Perioperative venous thromboembolism risk in patients undergoing hysterectomy for fibroids: a U.S. retrospective cohort study

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Abstract

Objective: Venous thromboembolism (VTE) occurs in 0.4-0.7% of benign hysterectomies. Pelvic vascular compression secondary to fibroids may represent a mechanism for elevated VTE risk. We aimed to evaluate the incidence and timing of VTE among individuals undergoing hysterectomy for fibroids and other benign indications. Design: Retrospective cohort. Setting: Vizient clinical database. Population: Adult patients without thrombophilias or malignancies who underwent hysterectomy January 2015-December 2021. Methods: Demographics, comorbidities, surgical characteristics, and VTE rates were compared by surgical indication. Main Outcome Measures: VTE consisted of pulmonary embolism or deep venous thrombosis diagnosed during three periods: 1) preoperative (one year before surgery until day before surgery), 2) early postoperative (surgery date through six weeks after surgery), and 3) late postoperative (six weeks to one year after surgery). Results: 467,027 patients were identified (263,844 with fibroids and 203,183 without) and 1.1% experienced VTE. On multivariable regressions adjusting for demographic confounders and route of surgery, the presence of fibroids was associated with higher odds of preoperative (aOR 1.12, 95% CI 1.03-1.22, p=0.011) and lower odds of late postoperative VTE (aOR 0.81, 95% CI 0.73-0.91, p<0.001). For individuals with fibroids, uterine weight ≥250 grams and undergoing hysterectomy via laparotomy were associated with preoperative (aOR 1.29, 95% CI 1.09-1.52, p=0.003 and aOR 2.32, 95% CI 2.10-2.56, p<0.001) and early postoperative VTE (aOR 1.32, 95% CI 1.08-1.62, p=0.006 and aOR 1.72, 95% CI 1.50-1.96, p<0.001), respectively. Conclusion: Patients with fibroids were at higher odds of having VTE in the year before hysterectomy. For those with fibroids, elevated uterine weight and open hysterectomy were associated with greater risk of preoperative and early postoperative VTEs. Funding: There was no funding source for this study.

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Conclusion: Patients with fibroids were at higher odds of having VTE in the year before hysterectomy. For those with fibroids, elevated uterine weight and open hysterectomy were associated with greater risk of preoperative and early postoperative VTEs.

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Introduction

Uterine fibroids, or leiomyomas, arise from clonal expansion of uterine smooth muscle cells. Fibroids affect up to 80% of black women and 70% of other racial and ethnic groups, with other risk factors including obesity,
nulliparity, older age, and late menopause. Treatment options for symptomatic fibroids include medical therapies to reduce bleeding and limit gonadotropin stimulation and procedural interventions involving fibroid excision, ablation, or hysterectomy. In the United States, approximately 30% of individuals with fibroids seek procedural management.

Growing evidence supports an association between fibroids and incidence of venous thromboembolism (VTE). The largest study to date from a nationwide database in Taiwan found that women with a history of fibroids were more likely to be diagnosed with VTE compared to those without fibroids. Overall, VTEs occur in approximately 0.4-0.7% of benign hysterectomies. In cases of hysterectomy for fibroids, a previous single-institution study found that uterine weight above 1000 grams was associated with increased incidence of preoperative VTE.

National guidelines in the United States vary regarding approaches to VTE prophylaxis for individuals with fibroids undergoing hysterectomy. While the American College of Obstetricians and Gynecologists (ACOG) does not characterize individuals with fibroids undergoing hysterectomy as high-risk, the AAGL recommends considering preoperative assessment for deep vein thrombosis for those with fibroids and uterine size > 20 weeks. Moreover, there are no current prospective or randomized controlled trials that describe the risk of VTE during minimally invasive hysterectomy. As such, preoperative assessment for VTE and perioperative VTE chemoprophylaxis are not uniformly implemented, and the extent to which uterine size impacts VTE risk is not well-described.

The primary objective of this study was to evaluate the incidence of preoperative, perioperative, and postoperative VTE in patients with and without fibroids undergoing hysterectomy. We also aimed to investigate for an association between uterine size, route of surgery, and VTE risk. For patients undergoing hysterectomy, we hypothesized that those with fibroids, elevated uterine sizes, and open hysterectomy have higher rates of VTE around the time of surgery than individuals with small, non-fibroid uteruses.

**Methods**

We performed a retrospective cohort study involving patients who underwent hysterectomy for fibroids and other benign indications between January 1, 2015 and December 31, 2021 in the Vizient clinical database. The Vizient clinical database is a national database that collects de-identified information from member institutions, which include approximately 95% of academic medical centers and over 300 community hospitals across the United States. This database receives administrative claims data along with detailed patient charge data. Diagnosis codes are validated against International Classification of Diseases (ICD)-10 coding standards and ICD-10 Procedure Coding System procedure code mappings. Any invalid diagnosis or procedure codes are identified and examined when inpatient and outpatient encounters are linked. On inpatient claims, the database receives ICD-10 diagnosis and procedure coding, but not the Centers for Medicare and Medicaid Services Part-B physician billings containing Common Procedural Terminology (CPT) codes. CPT codes and ICD-10 diagnosis codes are captured for all outpatient claims. A master “person identifier” from hospital billing and Electronic Health Record systems is used to link individual patients for longitudinal analyses and readmission algorithms. To ensure data accuracy, claims from a given month are compared to the previous 11 months and z-scores are created for all admission demographics. Both individual claims and batches of claims are rejected if z-score outliers are identified and detailed information about the probable root cause is collected.

Study participants were identified using ICD-10 diagnosis codes and CPT codes for hysterectomy. Patients were included if they underwent hysterectomy for fibroids or other benign indications during the study period. Exclusion criteria consisted of age < 18 years, previous or current malignancy of any type, and history of thrombophilias (homozygous factor V Leiden mutation, antiphospholipid syndrome, prothrombin gene mutation, and deficiencies in protein C, protein S, or antithrombin III).

Demographic data included age, race, ethnicity, body mass index (BMI), insurance type, hospital region, teaching hospital status, hospital bed size, and medical comorbidities. We examined smoking status and hypertension, as well as the specific comorbidities incorporated in the updated Charlson comorbidity index:
congestive heart failure, dementia, chronic obstructive pulmonary disease, connective tissue disorder, liver disease, diabetes, hemiplegia, chronic kidney disease, and acquired immunodeficiency syndrome (AIDS). Clinical data were abstracted, including surgical indication (fibroids vs. other benign indications), VTE chemoprophylaxis (administration of heparin or enoxaparin on the day of surgery), surgical route (minimally invasive or laparotomy), length of stay, uterine weight (dichotomized at 250 grams), and 30-day complication rates (blood transfusion, ileus, intraoperative bowel injury, intraoperative non-bowel injury, readmission, reoperation, sepsis, and death). Of note, coding of uterine weight was only recorded in the Vizient database for individuals who received outpatient surgery. For inpatient admissions, CPT codes were not available and uterine weight was coded as unknown.

The primary outcome of the study was diagnosis of VTE, defined as deep venous thrombosis or pulmonary embolism occurring up to one year before or after surgery. We evaluated three time periods during which VTE was diagnosed: 1) preoperative (one year before surgery until the day before surgery), 2) early postoperative (day of surgery through six weeks after surgery), and 3) late postoperative (six weeks to one year after surgery). Patients who were diagnosed with VTE preoperatively were classified in the preoperative group and were censored from early postoperative and late postoperative analyses.

Participants were stratified based on the presence or absence of fibroids. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as mean +/- standard deviation. We used student’s t-test to compare parametric continuous outcomes, Wilcoxon Rank Sum test for non-parametric and ordinal outcomes, and Pearson’s chi-square test or Fisher’s Exact test for categorical outcomes. Multivariable logistic regression models were created to investigate for relationships between fibroids and VTE diagnoses while controlling for other demographic and clinical factors. To avoid multicollinearity, only surgical route and not uterine weight were included in the primary multivariable analysis. We also performed sub-analyses of patients with fibroids to examine the impact of uterine weight and surgical route on VTE diagnosis. All results with p < 0.05 were considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

**Results**

A total of 514,381 individuals underwent benign hysterectomy were identified within the study period in the Vizient clinical database. We excluded individuals < 18 years of age (n=800), those with thrombophilias (n=12,569), and individuals with a history of malignancy (n=33,985). Ultimately, 467,027 patients comprised the study population, of which 263,844 (56.5%) underwent hysterectomy for fibroids and 203,183 (43.5%) for other benign indications (Figure 1).

Demographic and hospital characteristics are displayed in Table 1. Patients with fibroids were older than those who had surgery for other indications (48.3 vs. 47.6 years, p<0.001) and were more likely to be of Black (27.6% vs. 8.4%, p<0.001) or Asian race (3.3% vs. 1.9%, p<0.001) or Hispanic ethnicity (12.1% vs. 9.9%, p<0.001). Among those with BMI data available, individuals with fibroids more often had BMIs [≥]30 kg/m² compared to those without fibroids (23.4% vs. 20.6%, p<0.001). Patients in the fibroid group were more likely to have hypertension (31.5% vs. 26.9%, p<0.001) or AIDS (0.22% vs. 0.17%, p=0.013) and less likely to have congestive heart failure (0.47% vs. 0.52%, p<0.014), liver disease (2.7% vs. 3.1%, p<0.001), diabetes (9.6% vs. 10.3%, p<0.001) and chronic kidney disease (1.4% vs. 2.0%, p<0.001). When comparing insurance types, those with fibroids more often had commercial insurance (70.6% vs. 62.4%, p<0.001) and less frequently had Medicaid (13.8 vs. 16.4%, p<0.001) or Medicare insurance (8.3% vs. 15.1%, p<0.001).

Table 2 displays clinical data for the cohort, including rates of VTEs and other adverse events. Patients with fibroids were more likely to have hysterectomy performed via laparotomy than were patients undergoing hysterectomy for other indications (30.0% vs. 14.9%, p<0.001). Correspondingly, individuals with fibroids more often had hospital stays >24 hours than their non-fibroid counterparts (30.5% vs. 19.5%, p<0.001). Uterine weights for patients with fibroids were more often recorded as ≥250 grams than for those without fibroids (17.1% vs. 2.7%, p<0.001). Individuals with fibroids less commonly received perioperative VTE
chemoprophylaxis on the day of surgery (22.6% vs. 23.9%, p<0.001).

Overall, 1.1% of individuals (5,307) experienced VTE events in the year before and after hysterectomy. On univariate analysis, individuals with fibroids were more likely than those with other benign indications to have VTE diagnosed preoperatively (0.64% vs. 0.48%, p<0.001) or in the early postoperative period (0.39% vs. 0.27%, p<0.001). In contrast, patients with fibroids were less likely to have VTE diagnosed in the late postoperative period (0.31% vs. 0.35%, p=0.012).

Other adverse events that were more common in patients with fibroids included blood transfusion (1.9% vs. 0.65%, p<0.001), intraoperative non-bowel injury (0.88% vs. 0.64%, p<0.001), postoperative ileus (1.2% vs. 0.97%, p<0.001), and readmission (1.04% vs. 0.89%, p<0.001). In contrast, individuals with fibroids were less likely to experience intraoperative bowel injury (0.02% vs 0.03%, p=0.003), reoperation (0.18% vs. 30%, p<0.001), and postoperative death (0.01% vs 0.02%, p=0.002), though these complications were exceedingly rare throughout the cohort.

We used multivariable logistic regression modeling to examine the relationship between fibroids and occurrence of perioperative VTE, while adjusting for potential confounders of surgical route, age, race, smoking status, medical comorbidities, insurance, teaching hospital, and use of VTE chemoprophylaxis on the day of surgery. The presence of fibroids was associated with higher odds of VTE in the preoperative period (aOR 1.12, 95% CI 1.03-1.22, p=0.011) and lower odds of VTE in the late postoperative period (aOR 0.81, 95% CI 0.73-0.91, p<0.001). Hysterectomy via laparotomy was associated with higher odds of VTE events in the year before and after surgery (preoperative aOR 2.34, 95% CI 2.16-2.53, p<0.001; early postoperative aOR 1.59, 95% CI 1.42-1.77, p<0.001; late postoperative aOR 1.33, 95% CI 1.19-1.49, p<0.001).

We performed subgroup analyses to investigate the impact of 1) uterine weight and 2) surgical route specifically for individuals with fibroids in the cohort. Adjusting for potential demographic and clinical confounders as above, we found that compared to uterine weight <250g, uterine weight ≥250g was associated with higher odds of VTE in the preoperative (aOR 1.29, 95% CI 1.09-1.52, p=0.003) and early postoperative periods (aOR 1.32, 95% CI 1.08-1.62, p=0.006). A larger percentage of patients undergoing open/abdominal surgery were categorized as those with unknown uterine weight when compared to those undergoing minimally invasive surgery (71.0% vs 29.0%, n=104,431 vs 42,652). Unknown weight compared to uterine weight <250g was associated with higher odds of VTE in all three time periods (preoperative aOR 2.72, 95% CI 2.42-3.05, p<0.001; early postoperative aOR 2.09, 95% CI 1.80-2.43, p<0.001; late postoperative aOR 1.36, 95% CI 1.16-1.58, p<0.001). Similarly, for patients with fibroids, undergoing hysterectomy via laparotomy was associated with higher odds of VTE in the year before or after surgery (preoperative aOR 2.32, 95% CI 2.10-2.56, p<0.001; early postoperative aOR 1.72, 95% CI 1.50-1.96, p<0.001; late postoperative aOR 1.36, 95% CI 1.17-1.57, p<0.001).

Discussion

Main Findings

In this nationally representative study from the United States, we compared individuals with and without fibroids undergoing hysterectomy to assess the incidence of VTE in the year before and after surgery. Compared to those undergoing surgery for other benign indications, individuals with fibroids had higher odds of experiencing VTE in the year before surgery (aOR 1.12) and lower odds of experiencing VTE from six weeks to one year after surgery (aOR 0.81). For patients with fibroids specifically, both uterine weight ≥250 g and hysterectomy via laparotomy were associated with higher risk of VTE in the year before and six weeks after hysterectomy.

In this analysis, fibroids and elevated uterine weight were identified as potential risk factors for VTE in the year before patients undergo hysterectomy. Virchow’s triad may be applied to explain the mechanisms underlying this association. Virchow’s triad identifies factors that contribute to thrombosis formation: hypercoagulability, venous stasis, and endothelial injury. In the setting of fibroids, the weight of the uterus may contribute to venous stasis secondary to direct or secondary vascular compression. A predisposition for
thrombosis is seen in other compression syndromes, such as pelvic venous disorders (previously May-Thurner syndrome), thoracic outlet syndrome, and celiac artery compression syndrome.\textsuperscript{8,16} Our data suggest that individuals undergoing hysterectomy for fibroids with uterine size \( \geq 250\text{g} \) may be considered higher risk for VTE in the preoperative period than those undergoing hysterectomy with small, non-fibroid uteri. We also found that patients with fibroids had decreased odds of VTE more than 6 weeks after surgery. This observed reduction in risk could be secondary to the beneficial effects of eliminating vascular compression from fibroids following hysterectomy.

National society guidelines on perioperative VTE prophylaxis in the U.S. vary regarding the role for supplementary prophylaxis in patients undergoing surgery for large fibroids. ACOG recommends use of thromboprophylaxis based on a patients’ individualized risks for both VTE and major bleeding at the time of surgery according to the Caprini score.\textsuperscript{11} The Caprini score was adapted from the American College of Chest Physicians and not validated in gynecologic populations. It incorporates demographic and historical factors, physical exam findings, and surgical characteristics to estimate the risk of perioperative VTE.\textsuperscript{17} ACOG recommends using mechanical prophylaxis via intermittent pneumatic compression devices or graduated compression stockings for those at the lowest risk of perioperative VTE, while patients at higher risk of VTE without increased risk of major bleeding should receive pharmacologic or dual prophylaxis.\textsuperscript{11} Of note, ACOG does not describe specific VTE prophylaxis guidelines for individuals undergoing hysterectomy nor for patients with fibroids, elevated uterine size, or planned laparotomy. Although minimally invasive surgery is identified as a protective factor compared to laparotomy, any procedure over two hours in duration contributes equal weight to the Caprini score and subsequent individualized risk assessment for VTE.\textsuperscript{11}

In contrast to ACOG recommendations, the AAGL characterizes individuals with large fibroids as a high-risk group in their 2020 practice guideline on enhanced recovery and surgical optimization for minimally invasive gynecologic surgery.\textsuperscript{12} The AAGL guidelines highlight the following preoperative findings as indicators of increased surgical VTE risk: estimated uterine weight over 1000g or 20 weeks’ size on physical exam, lower extremity edema, iron deficiency anemia, thrombocytosis, and hydroureter on imaging. The authors recommend considering preoperative assessment for DVT in this patient population.\textsuperscript{12} Of note, this recommendation has not been validated using prospective data evaluating the outcomes of protocols for patients with large fibroids prior to hysterectomy. Our study suggests that individuals with fibroids and large uterine weights undergoing hysterectomy are more likely to experience preoperative and perioperative VTE. This suggests the need for further prospective and comparative investigation into VTE prophylaxis strategies to inform perioperative guidelines broadly.

Furthermore, estrogen-containing hormonal contraception is often prescribed as first-line medical treatment of abnormal uterine bleeding attributed to fibroids. The findings from our study highlight elevated VTE risks, and we propose there is a need to evaluate the effect of thrombogenic estrogen-containing medications in patients with large fibroids. There is currently limited large-scale data to assess the risk of combined hormonal contraceptive use in the setting of large fibroids.

Strengths

The strengths of this study include the use of a large, multi-centered network of hospitals across the United States. VTE diagnosis is a rare outcome and having a cohort of this size allowed us to elucidate a meaningful difference between VTE risks for individuals with and without fibroids. The rate of VTE identified in this cohort is higher than that previously reported (1.05-1.20% vs 0.4-0.7%), which is likely due to the inclusion of VTE events in the year preceding hysterectomy, while most studies collect data from the early postoperative period alone.\textsuperscript{9} Moreover, the Vizient clinical database also contained information about VTE chemoprophylaxis use, which is notably missing from previously published literature.\textsuperscript{5,6,10}

Limitations

The limitations of this study include those inherent to the retrospective cohort design and the information available within the dataset. Specifically, we were unable to abstract information regarding precise uterine weight measurements, concomitant use of combined hormonal contraceptives and operative times, which
may contribute to VTE risk in this population. Uterine weight was secondarily recorded from CPT coding in this dataset and obtained primarily in outpatient encounters. Due to large amount of unknown uterine weight, surgical route was included as a surrogate in our main multivariable models, given uterine weight and surgical route was highly correlated in this cohort. Further research will be helpful to establish more granular relationships between uterine weight and VTE risk.

**Conclusion:**

This study enhances our current understanding of the relationship between fibroids, large uterine weights, and VTE risk across multiple surgical time periods. Compared to those with no fibroids or small uterus, individuals with fibroids and elevated uterine weights experienced higher odds of VTE events prior to and following hysterectomy in this cohort. This presents an important target for prospective studies to investigate optimal strategies for risk reduction before and after surgery.

**Declarations:**

Annika Sinha - Project creation, protocol design, manuscript creation, editing
Meng Yao - Statistically analysis, manuscript editing
Ernie Shippey - Data collection
Deborah Hornacek - Expert consultation and advisement
Rosanne Kho - Protocol design, manuscript editing
Megan Orlando - Protocol design, manuscript editing

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**Ethical Statement:** Approved by Cleveland Clinic Foundation Institutional Review Board 20-721 Accepted 11/2021

**References**


Figure 1. Participants who underwent hysterectomy for benign indications within the Vizient database 2015-2021

Table 1. Demographic and hospital characteristics of participants undergoing hysterectomy for benign indications within the Vizient database 2015-2021.

Table 2. Surgical characteristics and adverse event data for patients undergoing hysterectomy for benign indications 2015-2021.

Table 3: Multivariable logistic regression examining occurrence and timing of venous thromboembolism for all patients undergoing hysterectomy for benign indications.

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