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Complications after benign hysterectomy, according to procedure

a population-based prospective cohort study from the Danish hysterectomy database, 2004–2015

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Running title: Complications after benign hysterectomy

Abstract

Objective: To compare the risk of complications associated with benign hysterectomy according to surgical method.

Design: Register-based prospective cohort study

Setting: Danish Hysterectomy Database 2004 to 2015

Population: All Danish women with benign elective hysterectomy (N =51,141)

Methods: Multivariate log-binomial regression to compute relative risks (RRs) stratified by calendar period, and adjusted for age, height, weight, smoking habits, use of alcohol, comorbidity, indications, uterine weight, and adhesions. Multiple imputation and 'intention to treat' analyses were performed.

Main outcome measures: Major (Grade III-V) and minor (Grade I-II) Clavien-Dindo modified complications within 30 days.

Results: Overall, major complications occurred in 3,577 (7.0%) hysterectomies and minor complications in 4,788 (9.4%). The proportions of major and minor complications according to type of hysterectomy were 10.3% and 9.6% for abdominal (AH), 4.1% and 12.1% for laparoscopic (LH), 4.9% and 8.0% for vaginal (VH) for non-prolapse and 2.3% and 6.4% for prolapse.

In multivariate analyses, compared to VH for non-prolapse, the risk of major complications was higher for AH [RR=1.82 (1.63-2.03)] but lower for both LH [RR=0.78 (0.68-0.90)] and VH for prolapse [RR=0.55 (0.41-0.75)]. For LH, the risk of major complications reduced from a RR=0.96 (0.75-1.22) in the time period 2004-2009 to a RR=0.72 (0.60-0.87) between 2010-2015.

Conclusion: Laparoscopic hysterectomy and VH for uterine prolapse are associated with fewer major complications, but AH is associated with more major complications, compared to VH performed in the absence of uterine prolapse.

Funding: The database is supported by the Danish Health Authorities (Danish Clinical Registries) as one of the 60 databases in Denmark. The grants are for the annual working reports and the annual national audit meetings.

Keywords: Complications, epidemiology, hysterectomy, laparoscopic, minimally-invasive, surgical morbidity

Tweetable abstract: Laparoscopic hysterectomy has fewer major complications compared to vaginal hysterectomy in the absence of uterine prolapse.

Accepted Article

Introduction

The recommendations and practices regarding methods for hysterectomy are changing internationally. According to the Cochrane review 2015 vaginal hysterectomy (VH) was still the best minimal access method for hysterectomy, but benefits and hazards seem to be dependent on the surgical expertise¹. Moreover, the authors recommend the evidence in this review to be interpreted with caution as adverse event rates were low, resulting in low power for these comparisons¹.

In daily practice VH is preferred for prolapse, but for other indications the ultimate decision depends upon the size and shape of uterus. Some favour laparoscopic hysterectomy (LH) over VH in general^{2,3}, some favour VH even for enlarged uteri⁴, others consider that LH is preferable when concomitant salpingectomy or oophorectomy is needed^{4,5}. The importance of the shared decision-making process is highlighted^{1,6}, and as the techniques improve, frequent re-evaluations may be needed⁶.

Some countries uphold high rates of VH: In Sweden they have 27% VH for non-prolapse (VHnp)⁷. Most countries report VHnp and VH for prolapse (VHp) together: Finland, Netherlands and Austria have 44%, 51%, and 47% respectively⁸⁻¹⁰. USA and Portugal report 19% and 21% respectively^{11,12}. In other countries, UK, Australia, and Denmark, LH is replacing both VHnp and abdominal hysterectomy (AH)¹³⁻¹⁵. In the 1990s most of the hysterectomies in Denmark were performed as AH¹⁶. In the 2000s, VHnp increased but only reached 20%^{17,18}. From 2010 a national implementation of LH has begun to replace AH, and LH became the most common method¹⁵.

In 2004 we established the hysterectomy database, prospectively registering patient-related factors and all postoperative complications with 100% follow-up in the National Patient Register (NPR)¹⁹⁻²¹. The aim of this national population-based study is to compare the overall complications within 30 days after benign elective hysterectomy according to methods and calendar periods, controlled for patient-related confounders. A complete cohort of all benign hysterectomies including more than 50,000 patients, allows comparison of complications of hysterectomy performed by local experts in daily practice.

Methods

In the early 2000s, a nationwide Danish Hysterectomy Database was established by gynaecologists from different regions in Denmark¹⁹. This effort to reduce complications and diminish regional variation was supported by The Danish Health Authority. They funded the work for further evidence-based knowledge for national recommendations regarding hysterectomy²⁰. The Danish Clinical Registers funded the database as well as annual national audit meetings and reports¹⁵. We have no patients in the database. All postoperative complications treated at the hospitals were registered with 100% follow-up in the National Patient Register (NPR)²¹.

In Denmark the national public health care system is free of charge for all inhabitants with a specific ten-digit-social security number in the Danish Civil Registration System (CPR) through life. It is mandatory to record operations, diagnoses, patient-related characteristics, and any readmission to the NPR. The registration of readmissions is linked to the primary operation by CPR. Of the total number of hysterectomies, eight percent are performed in private hospitals, primarily for women with supplementary private healthcare insurance to cut waiting time. The private hospitals also report to the NPR¹⁵.

Validation of data

Nationwide, each surgeon fills in a mandatory form including various patient characteristics and specific information about the operation and the local secretaries report the codes to the NPR. From 2004 to 2011 all data in the NPR were scrutinized by one single database secretary who compared registry data to the original forms. She retrieved missing NPR data from the surgeons (forms had to be refilled, and hospital records were rechecked).

At the national audit-meetings representatives from all gynaecological departments in Denmark discuss the results from the different departments, followed by validation of local procedures and readmissions to ensure correct benchmarking in the public reports. Ten quality indicators were defined in 2004 (and revised annually 2011-2017) and have been published in annual database working reports including the last three consecutive years for comparisons, with the purpose to conduct quality assessment and further validation both on a local and a national level: Total number of benign hysterectomies, number of minimally invasive methods, prophylactic antibiotics, length of stay, total and major complications and mortality within 30 days, readmissions and re-operations within 30 days.

Study design

A register-based prospective national cohort study of all elective benign hysterectomies in Denmark from January 2004 to April 2015. In this study, we investigated the hospital-related major and minor short-term complications within 30 days postoperatively related to different surgical methods.

Study population

51,141 elective benign hysterectomies performed for gynaecological indications, registered in NPR with exclusion of emergency cases, postpartum cases, and all gynaecological cancer cases. We included cervical dysplasia and endometrial hyperplasia without atypia. Further cases of other cancer diagnoses were excluded except for non-melanoma skin cancer. Additionally, hysterectomies concomitant to complex benign bowel surgery performed at non-gynaecological departments were excluded due to non-gynaecological indications.

Intervention and outcomes

We subdivided hysterectomy into four groups: AH (total and subtotal), LH (robotic and laparoscopic assisted vaginal), VHnp (cases with a decision-making process regarding the feasibility of vaginal or laparoscopic approach), and VHp (where a laparoscopic approach would not normally be clinically useful) by use of the Danish version of the Nordic NCSP, NOMESCO Classification of Surgical Procedure (Table S1).

We extracted complications within 30 days using ICD-10 classification codes for diseases and the Nordic Medico-Statistical Committee's classification of surgical procedures (NCSP 1996-present) directly from the NPR. The outcomes were originally defined by the steering committee in 2003. The latest adjustment is according to modified Clavien-Dindo classification which is internationally accepted as core outcomes for postoperative complications. In this study we used the current algorithm from 2018 on the data from 2004-2015 for the first time, thus these results differ from the annual working reports.

Major complications included per-operative bleeding of more than 1000ml, serious infections with sepsis, all organ lesions (bowel, bladder or ureteral), all thrombotic-embolic events, any reoperation regarding organ lesions, bowel obstruction, infection or haemorrhage, (including ureteral catheterization postoperatively), and all wound complications requiring operative treatment (haematoma, rupture, or abscess), major anaesthetic complications, shock, and death. Mortality was searched as a non-vital status in the CPR. We also linked to the Cause of Death Register. Major complications are comparable to modified Clavien-Dindo classification grades III to V^{22,23}.

Total complications were defined as any deviation from normal postoperative course, all re-visits regardless of the diagnosis and need for treatment, including minor therapeutic regimens and small wound infection, and observations for comorbidity conditions postoperatively as modified Clavien-Dindo classification grade I-V^{22,23}. Minor complications were calculated from total minus major.

Clinical data were also collected for age, height and weight as body mass index (BMI) (categorised <18.5, 18.5-24.9, 25-30, >30), smoking habits, use of alcohol, comorbidity (according to the American Society of Anaesthesiologists, ASA groups one to four) and uterine weight (categorised <300, 300-499, 500-999, >=1000gram). Diagnoses were according to the International classification of diseases ICD-10 diagnoses since 1990 and the indication for surgery categorised into one of eight exclusive subgroups (Table 1 and Table S2). Abdominal adhesions after previous surgery or inflammation were recorded. Data were stratified for the calendar periods 2004-2009 and 2010-2015, because the latter period coincided with the national implementation of LH.

Missing data

There were no missing data for any hysterectomy procedure, additional procedures, or readmissions used to define the major complications. All these data are mandatory to register in NPR and the method by which the national funds are disbursed. Thus, we have 100% follow-up for the complications. However, for uterine weight, body mass index, smoking, comorbidity and alcohol use there were some missing data: A total of 19.1% of the cases had incomplete records for one or more of the five patient-related variables; uterine weight (0.7%), body mass index (11.3%), smoking (10.4%), comorbidity (10.7%), and use of alcohol (14.8%). Uterine weight seemed to be missing completely at random (MCAR) and the other four showed a non-response pattern (missing at random, MAR). Of 51,141 cases, 41,373 were complete cases

The non-responses for these patient-related outcomes were more common for private clinics in the first calendar period (problems with IT systems), and for all hospitals in the last calendar period because the one single database secretary stopped after 2011 (national grant was reduced). Thus, the non-response pattern for the confounders was most common for LH (LH missing 16-19%, AH missing 9-14%, VHp missing 9-15%, and VHnp missing 6-12%).

The estimates in the multivariate analysis would thus be biased using complete case analysis as missingness is not MCAR. We then analysed the missing values as just another level for the categorical predictors, assuming the same reason for non-response presumably not related to the

predictors in the analyses. As this method might produce biased estimates, we also performed multiple imputation for comparisons of the estimates. We imputed the five categorical patient-related variables; uterine weight, body mass index, smoking, comorbidity, and use of alcohol. We used the fully conditional method with 50 iterations and 50 imputations in SPSS. For the multivariate analyses performed on the imputed datasets, we report the pooled estimates.

Statistical analyses

Log-binomial regression analyses were carried out to calculate relative risk (RR) and 95% confidence interval (CI) for the association between postoperative complications and predictive factors, in univariate and multivariate analyses. Predefined clinically important covariates were included in the latter. The multivariate analyses were performed as an 'as treated' analysis (including all cases), as a 'per protocol' analysis' (excluding all the converted cases), and as an 'intention to treat' analysis (including cases as the intended surgery). We tested for interaction between method and calendar period, and as it was significant, we present stratified results according to calendar periods. The multivariate stratified analysis was repeated after the multiple imputation. A p-value below 0.05 was considered as significant and all analyses were performed in SPSS Statistics 22.

Assuming a baseline 5% major complication rate with vaginal hysterectomy for non-prolapse and a 1% reduction in major complication rates for the laparoscopic hysterectomies. 6,745 cases would be required in each group to give a 5% type 1 error rate and 80% type 2 error rate (Chi-squared test comparing independent proportions).

The database was approved in 2003 by The Danish Clinical Registries (RKKP). This project was approved regularly by the Danish Data Protection Agency (j.nr. 2012-41-1218): 2011.09.01, 2016.12.01, and 2019.03.28. Informed consent was not required by Danish law as all data are retrieved from administrative registers.

Results

Characteristics of the study population:

Distribution of all the patient-related characteristics according to the method of hysterectomy is listed in Table 1. The surgical methods were used differently according to different indications and age groups. LH and VHnp was used less with increasing age, and VHp was most common in women over 55. AH was used for uteri with higher weight and leiomyomas, whereas LH was used for dysplasia, hyperplasia, bleeding, and as risk-reducing prophylactic. Furthermore, VH was

used less if adhesions were expected and LH if comorbidity was present, and there was an increasing use of LH in the last calendar period.

Nationally there were 51,141 hysterectomies, of these 4,788 (9.4%) had minor and 3,577 (7.0%) had major complications. The crude frequencies of postoperative complications within the first 30 days (minor, major, or mortality alone) according to the different covariates and methods are presented in Table 2. Major and minor complications varied especially with the type of hysterectomy, indication, comorbidity, uterine weight, BMI, calendar year and presence of adhesions.

Mortality decreased with calendar time, increased with age, was higher in women with comorbidity, and adhesions, and when the hysterectomy was performed as VHnp or as AH for large benign cysts with initial suspicion of malignancy. Out of 14 fatal cases, 11 were in the first calendar period 2004-2009, age over 55, for small uteri without adhesions, performed as AH or as VHp.

Length of stay:

Length of stay was longer for AH than any other method with 37.2% of AH staying more than five days and only 8% below 24 hours. Whereas length of stay was shorter for LH than any other method with 8.7% of LH staying more than five days and 37% below 24 hours. Length of stay over 5 days was associated with high number of major and minor complications, 29.1% and 16.2% respectively, but 65.3% of those who stayed more than 5 days did not have any complications. Women with a length of stay below 24 hours had lower major, but not lower minor complications compared to average, 4.0% and 9.1% respectively.

Conversions:

There were 48 conversions of 51,141 (0.1%), (Table S1). Eight of the 48 (16.7%) had major complications. Of the intended LH, 20 were converted to AH and 1 to VH. Of the intended VH, 13 were converted to AH and 3 to LH. Of the intended TAH, 5 were converted to SAH. The remaining 6 were recoded to another type of LH or due to concomitant procedures to VH.

Predictive risk factors for postoperative complications in univariate analyses:

AH had higher risk of major complications compared to VHnp [RR=2.08 (1.88-2.30)], but LH had less [RR=0.83 (0.73-0.95)] (Table 3). Major complications increased with leiomyomas, abnormal uterine bleeding, endometriosis, ovarian cysts (concomitant), larger uteri, adhesions, larger BMI, and comorbidity. VH performed for prolapse had significantly both fewer major and minor

complications compared to VHnp. Regarding minor complications, both AH [RR=1.20 (1.11-1.31)] and LH [RR=1.50 (1.37-1.65)] were associated with higher risk than VHnp (Table 3). Minor complications increased with younger age, smaller uteri, adhesions, larger BMI, comorbidity, endometriosis, dysplasia, pain, and calendar time.

We included the missing values as a separate level in the categorical predictors (Table 3) in the univariate analyses, and the missing categories were nearly all significantly associated with fewer complications (Table 3).

Predictors for complications in multivariate analyses

AH had higher risk of complications [RR=1.82 (1.63-2.03)] whereas both LH [RR=0.78 (0.68-0.90)] and VHp [RR=0.55 (0.41-0.75)] had lower risk compared to VHnp. Both AH [RR=1.33 (1.22-1.46)] and LH [RR=1.48 (1.35-1.63)] remained associated with more minor complications than VHnp (Table S4). The confounders included were age, indication, comorbidity, BMI, use of tobacco and alcohol, uterine weight, calendar period and adhesions. We performed three different analyses: 'as treated', 'per protocol', and 'intention to treat'. The estimates were practically unchanged (Table S4).

Calendar trend:

There was a significant interaction between LH and calendar period for both minor and major complications, thus we used stratified analyses. National implementation of LH began in 2010-2015¹⁵, and the risk of major complications decreased after LH [RR=0.72(0.60-0.87)], while the risk for minor increased [RR=1.55 (1.36-1.77)] both compared to VHnp (Table 4). We only had 40 robotic cases in the first calendar period. Robotic cases had only 3% major complications (Table S1).

We developed one set of multivariate analyses using the data with the missing values coded as separate categories and another using imputed data and a pooled estimate from the 50 imputed dataset. However, the estimates remained practically unchanged (Table 4).

Weight trend:

In the multivariate analyses (Table 4), major complications increased with larger uterine weight independent of the method. In total there were 1,934 uteri over 1,000 grams, of these 151 (7.1%) with minor and 382 (20.4%) with major complications. The proportion of major complications after AH were dependent on uterine weight <300 grams, 300-499 grams, 500-999 grams, and >1000 grams, 9.0%, 9.2%, 11.3%, and 20.6% respectively. The corresponding complications after LH

were 3.9%, 4.6%, 6.2% and 14.6% respectively, and after VHnp 4.8%, 4.7%, 7.0%, 25.9% respectively. In the multivariate analysis (Table 4) the relative risk of major complications for uterine weight <300, 300-499, and 500-999grams respectively, all compared to \geq 1000grams, were RR=0.42 (0.37-0.47), RR=0.45 (0.40-0.52), and RR=0.57 (0.50-0.64) respectively. For smaller uterine weight, LH and VHnp were comparable, and for larger uterine weight LH had fewer major complications than both VHnp and AH (Table S5).

Factors associated with major and minor complications:

To further explore the 4,788 minor complications, they were divided into 13 groups according to the diagnoses used in the register (Table S3): There were 32% postoperative bleeding complications, 30% infections, and 21% with unspecified pain, none of which required reoperations.

In the final analyses (Table 4), the independent predictors for increased risk of major complications were larger uterine weight and higher BMI in both periods. Comorbidity and endometriosis were significant predictors in 2004-09, whereas abnormal uterine bleeding and hyperplasia/dysplasia became significant in 2010-15. Adhesions were an independent predictor for increased major and minor complications in both periods. The independent predictors for minor complications were smaller uteri and normal BMI but only in 2004-09, and pain indications in 2010-15.

Discussion

Main Findings

LH was associated with a lower risk of major complications within 30 days of surgery, compared to VHnp, even in the calendar period following national implementation, where a national learning curve was expected to go from experts to general gynaecologists. This risk difference was even more apparent when uterine weight was over 500 grams. AH had a higher risk for major complications compared to VHnp both before and after the national implementation of LH.

Strength and Limitations

We used a comprehensive, nationwide data set of all hysterectomies and a mandatory registration of all operations, in public as well as in private hospitals. All patients can be treated at public hospitals regardless of economic status and without any costs, minimising the risk of socioeconomic bias. Mortality data were validated with cause of death certificates. Data regarding major complications were validated by the representatives from each department. Any

inexplicable complication was checked with the hospital records in connection with the national audit meeting.

In general, the randomised controlled trial (RCT) is considered the gold standard study design to compare different treatment methods as regards internal validity. In this cohort study, the different methods were not equally used for different patient characteristics. However, this long-term real-world study of evidence-based practice in a national population might have external validity²⁴. It allows representation of heterogeneity among the participants in an everyday setting, choosing the methods most suitable for the individual patient. We got the same results regardless of the analysis approach: 'as treated' analysis, 'per protocol', and 'intention to treat'.

Limitations include a potential overestimation of minor complications because all re-visits are automatically registered with a tentative complication diagnosis, although only part of them have a complication requiring treatment. Re-visits increased as the LH implementation went national. Intended outpatient-operations became registered as re-visits, and the reduced length of stay also caused more re-visits. This apparent increase in minor complications may also reflect surveillance bias because more intense follow up may have been instituted with a new surgical technique, less familiar. On the other hand, the complications included in our analysis relate to readmissions to hospital, and not those seen by the general practitioners. Thus this may cause an underestimation of the number of minor complications across all hysterectomy methods. However, it is unlikely that major complications would be missed as these invariably necessitate hospital readmission.

We had 1-15% missing values for five patient-related covariates and included them as separate categories in our multivariate analysis, which might produce biased estimates. However, we got the same results from analysis on the imputed dataset. We did not have enough robotic hysterectomies to analyse if there was any difference between laparoscopic and robotic surgery.

Interpretation:

In 2004-09 LH was performed by relatively few experts but had the same complications as VHnp. From 2010 LH was implemented nationally and had fewer complications than VHnp¹⁵. The risk of major complications increased with larger uterine weight, higher BMI and adhesions, but independently of these patient-related factors and the learning curve, LH seems favourable to VHnp and AH. During the implementation years of LH, unfortunately we had some cases with sarcomas after uncontained morcellation²⁵. In 2015 the Danish Health Authority recommended the use of contained morcellation in endobags²⁰. Future data might answer whether the

implementation of contained morcellation will influence the superiority of LH compared to VHnp in Denmark²⁶.

International comparisons of complications

The Cochrane review included 16 studies with 1,440 women comparing LH and VH and found no evidence of a difference between the groups for any of the primary outcomes, nor for ureteral injuries¹. There are only few national population-based studies of complications to hysterectomy. In Sweden 2009-2015, they excluded VHp, and found that VHnp and LH did not differ significantly in complications⁷. A Finnish study included VHp in their analysis and found LH to have less complications than VH in 1996, but VH had less in 2006⁸. We subdivided VH to explore the differences. The patients having a VHp were older, with more comorbidity, smaller uteri, less adhesions, and were not usually considered for laparoscopic approach. Thus, we chose to compare LH with VHnp. After national implementation of LH from 2010, LH had fewer major complications. The increase of minor complications for LH might be a mixed result of a general cautious monitoring of a new method, and our comprehensive registration.

Conclusion

In Denmark, LH for benign hysterectomy had fewer major complications than both AH and VHnp, independent of uterine weight. Continuing monitoring of rates and complications after different methods are important, preferably using standardized definitions of complications to aid international comparisons^{22,23}.

Disclosure of interests:

The authors report no conflicts of interest. Completed disclosure of interest forms are available to view online as supporting information.

Some of the authors (Settnes, Topsoe, Moeller, Joergensen, Dreisler, Dueholm, Gimbel) are in the Steering Committee for the Danish Hysterectomy Database and active in hysterectomy research, others are former members (Ottesen, Kopp, Froeslev).

Contribution to authorship:

AS, CM, MD, BO, HG conceived the study, and started the database. AS, CM, MD, HG, ED, AJ designed the study with input from the rest of the authorgroup (PAF, TIK, BO, MFT, CN, SCR). Data-management, searches and extraction were performed by PAF, TIK, SCR, CN, MFT, AS. Data-analyses were performed by AS, CN, SCR with input from CM, HG, ED, AJ, MFT. Finally, AS was responsible for writing the first draft and all authors contributed to finalising the manuscript.

Details of ethics approval:

The study was approved regularly by the Danish Data Protection Agency (J.nr. 2012-41-1218): 2011.09.01, 2016.12.01, and 2019.03.28. All data were retrieved from administrative registers and informed consent was not required according to Danish law.

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Table 1: Characteristics of the study population according to hysterectomy method.

Patient characteristics	Subgroups	N	AH	LH	VH prolapse	VH non-prolapse
All		51,141	49.2	19.7	15.4	15.7
Age	<40	6,509	41.8	29.2	3.3	25.7
	40-44	11,187	51.5	22.9	3.3	22.3
	45-49	13,995	57.4	21.6	4.1	16.9
	50-54	7,465	60.1	18.4	9.6	11.9
	>=55	11,985	34.8	9.9	50.1	5.2
Indications^a	Leiomyomas	22,008	69.9	16.8	1.6	11.7
	AUB, all	10,878	40.0	22.5	1.3	36.2
	Endometriosis	989	52.6	38.7	1.0	7.7
	Prolapse+incont	7,375	3.3	1.5	94.6	0.6
	Hyperpl+dyspl	1,530	36.3	34.3	2.8	26.6
	Dysp+dysm+pain	1,959	41.8	30.7	0.1	27.4
	Obs cancer/cysts	1,686	91.0	7.5	0.0	1.5
	Genetic+other	4,716	37.3	45.8	7.4	9.5
Comorbidity^b	Unknown	5,473	43.0	34.1	14.1	8.8
	1-2	44,914	49.9	18.0	15.4	16.7
	3-4	754	54.2	8.1	26.8	10.9
Body Mass Index^c	Unknown	5,779	45.6	28.7	15.4	10.3
	< 18.5	709	46.2	22.6	10.6	20.6
	18.5-24.9	21,523	49.0	19.2	15.0	16.8
	25-30	14,398	49.1	16.9	18.4	15.6
	>30	8,732	52.7	18.8	12.0	16.5
Smoking	Unknown	5,301	43.0	31.1	15.6	10.3
	No	32,248	49.0	18.7	18.0	14.3
	yes	13,592	52.1	17.5	9.0	21.4
Alcohol use^d	Unknown	7,590	47.9	23.8	15.9	12.4
	0	26,863	49.2	19.5	15.6	15.7
	1-7/week	13,113	47.9	18.6	15.3	18.2
	8-14/week	819	55.6	16.1	13.9	14.4
	>14/week	2,756	62.3	12.6	12.3	12.8
Uterine weight	unknown	372	61.0	9.4	15.1	14.5
	<300gr	38,085	38.4	22.1	20.3	19.2
	300-499gr	5,364	69.8	19.6	1.1	9.5
	500-999gr	5,386	87.4	9.4	0.3	2.9
	>=1000gr	1,934	95.7	2.5	0.4	1.4
Calendar yrs	2004 - 2009	27,772	59.7	6.5	15.3	18.5
	2010 - 2015	23,369	36.8	35.2	15.5	12.5
Adhesions	No	49,140	48.2	19.5	16.0	16.3
	Yes	2,001	73.3	23.8	0.7	2.2
Length of stay	0-1 day	8,303	24.3	44.8	18.2	12.7
	2-3 days	20,483	35.5	23.1	19.1	22.3
	More than 3 days	22,355	71.0	7.2	11.0	10.8

a Indications: AUB = Abnormal uterine bleeding, incont= urge and stress incontinence, Hyperpl+dyspl= endometrial hyperplasia without atypia and dysplasia of the cervix, Dysp+dysm+pain= dyspareunia +dysmenorrhoea +other pain. b ASA (American Society of Anaesthesiologists). c Body mass index = weight in kilograms kg/height in metres squared m². d Alcohol = units of alcohol (12gram alcohol) per week.

Table 2: Percentages of minor and major complications and per mille mortality within 30 days after benign hysterectomy in Denmark from 2004 to 2015 according to predictive risk factors.

Predictors	Subgroups	N	Minor n (%)	Major n (%)	Mortality n (‰)
Total population		51,141	4,788 (9.4)	3,577 (7.0)	14 (0.28)
Hysterectomy	AH	25,165	2,426 (9.6)	2,586 (10.3)	7 (0.28)
	LH	10,046	1,213 (12.1)	414 (4.1)	2 (0.20)
	VH prolapse	7,883	503 (6.4)	179 (2.3)	4 (0.51)
	VH non-prolapse	8,047	646 (8.0)	398 (4.9)	1 (0.12)
Age	<40	6,509	795 (12.2)	489 (7.5)	0 (0)
	40-44	11,187	1,161 (10.4)	862 (7.7)	1 (0.09)
	45-49	13,995	1,335 (9.5)	1,101 (7.9)	2 (0.14)
	50-54	7,465	622 (8.3)	557 (7.5)	0 (0)
	>=55	11,985	875 (7.3)	568 (4.7)	11 (0.92)
Indications^a	Leiomyomas	22,008	2,033 (9.2)	1,913 (8.7)	2 (0.09)
	AUB, all	10,878	1,138 (10.5)	760 (7.0)	2 (0.18)
	Endometriosis	989	131 (13.2)	108 (10.9)	0 (0)
	Prolapse+incont	7,375	486 (6.6)	181 (2.5)	5 (0.68)
	Hyperpl+dyspl	1,530	120 (7.8)	92 (6.0)	1 (0.65)
	Dysp+dysm+pain	1,959	280 (14.3)	124 (6.3)	0 (0)
	Obs cancer/cysts	1,686	147 (8.7)	136 (8.1)	3 (1.78)
	Genetic+other	4,716	453 (9.6)	263 (5.6)	1 (0.20)
Comorbidity^b	Unknown	5,473	461 (8.4)	284 (5.2)	3 (0.55)
	1-2	44,914	4,203 (9.4)	3,203 (7.1)	6 (0.13)
	3-4	754	124 (16.4)	90 (11.9)	5 (6.63)
BMI^c	Unknown	5,779	457 (7.9)	293 (5.1)	3 (0.52)
	< 18.5	709	76 (10.7)	68 (9.6)	0 (0)
	18.5-24.9	21,523	2,151 (10.0)	1,432 (6.7)	7 (0.33)
	25-30	14,398	1,262 (8.8)	964 (6.7)	2 (0.14)
	>30	8,732	842 (9.6)	820 (9.4)	2 (0.23)
Smoking	Unknown	5,301	421 (7.9)	241 (4.5)	3 (0.57)
	No	32,248	2,921 (9.1)	2,321 (7.2)	6 (0.19)
	yes	13,592	1,446 (10.6)	1,015 (7.5)	5 (0.37)
Alcohol use^d	Unknown	7,590	645 (8.5)	418 (5.5)	4 (0.53)
	0	26,863	2,625 (9.8)	1,998 (7.4)	8 (0.30)
	1-7/week	13,113	1,188 (9.1)	911 (6.9)	2 (0.15)
	8-14/week	2,756	254 (9.2)	188 (6.8)	0 (0)
	>14/week	819	76 (9.3)	62 (7.6)	0 (0)
Uterine weight	Unknown	372	28 (7.5)	20 (5.4)	0 (0)
	<300gr	38,085	3,659 (9.6)	2,165 (5.7)	11 (0.29)
	300-499gr	5,364	486 (9.1)	420 (7.8)	1 (0.19)
	500-999gr	5,386	477 (8.9)	577 (10.7)	2 (0.37)
	>=1000gr	1,934	138 (7.1)	395 (20.4)	0 (0)
Calendar yrs	2004 - 2009	27,772	2,394 (8.6)	2,004 (7.2)	10 (0.36)
	2010 - 2015	23,369	2,394 (10.2)	1,573 (6.7)	4 (0.17)
Adhesions	No	49,140	4,503 (9.2)	3,300 (6.7)	13 (0.26)
	Yes	2,001	285 (14.2)	277 (13.8)	1 (0.50)

a Indications: AUB = Abnormal uterine bleeding, incont= urge and stress incontinence, Hyperpl+dyspl= endometrial hyperplasia without atypia and dysplasia of the cervix, Dysp+dysm+pain= dyspareunia+ dysmenorrhoea+other pain. b ASA (American Society of Anaesthesiologists). c BMI = body mass index = weight in kilograms kg/height in metres squared m². d Alcohol is units of alcohol (12gram) per week.

Table 3: Relative Risk (95% confidence interval) for minor and major complications within 30 days after benign hysterectomy (log-binomial regression) according to predictors 2004 to 2015.

Predictors	Subgroups	N	Minor complications	Major complications
Hysterectomy	AH	25,165	1.20 (1.11-1.31)*	2.08 (1.88-2.30)*
	LH	10,046	1.50 (1.37-1.65)*	0.83 (0.73-0.95)**
	VH prolapse	7,883	0.80 (0.71-0.89)*	0.46 (0.39-0.55)*
	VH non-prolapse	8,047	ref	ref
Age	<40	6,509	1.67 (1.53-1.83)*	1.59 (1.41-1.78)*
	40-44	11,187	1.42 (1.31-1.55)*	1.63 (1.47-1.80)*
	45-49	13,995	1.31 (1.20-1.42)*	1.66 (1.51-1.83)*
	50-54	7,465	1.14 (1.03-1.26)*	1.57 (1.41-1.76)*
	>=55	11,985	ref	ref
Indications^a	Leiomyomas	22,008	0.96 (0.87-1.06)	1.56 (1.38-1.77)*
	AUB, all	10,878	1.09 (0.98-1.21)	1.25 (1.09-1.44)*
	Endometriosis	989	1.38 (1.15-1.65)*	1.96 (1.58-2.42)*
	Prolapse+incont	7,375	0.69 (0.61-0.78)*	0.44 (0.37-0.53)*
	Hyperpl+dyspl	1,530	0.82 (0.67-0.99)***	1.08 (0.86-1.36)
	Dysp+dysm+pain	1,959	1.49 (1.29-1.71)*	1.14 (0.92-1.40)
	Obs cancer/cysts	1,686	0.91 (0.76-1.08)	1.45 (1.19-1.77)*
	Genetic+other	4,716	ref	ref
Comorbidity^b	Unknown	5,473	0.51 (0.43-0.62)*	0.44 (0.35-0.54)*
	1-2	44,914	0.57 (0.48-0.67)*	0.60 (0.49-0.73)*
	3-4	754	ref	ref
BMI^c	Unknown	5,779	0.82 (0.74-0.91)*	0.54 (0.47-0.61)*
	< 18.5	709	1.11 (0.89-1.39)	1.02 (0.81-1.29)
	18.5-24.9	21,523	1.04 (0.96-1.12)	0.71 (0.65-0.77)*
	25-30	14,398	0.91 (0.84-0.99)***	0.71 (0.65-0.78)*
	>30	8,732	ref	ref
Smoking	Unknown	5,301	0.75 (0.67-0.83)*	0.61 (0.53-0.70)*
	No	32,248	0.85 (0.80-0.90)*	0.96 (0.90-1.04)
	yes	13,592	ref	ref
Alcohol use^d	Unknown	7,590	0.92 (0.73-1.15)	0.73 (0.56-0.94)***
	0	26,863	1.05 (0.85-1.38)	0.98 (0.77-1.25)
	1-7/week	13,113	0.98 (0.78-1.22)	0.92 (0.72-1.18)
	8-14/week	819	0.99 (0.79-1.27)	0.90 (0.68-1.19)
	>14/week	2,756	ref	ref
Uterine weight	unknown	372	1.06 (0.71-1.56)	0.26 (0.17-0.41)*
	<300gram	38,085	1.35 (1.14-1.59)*	0.28 (0.25-0.31)*
	300-499gram	5,364	1.27 (1.06-1.52)**	0.38 (0.34-0.44)*
	500-999gram	5,386	1.24 (1.03-1.49)***	0.53 (0.47-0.59)*
	>=1000gram	1,934	ref	ref
Calendar years	2004 - 2009	27,772	0.84 (0.80-0.89)*	1.07 (1.01-1.14)***
	2010 - 2015	23,369	ref	ref
Adhesions	No	49,140	0.64 (0.58-0.72)*	0.49 (0.43-0.54)*
	Yes	2,001	ref	ref

a AUB = Abnormal uterine bleeding, incont= urge and stress incontinence, Hyperpl+dyspl=endometrial hyperplasia without atypia & cervix dysplasia, Dysp+dysm+pain= dyspareunia+dysmenorrhoe+other pain. b ASA (American Society of Anaesthesiologists). c BMI = body mass index = weight in kilograms kg/height in metres squared m². d Alcohol is units of alcohol (12gram) per week *p<=0.001 **P<=0.01 ***P<0.05

Table 4: Multivariate log-binomial regression for major and minor complications within 30 days of elective benign hysterectomy in Denmark from 2004 to 2015 according to surgical method stratified by calendar periods.

Major complications: multivariate RR (95% CI) by calendar periods				
Method	2004-2009		2010-2015	
	Coded^a	Imputed^b	Coded	imputed
AH	1.80 (1.56-2.07)*	1.79 (1.55-2.06)*	1.85 (1.55-2.20)*	1.82 (1.53-2.16)*
LH	0.96 (0.75-1.22)	0.95 (0.75-1.22)	0.72 (0.60-0.87)*	0.72 (0.60-0.86)*
VH_{prolapse}	0.76 (0.47-1.23)	0.77 (0.48-1.24)	0.39 (0.25-0.61)*	0.39 (0.26-0.61)*
VH_{non-prolapse}	ref	ref	ref	ref

Minor complications: multivariate RR (95% CI) by calendar periods

AH	1.37 (1.23-1.54)*	1.35 (1.21-1.51)*	1.32 (1.15-1.53)*	1.30 (1.13-1.50)*
LH	1.26 (1.06-1.49)**	1.25 (1.05-1.48)**	1.55 (1.36-1.77)*	1.53 (1.33-1.74)*
VH_{prolapse}	0.93 (0.67-1.31)	0.94 (0.67-1.32)	0.90 (0.67-1.21)	0.90 (0.67-1.20)
VH_{non-prolapse}	ref	ref	ref	ref

a Including all 51,141 cases. The missing values are coded as a separate category in the patient-related predictors as showed in Table 2 and 3.

b Including all 51,141 cases. The missing values are imputed, the pooled estimate from the 50 imputation datasets are presented.

* $p < 0.001$ ** $p < 0.01$ *** $p < 0.05$

Confounder control for age, indication, comorbidity, body mass index, smoking, uterine weight, adhesions and use of alcohol.

Significant predictors for major complications independent of methods:

In 2004-2009: Endometriosis compared to prophylactic hysterectomy for genetic mutation RR=1.58 (1.18-2.12). Uterine weight <300 compared to >1000 RR=0.40 (0.35-0.47). Body mass index 18-24 compared to >30 RR=0.74 (0.66-0.82). Comorbidity ASA-group 1-2 compared to 3-4 RR=0.54 (0.43-0.67). No abdominal adhesions compared to difficult RR=0.57 (0.49-0.66).

In 2010-2015: Abnormal uterine bleeding [RR=1.24 (1.03-1.50)] and Hyperplasia+Dysplasia [RR=1.40 (1.05-1.88)] both compared to prophylactic hysterectomy for genetic mutation. Uterine weight <300 compared to >1000 RR=0.45 (0.38-0.54). Body mass index 18-24 compared to >30 RR=0.83 (0.74-0.94). No abdominal adhesions compared to difficult RR=0.69 (0.58-0.82).

Significant predictors for minor complications independent of methods:

In 2004-2009: Uterine weight <300 compared to >1000 RR=1.79 (1.38-2.31). Body mass index 18-24 compared to >30 RR=1.14 (1.02-1.27). Comorbidity ASA-group 1-2 compared to 3-4 RR=0.46 (0.38-0.56). No abdominal adhesions compared to difficult RR=0.75 (0.63-0.88).

In 2010-2015: Endometriosis [RR=1.32 (1.03-1.69)], Hyperplasia+Dysplasia [RR=0.73 (0.56-0.95)], and Dyspareunia+Pain [RR=1.69 (1.41-2.03)] all compared to prophylactic hysterectomy for genetic mutation. Comorbidity ASA-group 1-2 compared to 3-4 RR=0.65 (0.49-0.87). No abdominal adhesions compared to difficult RR=0.75 (0.65-0.88).