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a nationwide cohort study

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Venous thromboembolic complications to hysterectomy for benign disease. A nationwide cohort study.

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A nationwide cohort study using The Danish National Patient Register.

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Short title
Venous thromboembolism after hysterectomy

Précis

The risk of venous thromboembolism after hysterectomy for benign disease is generally low, highest with an abdominal procedure, and particularly low after laparoscopic and vaginal procedures.

Abstract

Study Objective: To estimate the risk of venous thromboembolic complications following abdominal, laparoscopic and vaginal hysterectomy when performed for benign disorders.

Design: Nationwide cohort study (Canadian Task Force Classification II-2).

Setting: Data from Danish national registers on all women undergoing hysterectomy for benign conditions in the period 1996-2015.

Patients: Women aged 18 and above who underwent hysterectomy for benign disease were stratified into 3 groups according to hysterectomy approach: abdominal, laparoscopic or vaginal.

Intervention: Hysterectomy.

Measurements and Main Results: 89,931 women met the inclusion criteria. Venous thromboembolism (VTE) as a diagnosis or cause of death was identified. Risk of postoperative VTE was examined with Cox proportional hazard models adjusting for age, surgical approach and relevant comorbidities. Mean age was 49.9, 47.9 and 54.3 years for women with abdominal, laparoscopic and vaginal hysterectomy, respectively. Crude incidences of VTE within 30 days after hysterectomy were 0.24% (n=142), 0.13% (n=12) and 0.10% (n=21). The most important predictors of VTE were approach to hysterectomy and a history of thromboembolic disease. In the multivariable analysis risk of VTE was significantly reduced with laparoscopic hysterectomy (HR 0.51; 95% CI 0.28-0.92, *P*=.03) and vaginal hysterectomy (HR 0.39; 95% CI 0.24-0.63, *P*<.001) when compared to the abdominal procedure. Data on postoperative heparin thromboprophylaxis were available in 53,566 patients and adjusted HR was 0.63 (95 % CI 0.42-0.96, *P*=.03) in patients receiving heparin thromboprophylaxis.

Conclusions: The 30-day cumulative incidence of VTE after hysterectomy for benign conditions was low overall (0.19%). Laparoscopic and vaginal hysterectomy carry a lower risk than the

abdominal procedure. Postoperative heparin thromboprophylaxis significantly reduces risk of VTE and should be considered especially if risk factors are present.

Keywords: Deep venous thrombosis; hysterectomy; pulmonary embolism; thromboprophylaxis.

Introduction

Postoperative venous thromboembolism (VTE) is the second-most common medical complication to general surgery and results in excess morbidity and mortality[1]. The most feared consequence, pulmonary embolism (PE), is the most common preventable cause of hospital death[1]. Deep vein thrombosis (DVT) and PE are preventable with proper thromboprophylaxis as demonstrated in clinical trials[2].

One of the most common gynecologic procedures is hysterectomy with 400- 600,000 procedures per year in the United States[3,4]. Few studies have focused on the incidence of VTE in women undergoing hysterectomy for benign conditions. There are three different approaches to hysterectomy: abdominal, laparoscopic and vaginal. In 2015, 20 % were performed as abdominal, 64 % as laparoscopic assisted (including robotic-assisted surgery) and 16 % as vaginal hysterectomies in Denmark[5]. The risk of postoperative DVT and PE, in patients undergoing surgery for benign conditions, is presumed to be low in general[6,7], and in particular when performed laparoscopically[8]. This is probably the reason, why pharmacologic VTE prophylaxis has not been used systematically. Despite being the recommendation in most clinical guidelines, the proportion of patients actually receiving thromboprophylaxis after hysterectomy may be as low as 11.9%[6]. Danish guidelines recommend postoperative venous thromboprophylaxis with low molecular weight heparin administered 4-12 hours following hysterectomy in prophylactic dose once daily until discharge from hospital, this can optionally be supplemented with graduated elastic compression stockings[9]. Few studies have focused on VTE in benign gynecologic surgery and recommendations on thromboprophylaxis have mostly been based on the experience from abdominal surgery and study populations with a broad variation of risk factors[10]. The striking difference between clinical practice and guidelines calls for a more precise estimation of risk of VTE after hysterectomy for benign conditions.

Materials and Methods

Data-sources

This study is based on data from national Danish administrative registries.

In Denmark, every resident is at the time of birth or immigration assigned a unique and permanent civil registration number, which enables linkage between nationwide administrative registers on the individual level. The Danish National Patient Register (DNPR) was established in 1977 and holds data on all hospitalizations in Denmark[11]. Each admission is registered at discharge with one primary and if appropriate one or more secondary diagnoses according to the International Classification of Diseases, the 10th revision (ICD-10). Surgical procedures are registered according to the Nordic Medico-statistical Committee's Classification of Surgical Procedures[12], together with the indication for the procedure. There could be multiple indications for hysterectomy.

We retrieved information on hormone substitution and anticoagulant treatment from The Danish Register of Medicinal Product Statistics where all prescription based pharmacy dispensings are stored. The National Population Register and the National Causes of Death Register hold information on vital status, date of birth and death including cause of death.

Study population

All patients who underwent hysterectomy from January 1st 1996 until December 31st 2015 were identified. The patients were separated into three groups according to the surgical approach: abdominal (subtotal or total abdominal hysterectomy comprised the codes KLCD00, KLCD96, KLCC10), laparoscopic (total, subtotal, vaginal and robotic assisted laparoscopic hysterectomy comprised the codes KLCD01, KLCD04, KLCC11, KLCD11, KLCD97) or vaginal (total or subtotal comprised the codes KLCD10, KLCC20, colpoperineoplasty and vaginal hysterectomy KLEF13). Patients diagnosed with any type of cancer within 1 month prior to surgery or two months following the surgical procedure were excluded (ICD10 codes DC00-96). Radical hysterectomies (KLCD30, KLCD31, KLCD40) were excluded because these procedures are only performed in the case of gynecologic malignancy. We did not include hysterectomies performed at the same time as cesarean section or hysterectomy performed at the same time as cystectomy in the case of urine

bladder malignancy.

Patients were excluded if the specific date of surgery was not defined.

Outcome

VTE comprised the following ICD-10 codes: I80.1 (phlebitis or thrombophlebitis in the femoral vein), I80.2 (deep phlebitis or thrombophlebitis in other veins in lower extremities), I80.3 (deep phlebitis or thrombophlebitis in other veins in lower extremities without specification), I80.8 (phlebitis or thrombophlebitis at other locations), I80.9 (phlebitis or thrombophlebitis without specification) and I26 (pulmonary embolism). If one of these codes occurred prior to the date of hysterectomy it was registered as a previous VTE. If the code was assigned to a patient within one month after hysterectomy it was registered as a postoperative VTE.

Confounders

Use of hormones or antithrombotic agents prior to surgery was defined as at least one claimed prescription within 180 days before surgery of the following agents: oral contraceptives with estrogen in combination with progesterone (Anatomical Therapeutic Chemical Classification G03A, G03HB01) or hormone therapy (estrogen as monotherapy or in combination with progesterone, both orally and transdermal administrated G03F, G03CX, G03CA and G03CB; low dose estrogen vagitories were excluded by product number). Antithrombotic agents were defined including antiplatelet drugs (B01AC) and anticoagulant drugs (B01 except B01AC).

Co-morbidities were defined as one of the following ICD-10 codes if the code was used at discharge within 365 days prior to the hysterectomy date: ischemic heart disease (I20, I23, I24, I25), cerebral vascular disease (I60-69), acute myocardial infarction (I21), varices of the lower extremities (I83), thrombophilia (D68), heart failure ((I50), chronic obstructive lung disease (J44).

Two time periods were compared as the Danish Board of Health in 2003 published a national guideline for benign hysterectomy including recommendations on postoperative VTE prophylaxis with heparin injections and graduated elastic compression stockings during hospitalization[13]. A Danish national hysterectomy database was established in October 2003 and one of the clinical

indicators is the use of VTE prophylaxis which is registered in the DNPR by the clinicians (BOHA03C).

Information on Body Mass Index (BMI) was obtained from the Danish Anesthesia Database (DAD). This information was not available for all patients since the database was established in 2004 and it does not cover all departments in Denmark.

Data are reported in accordance with the STROBE statement[14].

Statistics

Cumulative incidence was calculated for the competing risks VTE and death after abdominal, laparoscopic and vaginal hysterectomy respectively. Time to event was calculated from the date of surgery, follow-up time was 30 days and data were analyzed using univariable and multivariable Cox proportional hazard regression. Hazard ratios (HRs) of VTE after abdominal, laparoscopic and vaginal hysterectomy were hence estimated and presented with 95% confidence intervals (95% CI). A *P*-value less than 0.05 was considered statistically significant. Plots of Schoenfeld Residuals were used to examine the proportional hazard assumption. Linearity between the continuous variable age and outcome was tested. Interaction between approach to hysterectomy and presence of uterine fibroids was tested using analysis of variance.

Calculations were performed using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA) and R version 3.1.0 (R Core Team (2014))[15].

Ethics

The study was approved by The Danish Data Protection Agency (Re: 2007-58-0015, int.ref: GEH-2010-001). Permission from the ethics committee is not required for retrospective register studies in Denmark.

Results

We identified 89,931 patients who underwent hysterectomy for benign conditions in the period January 1st 1996 until December 31st 2015. Patients were divided into three groups according to the route of hysterectomy: Abdominal (n=59,231), laparoscopic (n=9,198) and vaginal (n=21,502) (figure 1). Table 1 shows the demographic data of the cohort according to age at surgery, length of stay, body mass index (BMI), concomitant disease, use of medicine before surgery, the indication for hysterectomy and postoperative pharmacologic VTE prophylaxis. Women undergoing vaginal hysterectomy were older and more likely to have comorbidities, although the general incidence of comorbidity was low in the total cohort. The indication for hysterectomy was uterine prolapse in more than 50 % of cases within the vaginal hysterectomy group. In the abdominal and laparoscopic hysterectomy groups, uterine fibroids and abnormal uterine bleeding were the dominant causes.

Comparing the two time periods before and after January 1st, 2004 showed that the proportion of minimally invasive hysterectomy was increasing during the study period with 29,060 abdominal approaches in 36,365 hysterectomies before 2004 ~80 %. After January 1st, 2004 44 % of hysterectomies were performed as laparoscopic and vaginal procedures.

During 30-day follow up after surgery we observed 175 cases of VTE with 100 cases of PE. There were 109 deaths in the abdominal hysterectomy group compared to one in the laparoscopic and 12 in the vaginal hysterectomy group.

Competing risk analysis of the cumulative incidence of VTE showed higher incidence with open surgery compared to the two minimally invasive methods. Cumulative incidence of mortality showed the highest incidence with open surgery compared to the two minimally invasive methods. (Figures S1 and S2 are provided in supplemental material).

Unadjusted HRs in different exposure groups are provided in table 2. The indication for hysterectomy could be strongly correlated to the choice of surgery approach as surgeons might prefer to perform abdominal hysterectomy in the presence of uterine and ovarian neoplasms. Statistical testing showed no evidence of interaction between hysterectomy approach and uterine fibroids (*P*=0.35).

Length of stay was associated with surgical approach (table 1) with median value highest in the abdominal hysterectomy group and univariable analysis (table 2) shows that it is significantly associated with HR of VTE.

Adjusting for age, time period, ovarian and uterine neoplasms, relevant drugs and concomitant disease, the laparoscopic (HR 0.51; 95% CI 0.28-0.92, *P*=.03) and vaginal (HR 0.39; 95% CI 0.24-0.63, *P*<.001) procedures are correlated with a significantly reduced HR of VTE when compared to abdominal hysterectomy (figure 2).

The use of oral hormonal contraceptives or hormone therapy did not influence on the HR of VTE in women undergoing hysterectomy (figure 2 and 3). In contrast, anticoagulant drugs, previous acute myocardial infarction (AMI) and previous VTE significantly increase the HR of VTE (figure 2 and 3).

Usage of postoperative heparin as VTE prophylaxis has been registered in the DNPR since 2004. There is no change in the impact of the different factors included in the first model (figure 2) when performing the same multivariable analysis on hysterectomies performed after 2003 including VTE prophylaxis instead of time period (figure 3). This subgroup analysis shows a reduced HR (0.63; 95% CI 0.42-0.96, P=.03) for VTE in patients receiving pharmacologic VTE prophylaxis.

Data on BMI were available in 11,177 patients with overall mean BMI 26.1 (SD ±5.0) and 19 VTE events (table 1). We found no difference in risk of VTE between BMI groups in a univariable Cox proportional hazard regression analysis. Because of the smaller number of events we did not attempt of multivariable analysis including BMI.

Discussion

This study demonstrates that the 30-day incidence of postoperative VTE after hysterectomy for any benign condition is low. The rate of VTE was lowest in patients treated with laparoscopic and vaginal hysterectomy compared to the abdominal approach.

A Cochrane review (2009) comparing the complication rates between different procedures concluded that vaginal hysterectomy was superior to abdominal on almost all outcome measures

and recommended laparoscopic surgery in cases where vaginal hysterectomy could not be performed[17]. However, there was no apparent difference in the VTE incidence according to surgical approach, probably due to limited power.

Barber et al (2014) found an overall incidence of VTE at 0.35 % in 44,167 women undergoing hysterectomy for benign conditions and showed abdominal hysterectomy to be associated with higher risk of VTE compared to minimally invasive surgery (OR 2.45; CI 1.77-3.40)[18]. Swenson et al (2015) registered 110 VTE events (0.5%) during 30 days of follow-up in 20,496 women with hysterectomy for benign, malignant and obstetric indications. Prominent risk factors were abdominal approach, cancer, BMI>35 and increased surgical time[19].

The frequency of VTE in these studies is consistent with our findings. The association between BMI and VTE is debated and experience from bariatric surgery suggests that it has been overestimated[20]. We found no association between BMI and VTE in a subgroup of the cohort; due to missing data, we could not include BMI in the multivariable analysis.

White et al (2003) showed, that the incidence of first-time VTE increases exponentially with age with a dramatically increase after the age of 60[21]. Ritch et al (2011) identified age as a significant risk factor of VTE after hysterectomy[6].

In accordance with these studies we found the crude HR of VTE increasing with age in the unadjusted model. This association could not be reproduced in the multivariable models, indicating a stronger association between VTE and approach to hysterectomy.

Several studies have reported an increased risk of VTE with hormone therapy (HT) [22]. In the present study we found no difference in HR between women on HT or oral contraceptives containing estrogen compared to women not exposed.

A benign pelvic mass might compress the iliac veins leading to venous stasis and subsequent thrombosis. Fletcher et al. (2009) found an increased risk of VTE (OR 3.75; CI 2.92-4.78, *P*<.001) among women with uterine fibroids with and without surgery when compared to the expected rate in hospitalized women[23]. Shiota et al. (2011) found an overall incidence of preoperative asymptomatic DVT at 3.7 % (31/843) in patients with benign ovarian tumors[24]. Our analysis

indicated no correlation between any benign indication for hysterectomy and risk of postoperative symptomatic VTE. Our dataset did not contain neoplastic size, therefore, the possible impact of large tumors on VTE risk cannot be assessed.

It must be emphasized that we can only report cases of symptomatic VTE´s. The incidence would probably be higher with more sensitive methods as demonstrated in randomized controlled trials[2].

In Denmark, thromboprophylaxis is administered by the hospital and was not registered in the DNPR before 2004. Hansen et al. (2008) reported an increase in heparin thromboprophylaxis administered following hysterectomy from 20 % in 2004 to more than 90 % of patients undergoing hysterectomy for benign disease in 2006[25]. Surgeons were probably paying more attention to VTE prophylaxis after the establishment of the Danish Hysterectomy and Hysteroscopy Database and implementation of recommendations on postoperative VTE prophylaxis. Our results indicate a significant reduction in risk of VTE following hysterectomy for benign conditions when pharmacologic VTE prophylaxis was administered during hospital stay after surgery. The ACOG Practice Bulletin (2007) recommends initiation of venous thromboprophylaxis with graduated compression stockings or pneumatic compression devices before surgery as VTE begins in the perioperative period[10]. Our results show a decrease in HR of VTE in patients receiving postoperative heparin which is supported by Hansen et al. (2008) who found preoperative administration associated with higher risk of bleeding complications compared to postoperative administration and no apparent difference in risk of VTE.[26] From our study we cannot draw any conclusions on the timing of VTE prophylaxis. Not all patients received prophylaxis, it is likely that patients within a fast track regimen undergoing MIS are discharged before heparin administration. Increasing length of stay increased the HR of VTE in a univariable analysis (table 2), despite this finding we did not include it in the multivariable analysis as we believe the variable is not a confounder because it is on the causal pathway between main exposure and outcome[27]. Talec et al (2016) suggest individual evaluation of thromboprophylaxis in each patient based on patient-

related risk factors, type of surgery including length of operation and duration to mobilization[28]. Our results support this approach to the planning of VTE prophylaxis.

The strength of epidemiologic research using national registries is the availability of a large patient cohort. Through our study, we found an important association between the risk of VTE and the approaches to hysterectomy. Groups were considered highly comparable according to baseline characteristics. The vaginal approach was used more often in case of pelvic organ prolapse and the abdominal approach in the presence of benign neoplasms, consistent with available gynecologic guidelines[29,30]. Bias could arise from misclassification of diseases and treatments. We calculated cumulative incidence of VTE considering mortality as a competing risk to illustrate how mortality affect the probability of a VTE event to occur. As mortality was highest in the abdominal hysterectomy group we found no reason to think mortality precluded the occurrence of VTE in the laparoscopic and vaginal hysterectomy groups.

The coding of co-morbidity and coexisting diseases in DNPR is validated by Thygesen et al. (2011), with a positive predictive value ranging from 82 to 100 %.[31]. The validity of VTE discharge diagnoses in DNPR was investigated by Severinsen et al. (2010) who found a positive predictive value of 75% for diagnoses coded at wards[32].

Confounding by indication could arise if the indication for hysterectomy carries a risk of developing VTE. Most other studies included patients with both benign and malignant diseases[6,19]. We chose to exclude patients with malignant disease and also obstetric patients, as these conditions are recognized risk factors for VTE[33,34].

Conclusion:

The risk of postoperative VTE in the first 30 days after hysterectomy is low (0.19 %). Laparoscopic and vaginal approach to hysterectomy significantly reduce the risk of VTE when compared to abdominal approach and adjusted for age and relevant risk factors. Our results indicate that postsurgical use of pharmacologic thromboprophylaxis reduce the risk of VTE. If heparin prophylaxis is not routinely used we suggest individual evaluation in each patient considering

approach to surgery, concomitant disease and previous thromboembolic events.

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Figure 1. Flowchart presenting the patient selection using Danish National Registries.

Figure 2. Multivariable Cox proportional Hazards Regression analysis presenting hazard ratios of venous thromboembolism associated with the approach to hysterectomy, adjusted for age, time period, ovarian and uterine neoplasm, use of sex hormones, a history of acute myocardial infarction (AMI) and previous venous thromboembolism (VTE).
Abdominal hysterectomy is used as reference in the main exposure group, among categorical variables in the confounder group exposed individuals are compared to non-exposed.

Figure 3. Multivariable Cox proportional Hazards Regression analysis presenting hazard ratios of venous thromboembolism associated with the approach to hysterectomy, adjusted for age, use of postoperative thromboprophylaxis, ovarian and uterine neoplasm, use of sex hormones and a history of acute myocardial infarction (AMI) and previous venous thromboembolism (VTE).

Stratified for period, showing results after 2003. Abdominal hysterectomy is used as reference in the main exposure group, among categorical variables in the confounder group exposed individuals are compared to non-exposed.

Figure S1. Cumulative incidence of venous thromboembolism 30 days following hysterectomy.

Figure S2. Cumulative incidence of death 30 days following hysterectomy.

453 **Table 1. Baseline characteristics and variables related to treatment**

Variable*	Abdominal hysterectomy N=59,231	Laparoscopic hysterectomy N=9,198	Vaginal hysterectomy N=21,502	Totals N=89,931
Mean age, years	49.9 ±10.4	47.9 ±10.5	54.3 ±13.2	50.7 ±11.3
Median length of stay, days (interquartile range)	3 (2,5)	1 (1,2)	2 (1,2)	3 (2,4)
Length of stay data missing	4	1	10	15
Body Mass Index (BMI)	26.2±5.2	25.7±5.3	25.9±4.7	26.1±5.0
BMI missing	52,706	8,394	17,654	78,754
Anticoagulant drugs	631 (1.1)	110 (1.2)	177 (0.8)	918 (1.0)
Antiplatelet drugs	2,243 (3.8)	359 (3.9)	1,633 (7.6)	4,235 (4.7)
Hormonal contraception	4,422 (7.5)	894 (9.7)	1,280 (6.0)	6,596 (7.3)
Hormone therapy	7,183 (12.1)	927 (10.1)	4,821 (22.4)	12,931 (14.4)
Hysterectomy before 2004	29,060 (49.1)	2,166 (23.5)	5,139 (23.9)	36,363 (40.4)
Hysterectomy after 2003	30,171 (50.9)	7,032 (76.5)	16,363 (76,1)	53,566 (59.6)
Indication for hysterectomy†				
Abnormal uterine bleeding	21,187 (35.8)	4,389 (47.7)	7,806 (36.3)	33,382 (37.1)
Benign ovarian neoplasm	4,910 (8.3)	292 (3.2)	189 (0.9)	5,391(6.0)
Uterine fibroids	34,849 (58.8)	3,314 (36.0)	4,888 (22.7)	43,051 (47.9)
Pelvic organ prolapse	1,209 (2.0)	319 (3.5)	10,935 (50.9)	12,463 (13.9)
Pelvic pain	8,536 (14.4)	2,061 (22.4)	3,115 (14.5)	13,712 (15.2)
Endometriosis	5,161 (8.7)	1,192 (13.0)	1,191 (5.5)	7,544 (8.4)
Cervical intraepithelial neoplasia	1,958 (3.3)	624 (6.8)	872 (4.1)	3,454 (3.8)
Endometrial hyperplasia	485 (0.8)	123 (1.3)	184 (0.9)	792 (0.9)
Urinary incontinence	628 (1.1)	66 (0.7)	588 (2.7)	1,282 (1.4)
Cancer predisposition	100 (0.2)	91 (1.0)	8 (0.04)	199 (0.2)
Concomitant diseases				
Ischemic heart disease	1,498 (2.5)	329 (3.6)	902 (4.2)	2,729 (3.0)
Cardiovascular disease	873 (1.5)	176 (1.9)	419 (1.9)	1,468 (1.6)
History of acute myocardial infarction	320 (0.5)	67 (0.7)	186 (0.9)	573 (0.6)
Thrombophilia	266 (0.4)	68 (0.7)	120 (0.6)	454 (0.5)
Varicose disease	1,838 (3.1)	350 (3.8)	1,166 (5.4)	3,354 (3.7)
Heart failure	345 (0.6)	53 (0.6)	158 (0.7)	556 (0.6)
Chronic obstructive lung disease	720 (1.2)	136 (1.5)	337 (1.6)	1,193

				(1.3)
Previous VTE	1,026 (1.7)	182 (2.0)	332 (1.5)	1,540 (1.7)
Postoperative VTE prophylaxis‡	N=30,171	N=7,032	N=16,363	N=53,566
No prophylaxis	13,755 (45.6)	2,797 (39.8)	5,623 (34.4)	22,175 (41.4)
VTE prophylaxis	16,416 (54.4)	4,235 (60.2)	10,740 (65.6)	31,391 (58.6)

* Data are expressed as N (column %), mean ± SD.
†There could be more than one indication for hysterectomy.
‡ Only registered in patients undergoing surgery after 2003.

Table 2. Unadjusted hazard ratios (HRs) of venous thromboembolism (VTE) in different exposure groups

	VTE events/N total	HR	95 % CI	*P* value
Age (by decade)	175/89,931	1.16	1.02-1.31	.019
Age<60 years	129/72,847	1.0 (reference)		
Age≥60 years	46/17.084	1.53	1.09-2.14	.013
Length of stay (LOS), days*	175/89,577	1.09	1.05-1.13	<.001
Abdominal hysterectomy	142/59,231	1.0 (reference)		
Laparoscopic hysterectomy	12/9,198	0.54	0.30-0.98	.042
Vaginal hysterectomy	21/21,502	0.41	0.26-0.64	<.001
Previous VTE	67/1,540	36.7	27.1-49.8	<.001
Previous acute myocardial infarction	6/573	5.7	2.5-12.8	<.001
Benign ovarian neoplasm	11/5,391	1.05	0.57-1.94	.867
Uterine fibroids	76/43,051	0.83	0.62-1.13	.834
Abnormal uterine bleeding	55/33,318	0.78	0.56-1.07	.117
Hormone therapy	24/12,931	0.95	0.62-1.46	.804
Contraceptives	13/6,596	1.01	0.58-1.78	.965
Anticoagulant drugs	31/918	21.5	14.6-31.7	<.001
Surgery after 2003				
After implementation of VTE prophylaxis	105/53,566	1.02	0.75-1.38	.907
VTE prophylaxis registered	43/31,391	0.49	0.33-0.72	<.001

*354 patients with missing data on LOS or LOS exceeding follow-up time of 30 days were excluded from the analysis. There were no cases of VTE within this group.

467 Figure 1.

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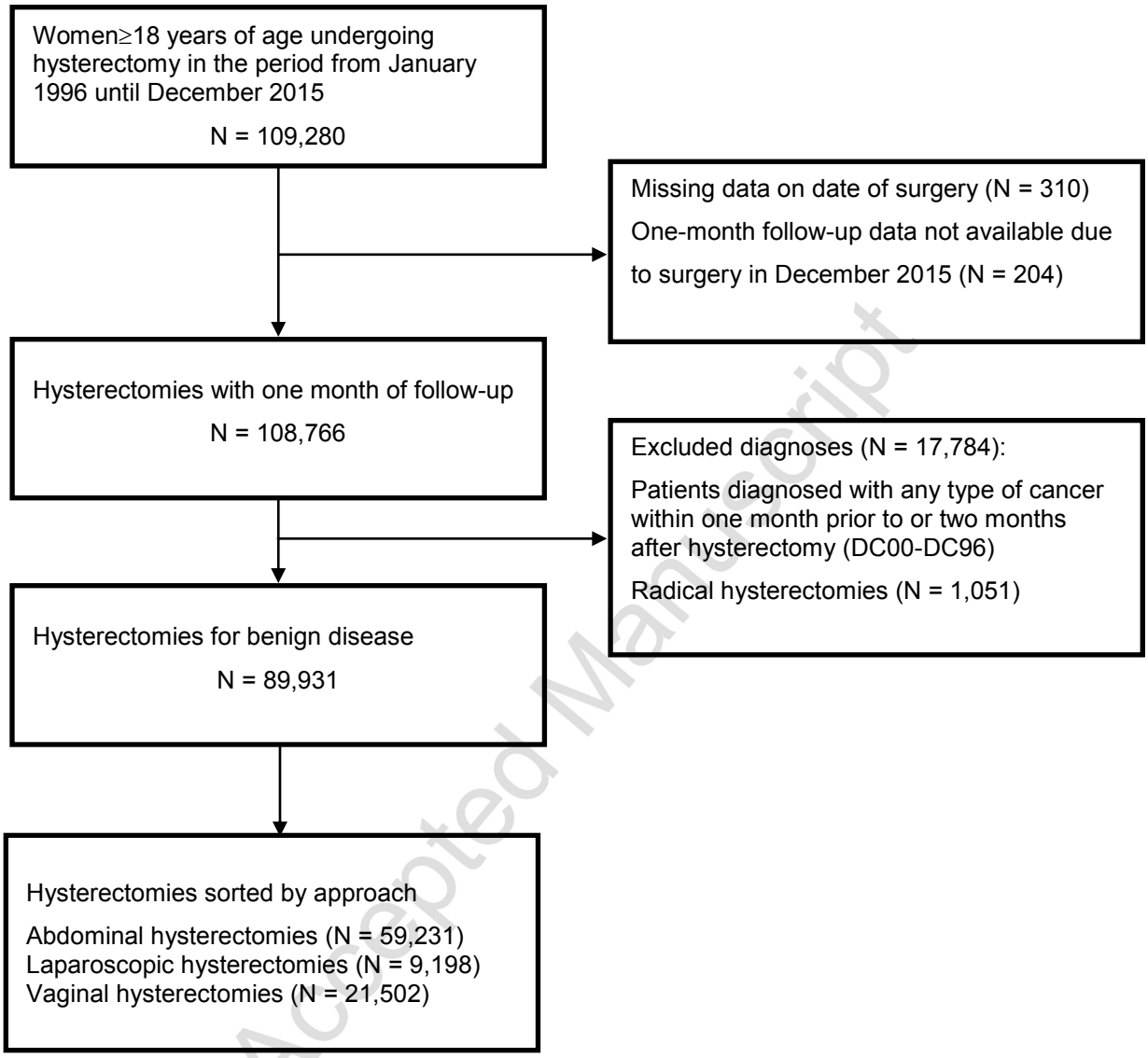

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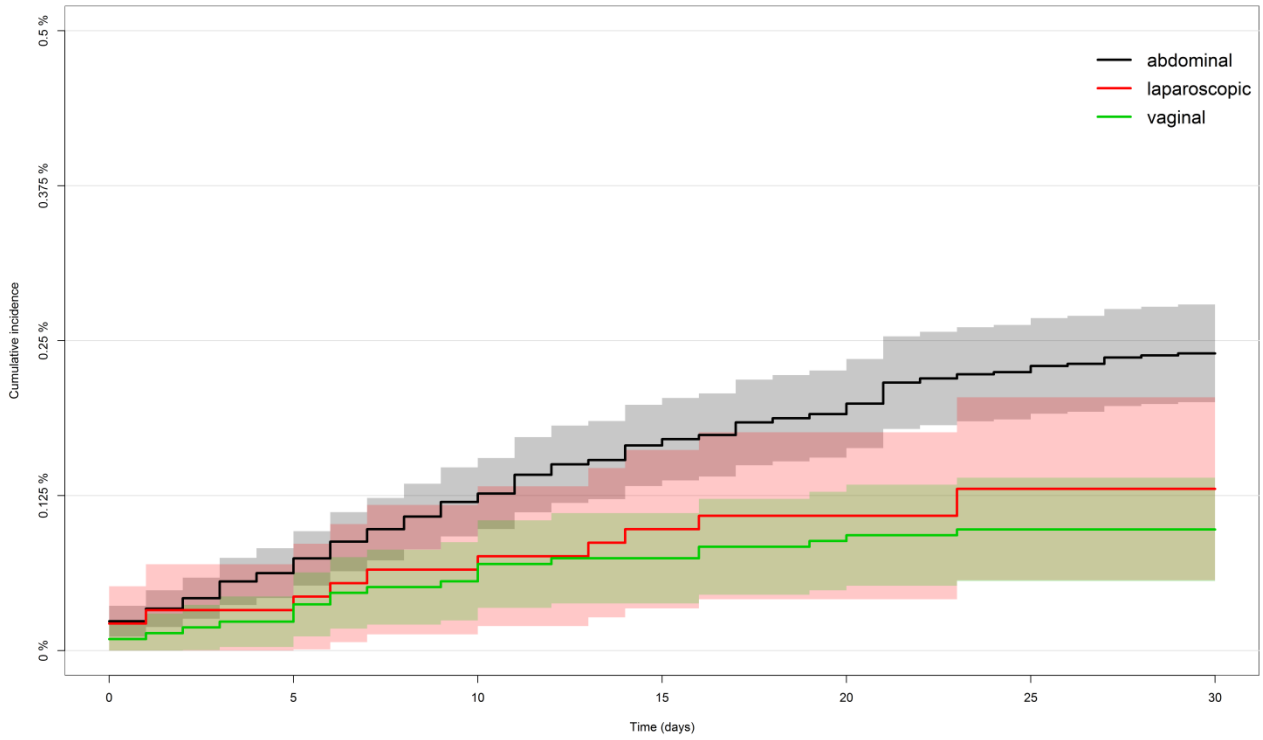
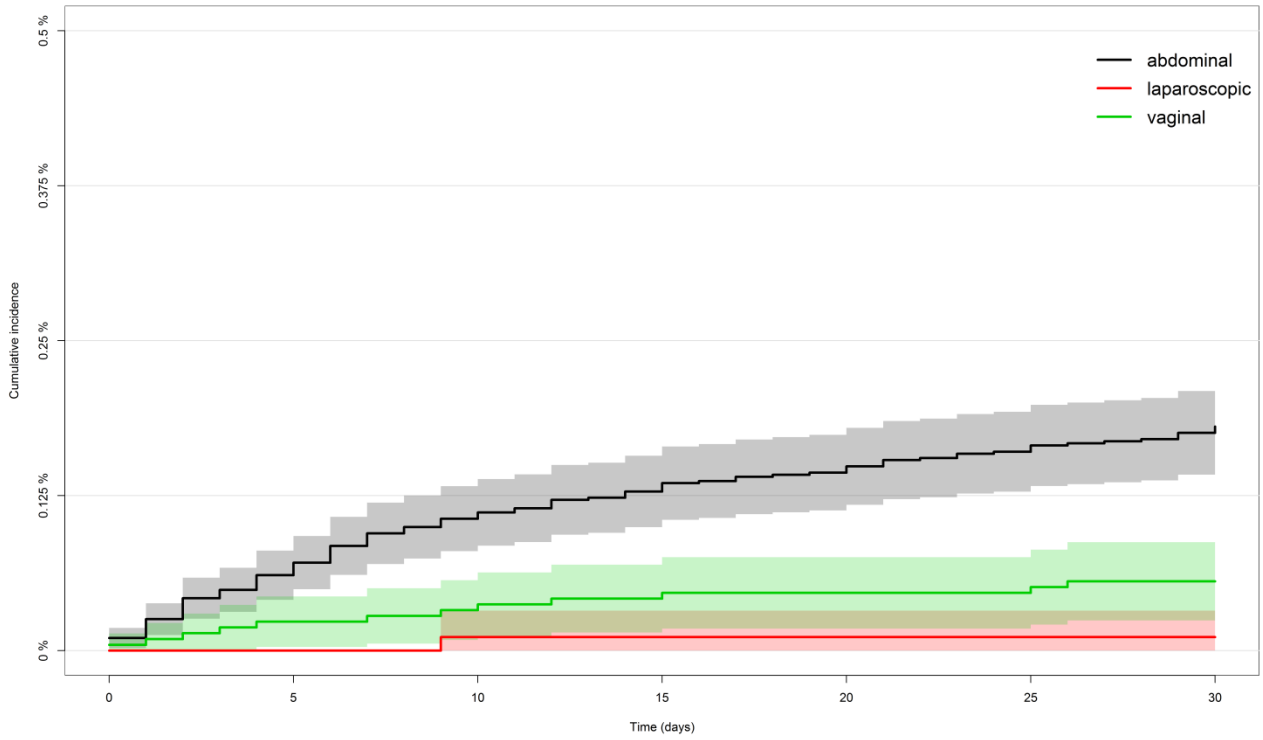


Figure S1_bestsetConverted.png



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476 Figure S2_bestsetConverted.png