58262-3, 58267, 58270, 58275, 58280, 58290-4, 58541-4, 58550,

58552-4, and 58570-3. Exclusion criteria included patients with malignant disease, patients who underwent emergency surgery, and patients who underwent other surgical procedure(s) within the prior 30 days.

Patient demographic characteristics collected included age, race, body mass index (BMI), and smoking status; clinical characteristics included the presence of comorbid conditions such as congestive heart failure, diabetes mellitus, hypertension requiring medication, and bleeding disorders. The American Society of Anesthesiologists (ASA) classification status was included to classify patients based on level of preoperative risk by evaluating physiologic status based on systemic illness.[19] Classification of BMI was completed according to the World Health Organization classification system.[20]

Using the International Statistical Classification of Diseases and Related Health Problems (ICD-9 and ICD-10) codes, indications for hysterectomy were classified into menstrual disorders (ICD-9 626.2-626.9, 627.0; ICD-10 N92, N93), fibroids (ICD- 9 218; ICD-10 D25), endometriosis (ICD-9 617; ICD-10 N80), pain (ICD-9 625.0-625.3, 625.5, 625.7; ICD-10 N94), genital prolapse (ICD-9 618; ICD-10 N81), and other. Both ICD-9 codes and ICD-10 codes were used because the U.S. Department of Health and Human Services implemented the update of the classification system from ICD-9 to ICD-10 in 2014, which falls within our study period.[21]

Perioperative variables assessed included route of surgery, categorized into abdominal, vaginal, or laparoscopic approaches; operative time; and occurrence of intraoperative or postoperative blood transfusion.

The main study outcome was VTE, including pulmonary embolism and deep vein thrombosis. As per NSQIP definitions, deep vein thrombotic events were diagnosed by duplex ultrasound, venogram, or computed tomography; pulmonary embolic events were diagnosed using ventilation perfusion scans, computed tomography spiral examination or angiogram, or pulmonary arteriogram within 30 days of surgery.[16]

Patients were compared for development of VTE based on their demographic characteristics and perioperative variables. For all categorical variables, the proportion of venous thromboembolic events was calculated. Mean values and standard deviations (SDs) were calculated for age and BMI. Chi-square tests were used to compare categorical variables, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each category of variables in the bivariate analysis.

To adjust for potential confounders, a multivariable logistic regression model was constructed to control for patient clinical factors (age, BMI, diabetes mellitus, smoking, cardiovascular disease, bleeding disorder, ASA classification) and perioperative factors (surgical approach, intraoperative blood transfusion, postoperative blood transfusion, and operative time). Adjusted odds ratios (aORs) with 95% CIs were calculated to generate the multivariable logistic regression model. Two-sided P values <0.05 were considered significant. SAS version 9.3 (SAS Institute Inc., Cary, NC) was used to perform all analyses.

RESULTS

Between 2011 and 2016, 169 593 hysterectomies were performed for non-malignant indications. The incidence of VTE was found to be 0.32%. The mean (SD) age of women undergoing hysterectomy was 47.76 (10.71) years.

Baseline characteristics of the patient population with VTE are presented in Table 1. Statistically significant differences in BMI and ASA classification were observed between the groups of patients who experienced VTE post-hysterectomy and those who did not ($P < 0.05$).

On univariate analysis, presented in Table 2, increased risk of VTE was associated with obesity, higher ASA classification status (ASA class ≥III), increased operative time (operative time >120 minutes vs. <90 minutes), and abdominal route of surgery. Intraoperative transfusion was found to have an OR of 4.26 (95% CI 2.94−6.17), whereas postoperative transfusion had an OR of 4.11 (95% CI 2.76−6.11).

Multivariable analysis was performed to adjust for potential confounders. After adjustment, variables found to be associated with the highest odds of developing VTE were observed among women who received intraoperative transfusion (aOR 2.65; 95% CI 1.78−3.95) and postoperative transfusion (aOR 2.98; 95% CI 1.95−4.55). Additional variables associated with VTE include operative times >150 minutes (aOR 1.88; 95% CI 1.46−2.42), abdominal hysterectomy compared with vaginal hysterectomy (aOR 2.31; 95% CI 1.62−3.28), and laparoscopic hysterectomy (aOR 1.81; 95% CI 1.48−2.21). Patients with higher ASA classification (ASA classes III−V; aOR 1.53; 95% CI 1.04−2.26) remained at increased risk of VTE after adjustment, but BMI was no longer found to be significant.

DISCUSSION

Our study found that the incidence of VTE after hysterectomy for benign conditions is low (0.32%), which is

Table 1. Baseline characteristics of women undergoing hysterectomy for benign indication with and without VTE, ACS NSQIP, 2011–2016

Patient characteristic	Total	VTE, no. (%)		*P* value
		No	Yes	
VTE	169 593	169 051 (99.7)	542 (0.3)	n/a
Age, y				0.42
<40	33 932	33 824 (99.7)	108 (0.3)	
40–44	36 389	36 2731 (99.7)	118 (0.3)	
45–49	39 621	39 498 (99.7)	123 (0.3)	
50–54	24 108	24 017 (99.6)	91 (0.4)	
≥55	35 543	35 441 (99.7)	102 (0.3)	
Body mass index category				<0.0001
Underweight	1360	1355 (99.6)	5 (0.4)	
Normal	40 115	40 018 (99.8)	97 (0.2)	
Overweight	49 875	49 744 (99.7)	131 (0.3)	
Obese I	37 122	36 990 (99.6)	132 (0.4)	
Obese II	21 617	21 531 (99.6)	86 (0.4)	
Obese III	18 872	18 782 (99.5)	90 (0.5)	
Race				0.07
White	100 445	100 130 (99.7)	315 (0.3)	
Non-White	49 946	49 761 (99.7)	185 (0.4)	
Diabetes	12 780	12 728 (99.6)	52 (0.4)	0.07
Smoking	29 349	29 263 (99.7)	86(0.3)	0.38
Hypertension	45 013	44 855 (99.7)	158 (0.3)	0.17
Congestive heart failure	110	109 (99.1)	1(0.9)	0.27
Bleeding disorder	1298	1290 (99.4)	8 (0.6)	0.06
ASA class				<0.0001
I	21 218	21 167 (99.8)	51 (0.2)	
II	114 262	113 930 (99.7)	332 (0.3)	
III–V	34 014	33 855 (99.5)	159 (0.5)	
Functional status				0.66
Dependent	458	456 (99.6)	2 (0.4)	
Independent	168 211	167 671 (99.7)	540 (0.3)	
Year of operation				0.80
2011	13 798	13 761 (99.7)	37 (0.3)	
2012	19 342	19 276 (99.6)	66 (0.4)	
2013	25 477	25 393 (99.7)	84 (0.3)	
2014	30 516	30 412 (99.7)	104 (0.3)	
2015	36 596	36 478 (99.7)	118 (0.3)	
2016	43 864	43 731 (99.7)	133 (0.3)	
Operative time, min				<0.0001
<90	47 798	47 691 (99.8)	107 (0.2)	
90–119	39 284	39 179 (99.7)	105 (0.3)	
120–149	30 207	30 116 (99.7)	91 (0.3)	
≥150	51 310	51 072 (99.5)	238 (0.4)	

(*continued*)

Table 1. (*Continued*)

Patient characteristic	Total	VTE, no. (%)		*P* value
		No	Yes	
Indication				0.09
Endometriosis	11 600	11 569 (99.7)	31 (0.3)	
Genital prolapse	22 451	22 393 (99.7)	58 (0.3)	
Menstrual disorders	37 245	37 134 (99.7)	111 (0.3)	
Other	36 027	35 909 (99.7)	118 (0.3)	
Pain	6432	6415 (99.7)	17 (0.3)	
Uterine fibroids	55 838	55 631 (99.6)	207 (0.4)	
Surgical approach				<0.0001
Abdominal	42 297	42 079 (99.5)	218 (0.5)	
Laparoscopic	97 004	96 740 (99.7)	264 (0.3)	
Vaginal	30 292	30 232 (99.8)	60 (0.2)	
Type of hysterectomy				0.58
Total	151 717	151 228 (99.7)	489 (0.3)	
Subtotal	17 795	17 742 (99.7)	53 (0.3)	
Transfusion				<0.0001
Intraoperative	2423	2393 (98.8)	30 (1.2)	
No transfusion	164 950	164 466 (99.7)	484 (0.3)	
Postoperative	2177	2151 (98.8)	26 (1.2)	

ACS NSQIP: American College of Surgeons National Surgical Quality Improvement Program; ASA: American Society of Anesthesiologists; VTE: venous thromboembolism.

consistent with previous studies of non-malignant disease (0.1%–0.6%).[1,3,22] The main finding of our study is a two-fold increase in the odds of VTE occurrence in women receiving intraoperative transfusion and nearly a three-fold increase with postoperative transfusion. This risk is consistent with findings from other disciplines[10,12,23] but less than that seen in gynaecologic oncology studies,[15] suggesting that patients with malignancy have a different risk profile for VTE compared with patients with noncancerous conditions. Indeed, in a study of patients with colorectal cancer, a linear relationship was observed between the number of units of blood transfused and risk of postoperative VTE.[10]

Also consistent with other reports, we found that VTE was associated with elevated BMI, abdominal surgical approach, prolonged operative times, and multiple comorbidities as indicated by ASA status. Although there may be overlap between ASA and BMI, the association persisted for each of these factors even after adjusting for other factors. Among these factors, surgical approach is potentially a modifiable risk factor.[1–3] This is supported by clinical practice guidelines that favor vaginal and laparoscopic approaches for hysterectomy over abdominal hysterectomy.[24,25] Prolonged length of surgery, related to immobilization, was also identified as a potentially modifiable factor, highlighting the importance of surgical efficiency in reducing VTE risk.[1–3]

In our study, we found that after adjustment for potential confounders, blood transfusion was associated with the highest odds of VTE, in comparison with the other more widely known risk factors included in our study. Given the relative importance of blood transfusion as a risk factor for VTE, greater attention to perioperative blood management is warranted. Among women electing to undergo surgical management of heavy menstrual bleeding, preoperative iron replacement and menstrual suppression are known to lead to increased preoperative hemoglobin concentration and lessen the need for blood transfusion.[26,27]

The results of this study suggest that patients undergoing gynaecologic surgery should have particular attention paid to preoperative and intraoperative blood management. Preoperative anemia has been found to be associated with both a significantly increased risk of receiving perioperative transfusion and increased risk of

Table 2. Effect of patient and process-of-care characteristics on venous thromboembolism among women undergoing hysterectomy for benign indication

Variable	Unadjusted OR (95% CI)	Postoperative adjusted OR (95% CI)[a]
Age, y		
<40	Referent	Referent
40–44	1.0 (0.78–1.32)	1.0 (0.72–1.25)
45–49	1.0 (0.75–1.26)	0.9 (0.66–1.16)
50–54	1.2 (0.90–1.57)	1.1 (0.79–1.46)
≥55	0.9 (0.69–1.18)	0.9 (0.64–1.25)
BMI category		
Underweight	1.5 (0.62–3.75)	1.6 (0.65–3.99)
Normal	Referent	Referent
Overweight	1.1 (0.84–1.41)	1.0 (0.78–1.36)
Obese I	1.5 (1.13–1.91)[b]	1.2 (0.94–1.65)
Obese II	1.7 (1.23–2.20)[b]	1.3 (0.93–1.76)
Obese III	2.0 (1.48–2.64)[b]	1.4 (0.99–1.91)
Race		
Non-White vs. White	1.2 (0.99–1.42)	0.9 (0.73–1.09)
Diabetes	1.3 (0.98–1.7)	1.0 (0.76–1.43)
Smoking	0.9 (0.72–1.13)	0.9 (0.72–1.17)
Hypertension	1.1 (0.95–1.37)	0.9 (0.73–1.13)
Bleeding disorder	2.0 (0.97–3.93)	1.3 (0.63–2.86)
ASA class		
I	Referent	Referent
II	1.2 (0.90–1.62)	1.1 (0.82–1.61)
III–V	2.0 (1.42–2.67)[b]	1.5 (1.04–2.26)[b]
Operative time, min		
<90	Referent	Referent
90–119	1.2 (0.91–1.56)	1.1 (0.82–1.47)
120–149	1.4 (1.01–1.78)[b]	1.3 (0.96–1.75)
≥150	2.1 (1.65–2.61)[b]	1.9 (1.46–2.42)[b]
Indication		
Menstrual disorders	Referent	Referent
Endometriosis	0.9 (0.60–1.34)	0.8 (0.52–1.22)
Genital prolapse	0.9 (0.63–1.19)	1.0 (0.69–1.65)
Other	1.1 (0.85–1.43)	0.9 (0.69–1.23)
Pain	0.9 (0.53–1.48)	1.0 (0.59–1.72)
Fibroids	1.2 (0.99–1.57)	1.0 (0.77–1.28)
Surgical approach		
Abdominal vs. laparoscopic	1.9 (1.59–2.27)[b]	1.8 (1.48–2.21)[b]
Abdominal vs. vaginal	2.6 (1.96–3.47)[b]	2.3 (1.62–3.28)[b]
Laparoscopic vs. vaginal	1.4 (1.04–1.82)[b]	1.3 (0.91–1.78)
Blood transfusion		
Intraoperative	4.3 (2.94–6.17)[b]	2.7 (1.78–3.95)[b]
Postoperative	4.1 (2.76–6.11)[b]	3.0 (1.95–4.55)[b]

[a] Adjusted for age, BMI, race, diabetes, smoking, hypertension, bleeding disorder, ASA classification, surgical approach, operative time, and blood transfusion.

[b] $P < 0.05$

ASA: American Society of Anesthesiologists; BMI: body mass index; OR: odds ratio.

VTE.[28] Thus, preoperative treatment of anemia or use of intraoperative techniques to minimize blood loss are indicated.[29] Furthermore, for patients who experience bleeding complications requiring transfusion, prophylactic anticoagulation may be withheld owing to the potential risk of re-bleeding. In such cases, the elevated risk of VTE among transfusion patients also needs to be considered when assessing the risk and benefits of thromboprophylaxis.

The strengths of this study include the use of a large, multi-institutional, multinational database, which allows for generalizability of the findings. All patients in the study were consistently followed for a period of 30 days after the date of surgery and after discharge for the development of complications, thereby avoiding confounding due to differences in length of stay or loss to follow-up. Furthermore, the availability of a large number of patient clinical and surgical process-of-care variables allowed for restriction and multivariate regression modeling to control for potential confounding effects.

Limitations of this study include the lack of detailed clinical information regarding patient history of thrombophilia, previous VTE, and use of hormonal therapy. Furthermore, the database does not include information on the use of VTE prophylaxis, which may result in bias. However, the associations observed were robust, even after adjustment for multiple potential patient and process-of-care variables.

CONCLUSION

Although clinical practice guidelines on VTE prevention refer to the elevated risk of VTE with blood transfusion, there are no recommendations regarding the prevention of VTE among patients who have received transfusion, aside from the usual recommendations for postoperative thromboprophylaxis.[30] However, our study shows a substantial risk of VTE development after blood transfusions, and these findings warrant consideration in future updates of clinical practice guidelines for surgical thromboprophylaxis. Given that both VTE and transfusion have been shown to be strong predictors of mortality,[11,12] it is critical to implement strategies to prevent such complications among women undergoing hysterectomy.[11,23]

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