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Hysterectomy for benign indications in Finland

Tea Brummer

ACADEMIC DISSERTATION

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Brummer TH, Seppälä T, Härkki P. National learning curve of laparoscopic hysterectomy and trends in hysterectomy in Finland 2000-2005. Hum Reprod 2008; 23(4): 840-845.

II Brummer TH, Jalkanen J, Fraser J, Heikkinen A, Kauko M, Mäkinen J, Puistola U, Sjöberg J, Tomás E, Härkki P. FINHYST 2006 - National prospective 1-year survey of 5 279 hysterectomies. Hum Reprod 2009; 24(10): 2515-2522.

III Brummer TH, Jalkanen J, Fraser J, Heikkinen A, Kauko M, Mäkinen J, Seppälä T, Sjöberg J, Tomás E, Härkki P. FINHYST, a prospective study of 5 279 hysterectomies: Complications and their risk factors. Hum Reprod 2011; 26(7): 1741-1751.

IV Brummer TH, Heikkinen A, Jalkanen J, Fraser J, Mäkinen J, Tomás E, Seppälä T, Sjöberg J, Härkki P. Pharmaceutical thrombosis prophylaxis, bleeding complications, and thromboembolism in a national cohort of hysterectomy for benign disease. Hum Reprod 2012, in press.

V Brummer TH, Heikkinen A, Jalkanen J, Fraser J, Mäkinen J, Seppälä T, Tomás E, Sjöberg J, Härkki P. Antibiotic prophylaxis for hysterectomy, a prospective cohort study: Cefuroxime, metronidazole, or both? BJOG 2012, in press.

In addition, some unpublished data are presented. The publications are referred to in the text by their roman numerals, and reproduced with permissions of the copyright holders.

ABBREVIATIONS

AC	anterior colporrhaphy
ACCP	The American College of Chest Physicians
ACOG	The American College of Obstetricians and Gynaecologists
AH	abdominal hysterectomy
AP	antibiotic prophylaxis
BMI	body mass index
BSO	bilateral salpingo-oophorectomy
DVT	deep venous thrombosis
GCS	graduated compression stockings
GKS	The Society of Gynaecological Surgery in Finland
CI	confidence interval
CS	cesarean section
HDR	The Hospital Discharge Register
ICD-10	The International Classification of Diseases (10th Revision)
ICU	intensive care unit
IPC	intermittent pneumatic calf compression
LAVH	laparoscopically assisted vaginal hysterectomy
LH	laparoscopic hysterectomy
LH(a)	laparoscopic hysterectomy (arteries coagulated laparoscopically)
LMWH	low-molecular fractionated heparin
LSH	laparoscopic subtotal hysterectomy
NCSP	Nordic Medico-Statistical Committee Classification of Surgical procedures
NICE	The National Institute for Health and Clinical Excellence (the UK)
OR	odds ratio
PC	posterior colporrhaphy
PE	pulmonary embolism
SAH	subtotal abdominal hysterectomy
SSI	surgical site infection
TAH	total abdominal hysterectomy
THL	The National Institute for Health and Welfare (Finland)
TP	thrombosis prophylaxis
UFH	unfractionated heparin
VH	vaginal hysterectomy
VTE	venous thromboembolism
VVF	vesicovaginal fistula

ABSTRACT

In the 1990's and up until 2002, annual numbers of hysterectomies for benign disease in Finland exceeded 10 000; only cataract surgeries and cesarean sections were more commonly performed on women. Hysterectomy is traditionally performed through laparotomy, meaning abdominal hysterectomy (AH), which currently is still the most common surgical approach for hysterectomy worldwide. In Finland, as well, a national cohort of hysterectomy for benign disease in 1996 showed AH as being the most common method, with 58%, but unlike in other nations, laparoscopic hysterectomy (LH) was fairly common, and performed for as many as 24%. Current guidelines state, that vaginal hysterectomy (VH) should be performed in preference to AH when possible. When VH is not possible, LH may avoid the need for AH; but LH is associated with an increased risk for urinary tract injuries.

The aim of this study was to evaluate in a national setting the current trends of hysterectomy for benign disease, focusing on the incidence and risk factors for various complications. In addition, analysis concerns the coverage and effect of thrombosis and antibiotic prophylaxis. Prior to the national prospective FINHYST study in 2006, major complications of LH in 2000-2005 were analysed from the registers of the Patient Insurance Centre in Finland and compared to those of the previous decade. This register also served in verification of major complications involved in FINHYST, in which all 46 public hospitals where hysterectomies were performed collaborated, in addition to 7 private clinics. Detailed data were collected on intraoperative and on early- and late-onset postoperative complications. Risk factors for complications were analysed by logistic regression adjusted for confounders. In this thesis, also complications of FINHYST in 2006 were compared to the prospective national hysterectomy study in 1996, as a 10-year follow-up

Since 2002, annual numbers of hysterectomies for benign disease in Finland gradually declined, and in 2007-2010 remained stable at an average 5 750 per year. By method, VH has been the most common approach in Finland since 2002, and LH surpassed AH in 2005. Urinary tract injuries, particularly ureter injuries with LH, were reduced to 0.3% in 2000-2005, representing a nearly three-fold reduction since the 1990's. The FINHYST study in 2006, which covered 79.4% of national hysterectomies for benign disease, comprised 1 255 AHs (24%), 1 679 LHs (32%), and 2 345 VHs (44%), with respective overall complications occurring in 19.2%, 15.4%, and 11.7%, and major complications (organ injuries, reoperations or venous thromboembolism) in 4.0%, 4.3%, and 2.6%. No deaths occurred. Most bladder and bowel injuries were detected and repaired intraoperatively (88% and 83%).

Risk factors for complications overall were adhesiolysis (OR 2.48), uterine size of 500 g or more (OR 1.44), and concomitant surgery (OR 1.28). Major complication risk factors were adhesiolysis (OR 2.41), more specifically bladder injuries associated with caesarean section (OR 4.01) and uterine size of 500 g or more (OR 2.88). Postoperative infections were associated with those overweight (OR 1.61), obese (OR 1.67), or extremely obese (OR 1.82), compared to those of normal weight. Pharmaceutical thrombosis prophylaxis (TP) was given to 64.8%. TP was associated with postoperative haemorrhage or haematoma in VH performed for prolapse (OR 4.82), and in AH (OR 2.87).

Age of 55 or over reduced the risk for complications overall (OR 0.61), and for infections (OR 0.66); operative haemorrhage decreased with age. Antibiotic prophylaxis was given to 97.5%: cefuroxime alone to 38.5%, metronidazole alone to 9.9%, and metronidazole in combination with cefuroxime to 43.0%. Overall, 54% received metronidazole, which had no significant independent risk-reducing effect, nor any interactive effect when combined with cefuroxime, for total infections in any type of hysterectomy. Cefuroxime, however, had a risk-reducing effect (OR 0.29); also for all hysterectomy methods separately. No method was independently associated with complications, except for infections, for which AH, compared to LH, led to a risk for febrile events, wound infections, and urinary tract infections. Compared to AH, in both the hysterectomy methods (LH and VH) in which the vault is closed vaginally, the risk for pelvic infection was 5-fold.

In conclusion, while numbers of hysterectomies in Finland have declined, the minimally invasive methods have overtaken AH. Such a trend promoting faster recovery from surgery has reduced complications, particularly infections. The follow-up also showed a reduction in ureter injuries in LH, and bowel injuries in VH. During the time that VH became the most common method for hysterectomy, its complications nearly halved.

SUMMARY IN FINNISH

1990-luvulla aina vuoteen 2002 asti, kohdunpoistoja hyvänlaatuisesta syystä tehtiin vuosittain yli 10 000. Kohdunpoisto olikin kaihikirurgian ja keisarileikkauksen jälkeen yleisin naisten toimenpide. Ensimmäiset laparoskooppiset kohdunpoistot (LH) tehtiin maassamme 20 vuotta sitten, jolloin avointen kohdunpoistojen (AH) osuus oli yli 90 %. LH yleistyi nopeasti, ja vuonna 1996 kansallisessa kohorttitutkimuksessa AH:n osuus oli 58 %, LH:n 24 % ja vaginaalisten kohdunpoistojen (VH) 18 %.

Tutkimuksen tarkoituksena oli selvittää hyvänlaatuisesta syystä tehtävien kohdunpoistojen määriä, menetelmiä, komplikaatioita sekä komplikaatioiden esiintymiseen vaikuttavia riski- ja suojatekijöitä. Valtakunnallista kalenterivuoden 2006 käsittänyttä prospektiivista FINHYST-kohorttitutkimusta edelsi retrospektiivinen Potilasvakuutuskeskuksen laparoskooppisen kohdunpoiston vakavien komplikaatioiden määrän selvitys ajalta 2000–2005. FINHYST-tutkimukseen kerättiin kohdunpoistojen tiedot kaikista 46 julkisesta sairaalasta, joissa ko. leikkauksia tehtiin; lisäksi 7 yksityissairaalasta. Tutkimuksessa selvitettiin myös tromboosi- ja infektioprofylaksian toteutusta ja tuloksia. Lisäksi väitöskirjassa analysoitiin komplikaatioiden esiintymisen 10-vuotismuutos edeltäneeseen valtakunnalliseen 1996 aineistoon verraten.

Tulokset osoittavat, että hyvänlaatuisen syyn vuoksi tehtävät kohdunpoistot maassamme ovat vähentyneet. Vuoden 2002 jälkeen määrä laski tasaisesti, kunnes 2007–2010 toimenpiteitä tehtiin vuosittain enää keskimäärin 5 750. Samalla vähäinvasiiviset menetelmät syrjäyttivät perinteisen avoleikkauksen (AH). Alatieleikkaus VH ylitti AH määrän vuonna 2002, ja LH teki saman vuonna 2005. Mistään muusta maassa ei vastaavaa trendiä ole julkaistu; muissa Pohjoismaissa sekä anglosaksisissa maissa suositaan edelleen perinteistä avoleikkausta. Suomen lisäksi Saksassa ja Hollannissa VH on jo menetelmistä yleisin. Suomalainen erityispiirre onkin muualla harvinaisen LH-leikkauksen laaja-alainen hallitseminen, mikä heijastelee gynekologisen tähystyskirurgian yleisesti korkeaa tasoa maassamme. Potilasvakuutuskeskuksen tietojen perusteella LH-leikkauksen vakavat komplikaatiot vähenivät verraten 90-luvun tulokseen. Virtsajohdinvaurioita esiintyi 1992–1999 0,9 prosentilla, ja 2000–2005 enää 0,3 prosentilla. Terveyden ja hyvinvoinnin laitoksen hoitoilmoitusrekisterin perusteella FINHYST-tutkimuksen 5 279 potilasta edustavat 79,4 % vuonna 2006 maassamme tehdyistä kohdunpoistoista hyvänlaatuisesta syystä. Kohdunpoistomenetelmät olivat AH 24 %, LH 32 %, ja VH 44 %. Komplikaatiota ilmeni AH leikkauspotilailla 19,2 prosentilla, LH:ssa 15,4 prosentilla ja VH:ssa 11,7 prosentilla, vakavia komplikaatioita (elinvaurioita, uusintaleikkauksia, tai veritulppia) vastaavasti 4,0, 4,3 ja 2,6 prosentilla. Leikkaukseen liittyviä kuolemia ei esiintynyt. Rakkovaurioista 88 % ja suolivaurioista 83 % havaittiin ja korjattiin jo kohdunpoistoleikkauksen aikana, ja uusintaleikkauksilta vältyttiin.

Komplikaatioihin liittyviä riskitekijöitä olivat vatsaontelon kiinnikkeet, 500 g tai kookkaampi kohtu ja lisätoimenpiteet leikkauksen aikana. Myös vakavien komplikaatioiden osalta kiinnikkeet olivat tärkein riskitekijä. Kohdunpoiston virtsarakkovaurioiden riskitekijöitä olivat aiempi keisarileikkaus ja suuri kohtu. Ylipaino lisäsi komplikaatioiden riskiä, mm. haavatulehdusten riski oli ylipainoisilla avoleikkauksessa yli viisinkertainen normaalipainoisiin

verrattuna. Lääkkeellinen tromboosiprofylaksia annettiin 65 % leikkauksista ja se lisäsi leikkauksen jälkeisten vuotokomplikaatioiden riskiä laskeumapotilaiden alatieleikkauksessa ja avokohdunpoistossa.

Alle 45-vuotiaisiin verraten, potilaan korkeampi ikä, 55 v. tai enemmän, vaikutti suojaavasti kokonais- ja infektiokomplikaatioiden esiintymiseen, minkä ajatellaan liittyvän verekkyyden eli leikkausvuodon vähenemiseen iän myötä. Antibioottiprofylaksian sai 98 %. Kefuroksiimi-antibiootilla oli tehokas itsenäinen riskiä vähentävä vaikutus. Metronidatsoli antibioottia annettiin kaiken kaikkiaan 54 %:lle potilaista, mutta se ei yksinään eikä kefuroksiimin lisänä annettuna suojannut leikkauksen jälkeisiltä tulehduksilta. Itse leikkausmenetelmien osalta komplikaatioiden esiintymisessä ei havaittu tilastollisia eroja lukuun ottamatta infektioiden alaryhmiä: LH:ssa esiintyi vähemmän leikkauksen jälkeistä kuumeilua, haavainfektioita ja virtsatietulehduksia kuin AH:ssa. Molemmissa kohdunpoistomenetelmissä, joissa emättimen haava ommellaan alateitse (LH ja VH), esiintyi leikkauksen jälkeisiä lantion verenpurkaumia tai märkäkertymiä avokohdunpoistoa enemmän.

Kohdunpoistojen ajatellaan vähentyneen hormonikierukan käytön ja kohdun tähystysten lisäännyttyä. Kohdun tähystyksessä voidaan poistaa vuotohäiriöitä aiheuttavia kasvaimia. Molemmilla menetelmillä voidaan tehokkaasti hoitaa runsaita kuukautisvuotoja. Myös vaihdevuosien jälkeisen hormonihoidon käytön väheneminen on voinut vähentää kohdunpoistoja. Kohdunpoistojen menetelmien muututtua avoleikkausta kevyemmiksi suomalaiset naiset toipuvat toimenpiteestä nopeammin. 10-vuotisseurannassa infektiokomplikaatiot vähenivät. Samalla vähenivät myös vähäinvasiivisten kohdunpoistojen elinvauriot: LH:n virtsajohdinvauriot ja VH:n suolivauriot. Suurin muutos tapahtui VH:ssa, jossa kokonaiskomplikaatiot lähes puoliintuivat kohdunpoistomenetelmän tultua yleisimmäksi.

INTRODUCTION

Hysterectomy, meaning removal of the uterus, has been more common in Finland than in most Nordic countries. A questionnaire study of over 1 700 women aged 45 to 64, representative of the Finnish population in 1989, showed as many as 19% had had their uteruses removed (Luoto et al. 1992). The majority of hysterectomies are being performed due to benign tumours of the uterus: myomas (Vuorma et al. 1998, Whiteman et al. 2008, Lundholm et al. 2009). The dominant method has been the abdominal hysterectomy (AH), in Finland (Mäkinen et al. 2001), as in other parts of the world.

In Finland, the national quality assessment tradition concerning hysterectomy for benign disease began after introduction of the laparoscopic hysterectomy (LH) in 1992 (Mäkinen and Sjöberg 1994), and revealed a high incidence of ureter injuries (1.3%) (Härkki-Sirén et al.1997). A database of 10 110 surgeries including all hysterectomy methods was collected in 1996. Vaginal hysterectomy (VH) was the least common approach with 18%, and it predominated in the number of resultant complications (Mäkinen et al. 2001). The CREST study, during its era noted for VH a lower overall complication rate compared to AH; the superiority of VH was already being considered (Dicker et al. 1982). A large American observation study discovered no difference in complications among the three approaches, but VH was recommended because of its low cost (Campbell et al. 2003). These recommendations on choice of method were confirmed by a meta-analysis on randomized controlled trials (RCT), which stated that VH should be performed in preference to AH if possible, and if not, LH may avoid the need for AH. These guidelines state, however, that in LH, compared to AH, urinary tract injury rates are increased (Nieboer et al. 2010).

Complications of hysterectomy are affected by experience of the gynaecologic surgeon (Mäkinen et al. 2001), hospital type (Härkki-Siren et al. 1999), and patient characteristics, such as obesity (David-Montefiore et al. 2007). Complications of hysterectomy have been observed to be reduced for the elderly, but this phenomenon has been left unexplained (Hemsell et al. 1995, McPherson et al. 2004, Löfgren et al. 2004). A meta-analysis on pharmaceutical thrombosis prophylaxis (TP) in the context of gynaecological surgery for malignant disease observed no increased risk for bleeding complications with TP (Einstein et al. 2007), yet not much is known about the TP-associated risk for bleeding complications with benign disease. Infections, which are responsible for most postoperative morbidity after hysterectomy, are polymicrobial, with the majority of pelvic infections involving anaerobic bacteria (Hager 2003). Additional anaerobic coverage is recommended in antibiotic prophylaxis for colorectal surgery (Nelson et al. 2009), but the role of additional coverage against anaerobes has not been clarified for hysterectomy. Current guidelines for antibiotic and thrombosis prophylaxis for hysterectomy vary considerably.

This study evaluates the current trends in hysterectomy in Finland, incidences, and risk factors for complications, and describes results on prophylaxis for infection and venous thromboembolism, in a national setting.

REVIEW OF THE LITERATURE

History and hysterectomy methods

The hysterectomy methods introduced earlier in time are described simply by the route the surgery is performed, and the uterus removed: vaginally as in VH, or by laparotomy through the anterior abdominal wall, as in AH. A total hysterectomy means the removal of the uterus with the cervix, as distinguished from the subtotal hysterectomy, i.e. the supracervical hysterectomy, or by the name in the older literature, supravaginal uterine amputation. The total and subtotal versions of AH can be abbreviated as TAH and SAH. Classification of the laparoscopic hysterectomy (LH) has been more ambiguous: One review observed that "many authors used the term laparoscopically-assisted vaginal hysterectomy (LAVH) to represent anything from a look-see with the laparoscope before a VH, to complete removal of the uterus by laparoscopic techniques"; the surgeries in these studies were classified on a five-point scale (Meikle et al. 1997). Two classifications had been already proposed earlier (Johns and Diamonds 1994, Munro and Parker 1993). The early predecessor of the simplified current definition (Garry 1994) led to three distinguishable operations: LAVH, LH, and total laparoscopic hysterectomy (TLH). LAVH means surgery in which the laparoscopically conducted part does not involve the uterine vessels. It can include anything from the ligation of the upper ligaments of the uterus, to only adhesiolysis or salpingo-oophorectomy conducted laparoscopically prior to VH. To distinguish from any hysterectomy involving laparoscopy, the abbreviation LH(a) for LH is used by several important publications (Johnson et al. 2005, Nieboer et al. 2010). LH(a) means surgery where also the uterine vessels are ligated laparoscopically, but part of the operation is performed vaginally. TLH means surgery performed entirely laparoscopically: the freely lying uterus is removed vaginally, and the vaginal vault is closed laparoscopically (Reich and Roberts 2003). Thus TLH is not the reverse of the laparoscopic subtotal hysterectomy (LSH), in which the supracervically cut uterus is removed, while being morcellated, through the trocars penetrating the abdominal wall.

Earlier references to vaginal excision of a prolapsed uterus exist, the first ones from the 16th century. In the published history of medicine, the first laparotomy took place in the USA in 1809, the first VH was performed by Conrad Langenbeck (1776-1851) of Göttingen in 1813 (Langenbeck 1817), and the first AH by Charles Clay (1801-1893) of Manchester in 1843 (Clay 1863). Langenbeck's VH was successful, meaning the patient survived; but the first successful AH was performed not until in 1853, by Walter Burnham (1808-1883) of Lowell, Massachusetts (Baskett 2005).

In Finland, AH was the first method to be introduced: The first laparotomy, an operation on an ovarian tumor, was performed by Carl Frans Gabriel Haartman (1819-1888) of Helsinki in 1849. The first successful laparotomy was performed in 1869 by Jakob August Estlander (1831-1881), who also performed the first "laparomyomotomy", namely AH on a myomatous uterus, in the same year (Kajanoja 2008). The first VH was performed by Otto Ingemar Engström (1853-1919) of Helsinki in 1882, for the indication of cervical cancer; that operation, taking place in a private home in Helsinki, was successful (Vesterinen 2008).

Kurt Semm (1927-2003) of Kiel, a gynaecologist and pioneer of laparoscopy who in 1981 performed the first laparoscopic appendectomy, was the first to describe laparoscopy combined with VH (Semm 1984). The first LH, conducted laparoscopically until colpotomy, was performed by Harry Reich in Pennsylvania in the USA, in 1988 (Reich et al. 1989). In Scandinavia, LH was first introduced to Norway in 1991 (Langebrekke et al. 1992). In 1992, LH was introduced to Finland by Juha Mäkinen and Jari Sjöberg (Mäkinen and Sjöberg, 1994).

Hysterectomy trends

In the mid-1990s, the estimated number of hysterectomies performed annually for benign indications was over 80 000 in the UK, excluding Scotland (Maresh et al. 2002). In England between 2000 and 2005, annual numbers of AH have declined from around 37 500 to 31 000, while the same trend is seen for VH: from around 8 000 to 7 000 (Chapman and Magos, 2006). In 2000-2004 in the USA, annual numbers were over 600 000 (Whiteman et al. 2008), with no reduction since the 1990s (Farquhar and Steiner, 2002). Yet, the age-adjusted rate per 10 000 women has declined slightly in the USA since 1980, when it was as high as 71.0 (Lepine et al. 1997, Figure 1). In Canada, the corresponding rates were even higher: in 1981 at 100.4, and in 1988 at 67.4 (Allard and Rochette, 1991). In Australia, rates overall were much lower; declining from 34.8 to 31.2 between 2000 and 2005 (Hill et al. 2010). The lowest rate comes from the Netherlands in 2003-2005, 15.1 per 10 000 women (Hanstede et al 2012). Observing the NOMESCO database of Nordic countries, a comparison of Finland to others reveals a considerably higher rate (Figure 1).

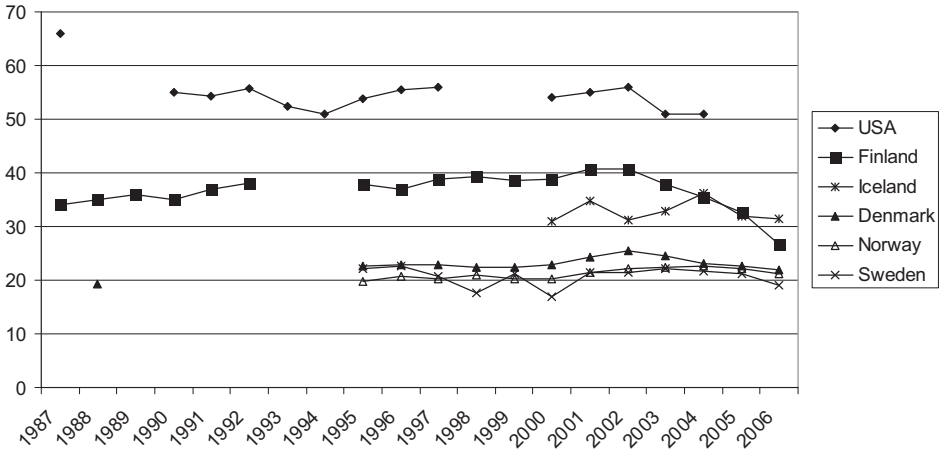

Figure 1 *Age-adjusted annual rates of hysterectomies per 10 000 women. Data from Lepine et al. 1997, Farquhar et al. 2002, Whiteman et al. 2008, Gimbel et al. 2001, Vuorma et al. 1998, and the NOMESCO database (1998-2008).*

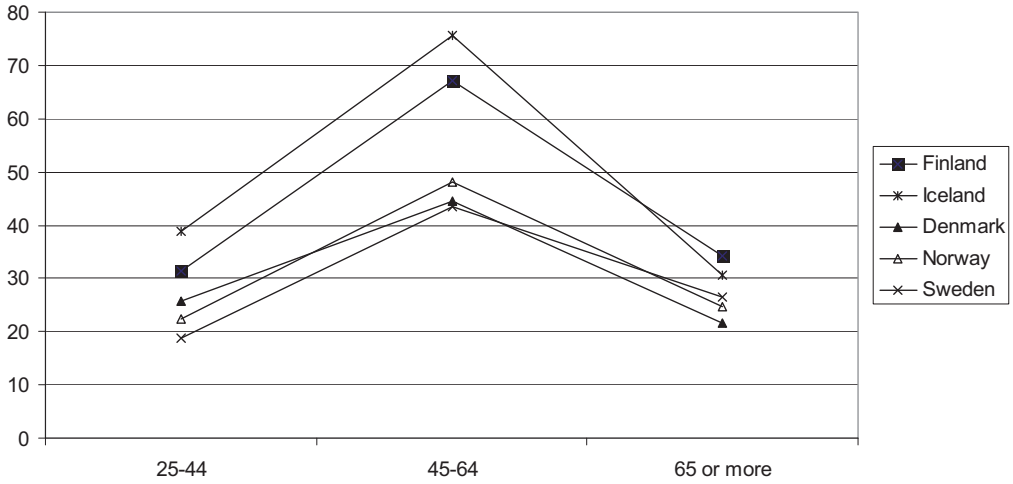

Figure 2 *Rates of hysterectomy per 10 000 women, by age group in Nordic countries in 2005. Graphics produced from data provided by NOMESCO (NOMESCO 2007).*

In Finland between 1987 and 1992, hysterectomies increased, particularly in the postmenopausal age-groups: for those older than 55, the rate had increased by 53%, whereas it simultaneously diminished by 6% in those younger than 45 – the cause suspected to be the use of hormone therapy for postmenopausal women (Vuorma et al. 1998). Hysterectomy rates in Finland are high within all age-groups: compared to the Nordic country with the lowest rate in 2005, the rate per 10 000 women in Finland was 35% higher for the age-group 45-64 (67.2 in Finland vs. 43.6 in Sweden), and 37% higher for the age-group over 65 (34.1 in Finland vs. 21.6 Denmark), (Figure 2).

Considerable regional variation was observable in Finland in 1987-1988. Surgical procedures showing the most variation were surgery for haemorrhoids, intervertebral disc protrusion, and hysterectomy (Keskimäki et al. 1994). For hysterectomy, regional variation has also occurred in the USA (Wu et al. 2003), in Denmark (Møller et al. 2002), and in England (Newton et al. 1994). In Finland, differences between areas have evidently evened out to some extent (Figure 3). Reduction did not appear everywhere: the rates in Pohjois-Karjala, Etelä-Pohjanmaa, and Etelä-Karjala remained similar, whereas in Pohjois-Pohjanmaa and Kainuu, rates increased (Figure 3).

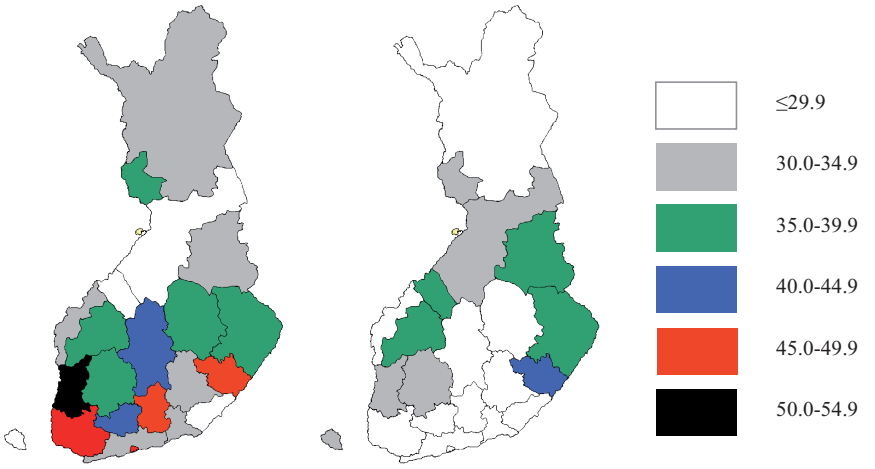

Figure 3 *Rates of hysterectomies per 10 000 women in the hospital districts of Finland in 1996 (left) and in 2006 (right). Data provided by Prof J Mäkinen, University of Turku.*

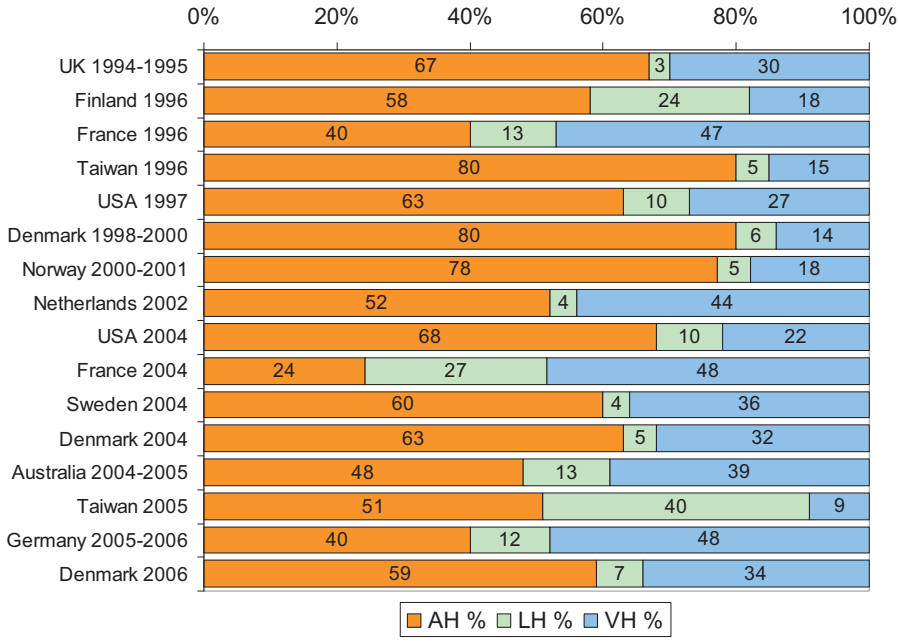

Figure 4 *Distribution of hysterectomy methods from around the world. Figures from France represent samples from university clinics only, otherwise national data are presented, apart from the UK, which excludes Wales, and represents 45% of national hysterectomies. References: UK (Maresh et al. 2002),Finland (Mäkinen et al. 2001), France (Chapron et al. 1999, David-Montefiore et al. 2007), USA (Farquhar and Steiner, 2002), Denmark (Møller et al. 2002, Hansen et al. 2008a), Norway (Oma 2004), USA (Whiteman et al. 2008), Netherlands (Kolkman et al. 2007), Sweden (Persson et al. 2009), Australia (Hill et al. 2010), Taiwan (Wu et al. 2010),Germany (Stang et al. 2011).*

In the UK, until the end of 1989, 88.1% of hysterectomies were abdominal, and VH represented only 11.9% (Vessey et al. 1992). Similarly, in Finland in 1987-1989, only 7.8% were vaginal (Luoto et al. 1994). A 5-year study (1991-1995) at a French university clinic which followed the principle of performing hysterectomy vaginally whenever possible, observed that VH was performed for 79.8%, and LAVH in 10.3% (Cosson et al. 1996). Other publications from France also seem to report wide early implementation of the vaginal approach (Figure 4). Similarly in a Vienna University clinic, of the nearly 10 000 hysterectomies performed in 1955-1985, VH accounted for 61% (Gitsh et al. 1991). The increasing popularity of VH is also evident in the Netherlands, with a proportion as high as 53% in 2003-2005. Laparoscopic approaches were rare; in fact no specific information was available on LAVH/LH, as these were not even recognised by the Dutch national register prior to 2005 (Hanstede et al 2012), but a nationwide questionnaire study in 2002 observed LAVH in 4% (Kolkman et al 2007). The Finnish area of expertise has been the early implementation of laparoscopic hysterectomy (Figure 4).

Finnish results on hysterectomy methods have influenced clinical practise: Interest in "the hysterectomy that better preserved sexual function" (Garry 2008) arose after findings published by Pentti Kilkku, who compared SAH and TAH operations as to dyspareunia, coital frequency (Kilkku 1983), libido, and orgasm (Kilkku et al. 1983). At a similar coital frequency, SAH and TAH both relieved dyspareunia, but at 12 months, dyspareunia was more frequent after TAH (Kilkku 1983). In addition, the proportion of such women, who had orgasmic coituses less than one time out of four had increased more with TAH (Kilkku et al. 1983). This is considered to be the most cited study on SAH, but criticized because of not being randomised, and not being blinded to the interviewer (Cosson et al. 1996). In addition, the results have not been confirmed by other studies (Garry 2008) – sexual function seems to improve regardless of type of hysterectomy (Roovers et al. 2003, Roussis et al. 2004).

In Scandinavia, the rate of subtotal hysterectomy is traditionally high; in Oslo it is the recommended procedure for women with no previous cervical dysplasia (Lieng et al. 2010). In Denmark between 1988 and 1998, the number of subtotal procedures increased to 4.5-fold (Gimbel et al. 2001), and the studies of Kilkku et al. are still considered to affect attitudes towards type of hysterectomy in Sweden (Persson et al. 2009). In Sweden in 2004, AH represented 60% (Figure 4), of which more than one-third were subtotal. In Finland, the trend has been the opposite: The subtotal procedure represented 23% in 1987, and 22% in 1992 of all hysterectomies (Vuorma et al. 1998), but in 1996, for benign indications only, the rate was 7.3% (Mäkinen et al. 2001). This change in trend against SAH arose after a cohort of 711 operations on symptomatic pelvic relaxation, i.e. prolapse. 87 had undergone hysterectomy earlier in life, with methods being VH for 25, TAH for 16, SAH for 46; the investigators concluded that the difference in between SAH and TAH was statistically significant (Virtanen and Mäkinen, 1993).

With LSH, over a year after surgery, bleedings continued for 24% (Lieng et al. 2010). New long-term adverse effects are also iatrogenic adenomyomas presenting 5 years after surgery; arising from unremoved morcellated tissue. The incidence in one specialised clinic was low (0.6%), but reoperations were necessary, as iatrogenic adenomyomas cause deep dyspareunia (Donnez et al. 2006).

Indications

Hysterectomy is common, because the prevalence of myomas, the cause for the majority of operations, is high: 25 to 30% of all women (Thomas 1992). In the USA, myomas were the cause for AHs in 40.2% in 1997 (Farquhar and Steiner, 2002), and for all hysterectomy types together in 40.7% in 2000-2004 (Whiteman et al. 2008). In the UK, until the end of 1989, in the age-groups 40 to 44, and 45 or older, myomas were the main indication for hysterectomy by 41.3% and 49.6%, whereas in the younger age-groups, less than 35, and 35 to 39 "menstrual problems, no fibroids found" accounted for the majority: 43.1% and 47.9% (Vessey et al. 1992). In Sweden, in a follow-up of benign hysterectomy indications in 1987-2003, the rates for dysfunctional bleeding at 13% and for endometriosis at 7% stayed stable throughout those years, but with uterine prolapse, an increase occurred from 4% in 1987-1990 to 14% in 2001-2003. Myomas were the most common indication and during the same period, declined from 56% to 42% (Lundholm et al. 2009). Similarly in Finland, myomas have predominated throughout the years (Table 1).

Table 1. *Distribution of the five most common benign indications for hysterectomy in Finland, in percentages. The one principal (discharge) diagnosis was recorded, except for the 1996 prospective evaluation in which indications overlap (= prevalence of different pathologies in a one-year-population undergoing hysterectomy for benign disease.) Bleeding disorder refers to both menorrhagia and dysfunctional uterine bleeding.*

Reference	Year of operations	Myomas	Bleeding disorder	Prolapse	Endo-metriosis	Benign ovarian tumor
Sample from the Mini-Finland health study 1980 (Luoto 1994)	1944-1979	62.8	7.8	11.9	7.8	5.0
Hospital Discharge Register (Luoto et al 1994)	1987-1989	48.0	8.0	8.1	11.1	4.2
Hospital Discharge Register (Vuorma et al. 1998)	1992	45	12	9	9	6
National Finhyst cohort (Mäkinen et al 2001, with partly unpublished data)	1996	54.9	31.1	16.8	7.1	9.5

Alternative treatments

Surgery involves a constant flow of decision-making. The first, and some may consider the most important, choice is made prior to surgery: to operate or not. An individual plan in the light of other current means of treatment modalities is essential. Alternative treatments have gained in

popularity: In 2000-2005 in England, while a steady decrease in hysterectomies occurred, simultaneously a gradual increase in open myomectomies emerged (Chapman and Magos, 2006). This could have been an indirect effect of the more recent interest in uterine artery embolisation (UAE), to which myomectomy can be a surgical alternative (Gupta et al. 2006). UAE has not yet gained popularity in the treatment of symptomatic myomas in Finland; cases have only been sporadic. In 2009, nine patients were treated at Kuopio University Hospital, which has been the only centre to study this modality in Finland (Hippeläinen et al. 2011). Interestingly, in this 2-year follow-up, of the 26 randomised to hysterectomy, 8 showed no improvement in pressure symptoms; suggesting that not all pressure symptoms originate from the uterus. In comparison, only 1 of 19 reported the same with UAE (Ruuskanen et al. 2010). UAE is a satisfactory alternative to surgery for myomas, and at 1- to 2-year follow-up, is cost-effective (Hippeläinen et al. 2011). Five-year results do not support cost-effectiveness: One study, with no upper limit on the size or number of myomas, randomised 106 patients to UAE and 51 to surgery and observed no difference in symptom score reduction, patient satisfaction, or rates of adverse effects. Nevertheless within the UAE group, 18 had undergone hysterectomy, and 8 underwent repeat embolisations; thus treatments appeared to be cost-neutral (Moss et al. 2011).

Since the mid-1990's in England, annually hysterectomies for menorrhagia have declined by nearly 65%, from over 23 000 to around 8 000 in 2002-2003 (Reid et al. 2005); simultaneously a 25% decline occurred also in the Netherlands (Hanstede et al 2012). This trend was initiated after a study from Finland of the levonorgestrel-releasing intrauterine system (LNG-IUS), a Finnish invention (Nilsson et al. 1981), cancelling in a 6-month follow-up the need for hysterectomy for 18 of 28 women (64.3%) (Lähteenmäki et al. 1998). Later, important results from a study randomly assigning 117 women to hysterectomy versus 119 to treatment with the LNG-IUS showed the LNG-IUS to be more cost-effective than hysterectomy at 12 months; at 5 years, the costs in the LNG-IUS group still were less than 40%. This occurred despite 24 (20%) from the LNG-IUS-group having eventually undergone hysterectomy at 12 months, with an additional 26 (42% in total) at the 5-year follow-up. The scores for pain were significantly less improved in the LGN-IUS group at 12 months, but the difference was non-significant at 5 years. Otherwise, the groups did not differ in terms of health-related quality of life, which improved in both groups (Hurskainen et al. 2001 and 2004). The guidelines for treatment of menorrhagia were released in Finland in 2005 (Current Care editorial office 2005, updated 2009), 2 years earlier than in the UK (NICE 2007).

As a surgical alternative treatment for heavy menstrual bleeding, one review of RCTs concludes that endometrial resection and ablation offers an alternative to hysterectomy, with a shorter recovery time and hospital stay, and fewer adverse effects at the index hospitalisation; after discharge, the only difference reported was a higher infection rate for hysterectomy. The total cost of the alternative treatments was significantly lower than for hysterectomy, but the difference narrowed over time because of the re-treatments in the endometrial destruction group (Lethaby et al. 1999, ed. 2010).

An effective treatment with minimal harm and quick recovery has also been the goal in the surgical alternative treatment of operative hysteroscopy, used in resection of endometrial polyps and submucosal myomas. This treatment modality has gained popularity in Finland: In 2005, compared to 1997, the number of operative hysteroscopies was more than 3.5-fold; the average annual increase being 17.4%. Up to 2009, however, the numbers for myomectomies, on average 246 per year, and endometrial destruction procedures on average 263 per year have stayed fairly stable (Figure 5). Similarly, the rate of myomectomies performed laparoscopically was relatively stable: on average 26%.

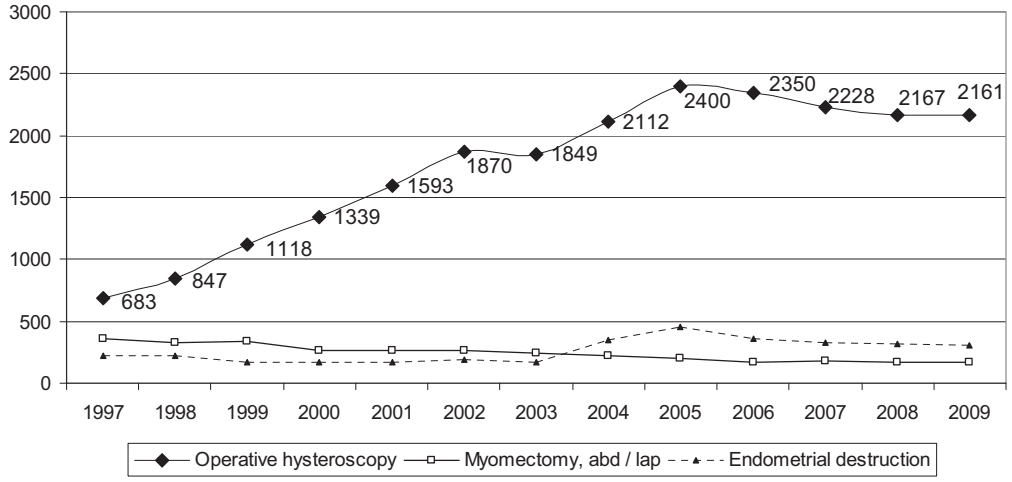

Figure 5 *Annual numbers of operative hysteroscopies (NCSP codes LCB25, LCB14, LCB98), abdominal or laparoscopic myomectomies (LCB10, LCB11), and endometrial destruction and ablation procedures (LCA16, LCB 28, LCB32) in Finland 1997-2009 (Hospital Discharge Register, unpublished data).*

Salpingo-oophorectomy

The elimination of future ovarian cancer, with a lifetime risk of 1.4%, is the main reason for prophylactic oophorectomy (ACOG 2008). Hysterectomy in itself, without oophorectomy, affects ovarian function by hastening menopausal age by an average of 4 years (Siddle et al. 1987, Farquhar et al. 2005); consequently, the risk for ovarian cancer is also reduced (Hankinson et al. 1993).

Concomitant to hysterectomy for benign disease, bilateral salpingo-oophorectomy (BSO) was performed in the UK from 1994 to 1995 on 43% of patients (Maresh et al. 2002), in Norway in 2004 on 31% (Oma 2004), in Denmark in 2006 on 16% (Hansen et al. 2008a), and in Germany in 2005-2006 on 12% (Stang et al. 2011). For any hysterectomy, the USA rates declined between 2001 and 2004 from 57% to 50% (Whiteman et al. 2008), and for benign disease only,

excluding indications with history of breast cancer, family history of cancer, or genetic susceptibility for ovarian cancer, in the USA the BSO rate in 1998-2006 was 39% (Asante et al. 2010).

As expected, removal of the postmenopausal ovaries is most frequent: with AH or LH at an age older than 50, the BSO rate was over 90% (Maresh et al. 2002). For premenopausal women, increasing age also has an effect (Jacoby et al. 2009); in the UK, particularly with LH, the BSO rates were relatively high in the age-groups 40-44 and 45-49, being 55% and 83% (Maresh et al. 2002). In Germany, however, for those aged under 50, BSO was performed on no more than 3.9%, and for those aged 50 or more, on 26% (Stang et al. 2011).

Typically, BSO is less frequently performed vaginally, however, a need for oophorectomy should not be a contraindication for VH (Davies *et al.* 1997). In the USA, of over 460 000 hysterectomies for benign disease in 2005, BSO was performed concomitant to AH on 63%, to LH on 55%, and to VH on 21% (Jacoby et al. 2009). In the UK in 1994-1995, the overall BSO rate with VH was 10% (Maresh et al. 2002). An evaluation of 710 000 VHs including over 130 000 with BSO, a comparison with hysterectomy only showed the risk for a surgical complications to be increased for those with vaginal BSO (OR 1.16); other hysterectomy types showed no adverse effects related to BSO (Asante et al. 2010). Awareness of the risk for bleeding has led to descriptions of techniques to enhance the safety of the vaginal BSO procedure (Jelen and Bachmann 1996).

Prophylactic BSO before age 45 is associated with higher overall mortality (Rocca et al. 2006, Rivera et al. 2009), but those having estrogen therapy through at least age 45 were not affected (Rivera et al. 2009). The association of higher mortality mainly from cardiovascular disease (CVD) was suggested not to be confined to premenopausal patients alone: a Markov decision analysis study suggested ovarian conservation up to age 65 (Parker et al. 2005). A risk profile in general associated with women undergoing hysterectomy may be the explanatory factor. A higher CVD risk, irrespective of oophorectomy, was observed with postmenopausal women having undergone hysterectomy due to their higher proportion of hypertension, diabetes, high cholesterol, and obesity, compared to women without hysterectomy (Howard et al. 2005). In the 1980 Mini-Finland study with its follow-up of up to previous two decades, the prevalence of CVD with hysterectomy was 18.2% with BSO, and 11.7% without BSO, whereas it was 10.8% without hysterectomy. The risk association of both hysterectomy groups adjusted for BMI, age, hormone therapy, smoking, and cholesterol levels, among other variables, however, was only close to statistical significance (Luoto et al. 1995). The controversial study of Parker et al. (2005) has not affected the current ACOG guidelines suggesting concomitant BSO for the postmenopausal, and a strong consideration for retaining the normal ovaries in such premenopausal women who are not at increased genetic risk for ovarian cancer (ACOG 2008).

Complications

Primum non nocere.

Hippocrates

Translated from Latin: "Above all, do no harm".

In Finland in 1986-1991, overall mortality rates per 1 000 procedures were 1.20 for TAHs, 1.76 for VHs, and 3.63 for radical hysterectomies (Virtanen and Mäkinen 1995), and in 1996, for any hysterectomy for benign disease, 0.30 (Mäkinen et al. 2001). Corresponding rates for the latter were 0.38 in the UK in 1993-1994 (Maresh et al. 2002, McPherson et al. 2004), 0.59 in Denmark in 1998-2000, 0.55 in Australia in 1981-2003 (Møller et al. 2002, Spilsbury et al. 2009), and 0.21 in the USA in 1999-2003 (Juillard et al. 2009). In the VALUE cohort study, of the 14 deaths occurring with 37 298 hysterectomies, three were caused by pulmonary embolisms (Maresh et al. 2002).

Increasing hospital volume, and particularly surgeon volume, reduces operative mortality during surgery for cancer (Birkmeyer et al. 2003). Analysis of over 6 000 AHs for endometrial cancer have showed that operative mortality is unaffected, yet those treated in a high-volume centre are less likely to require ICU care, and a high-volume surgeon (> 30 per year) reduced the odds for perioperative complications; although organ injuries were unaffected (Wright et al. 2011). For over 172 000 AHs for myomas, no difference emerged in mortality by hospital volume, or by academic medical centre status. Compared to non-academic community hospitals, academic centres were associated with 34% increased odds of overall morbidity and also individually for infections, transfusions, VTEs, and bladder and intestinal injuries, in a model adjusted for age, race, year, hospital volume, and patient comorbidity (Juillard et al. 2009). Perioperative complications of over 78 500 hysterectomies were higher for teaching hospitals than for urban public hospitals, but were lower both for private hospitals and for public hospitals located in rural areas (Spisbury et al. 2008). In Finland, during the first 5 years after the introduction of LH, the appearance of major complications in the Patient Insurance Centre was significantly higher for local hospitals (2.6%), than for university (0.9%) and central hospitals (1.1%) (Härkki-Siren et al. 1999).

Complications of the first 500 LHs in one single-surgeon series showed steady improvement: The overall complication rate (15.2%) declined after the first 250 LHs (to 7.2%); the same occurred with major complications (6.0% down to 2.0%) (Jones 2000). One Finnish single-surgeon series showed, for first 100 LHs, no pattern related to experience, with its few complications (10%) (Härkki-Sirén and Sjöberg 1995). Organ injuries during AH, LH, and VH were analysed by experience nationally in 1996: With experience exceeding 30 hysterectomies, compared to lower experience, bowel injuries in VH, and bladder and ureter injuries in LH were significantly fewer (Mäkinen et al. 2001). In 668 LHs, a similar outcome with perioperative complications appeared at the same threshold of 30 (Altgassen et al. 2004). Such arbitrary thresholds were abandoned in a retrospective evaluation dividing 77 109 VH patients into

equivalent numbered groups by their gynaecologists' surgical volume: low, intermediate, or high. Strikingly, 80% of gynaecologists had a low vaginal-surgery volume. For any gynaecologic surgery, low volume meant fewer than 29.5 procedures annually, whereas high volume was more than 54.4; equivalents for vaginal surgery were 5.4 and 13.0. High-volume gynaecologists reduced the odds for perioperative complications, including operative injuries, and their patients were more likely to reside in rural areas, and have surgery in non-teaching hospitals (Rogo-Gupta et al. 2010).

Analysing predisposing factors for perioperative complications overall, one study combining various hysterectomy methods in over 600 surgeries observed that the risk was more than doubled with obesity, history of pelvic surgery, and history of caesarean section (David-Montefiore et al. 2007).

Urinary tract injuries

Injuries to the urinary tract include injuries to the bladder or the ureters; rarely a vaginal fistula may result. In 1998-2000 in Canada, urinary tract injuries occurred in 515 of 70 047 hysterectomies (0.74%), and only 18% of these urinary tract injuries were discovered intraoperatively – none of the ureteral, and a third of the bladder injuries (Gilmour and Baskett 2005). In 1979-2006 in the USA, the rate for bladder injuries was 6.9 per 1000 women in TAH; corresponding rates were 10.3 for SAH, 0 for LSH, 13.8 for LAVH, 13.1 for VH; and for ureteral injuries, 1.2 for TAH, 0.6 for SAH, 0.6 for LSH, 0 for LAVH, and 0.7 for VH (Frankman et al. 2010). These data conflict with previous results particularly for the ureteral injuries with LAVH / LH (Table 2), because the large-scale evaluation by Frankman et al. (2010) included only those injuries diagnosed at the index surgery. In fact, ureteral injuries are rarely recognised intraoperatively, only in 5% to 13% of cases (Härkki-Sirén et al. 1998, Donnez et al. 2009, Daahlgard-Hove et al. 2010), but bladder injuries more often, in 58% to 100% (Härkki-Sirén et al. 1998, Cosson et al. 2001, Lafay Pillet et al. 2009). With a total of 1 850 operations in ten studies, in an important review of RCTs, LH was associated with an increased risk for urinary tract injuries compared to AH (OR 2.72, 95% CI 1.31-5.63). A comparison of ureter injuries alone, with 1 367 hysterectomies and six studies in total, did not reach statistical significance (OR 3.46, 95% 0.94-12.71) (Nieboer et al. 2010).

In Finland in 1990-1995, the mean (SD) diagnostic delay of ureteral injuries in days was similar in both LH with 22.5 (26.9), and AH with 22.1 (32.2) (Härkki-Sirén et al. 1998). In a large Taiwanese series, a mean (SD) of 19.9 (16.5) days was observed when diagnosis was done by signs and symptoms, but with intraoperative cystoscopy or early ureteral jet ultrasonography, the delay could be shortened (Wu et al. 2006). In detection of urinary tract injuries, one review analysed the effect of routine cystoscopy: all were diagnosed intraoperatively, whereas without cystoscopy, only 3%. The incidence of ureter injuries was higher with cystoscopy (5 of 289; 1.7%), than without (160 of 20 492; 0.8%), the same was observable for bladder injuries (2.9% vs. 0.6%) (Gilmour et al. 2006).

Table 2. *Review of ureter injuries in hysterectomy for benign disease.*

Study	Surgery years	AH n/N	AH %	LH n/N	LH %	VH n/N	VH %
Dicker et al. 1982	1978-1981	3/1289	0.2			0/568	0.0
Härkki-Sirén et al. 1997	1993-1994			15/1165	1.3		
Härkki-Sirén et al. 1998	1990-1995	18/43149	0.04	38/2741	1.4	1/5636	0.02
Meltomaa et al. 1999	1993-1994	1/518	0.2	0/66	0.0	0/105	0.0
Mathevet et al. 2001	1970-1996					1/3072	0.03
Cosson et al. 2001	1991-1998	0/166	0.0	1/190	0.5	0/1248	0.0
Mäkinen et al. 2001	1996	9/5875	0.2	27/2432	1.1	0/1801	0.0
Wattiez et al. 2002	1989-1995			4/695	0.6		
	1996-1999			2/952	0.2		
Carley et al. 2002	1993-1998	6/1722	0.4			0/590	0.0
Davies et al. 2002	1990-1995	0/345	0.0	0/62	0.0	0/105	0.0
Shen et al. 2003a	10 years			4/2702	0.2		
Garry et al. 2004	1996-2000	0/292	0.0	5/584	0.9		
				1/336	0.3	0/168	0.0
Vakili et al. 2005	2000-2003	6/278	2.2	0/49	0.0	2/144	1.4
Kafy et al. 2006	1997-2004	1/1349	0.1	0/223	0.0†	0/220	0.0
Wu et al. 2006	1998-2003	0/1844	0.0	15/2836	0.5	0/270	0.0
Bojahr et al. 2006				1/1706	0.1†		
Léonard et al. 2007	1993-2005			4/1300	0.3		
Morelli et al. 2007	2002-2004			5/200	2.5	0/200	0.0
Siow et al. 2007	2001-2004			1/495	0.2		
Soong et al. 2007	11 years			8/7725	0.1		
Donnez et al. 2009	1990-2006	0/409	0.0	5/1577	0.3	3/906	0.3
				3/1613	0.2†		
Lafay Pillet et al. 2009	1993-2007			5/1501	0.3		
Juillard et al. 2009	1999-2003	19/172344	0.01				
Song et al. 2011	2000-2008			1/2012	0.05		
Total		63/229580	0.3	145/33162	0.4	7/15033	0.05

† LSH

Ureter injuries have occurred in 80% of cases at the level of the cardinal ligaments (Dahlgaard Hove et al. 2010). Surgical difficulties such as heavy bleeding, enlarged uterus, or endometriosis have been observed in two-thirds of cases occurring with AH, and in half occurring with LH; in LH the difficulty usually was heavy bleeding, and the cause thermal injury (Härkki-Sirén et al. 1998). In performing a hysterectomy, the ureters should be identified, and the uterine vessels found at the level of the internal cervical os skeletonized from the broad ligament and ligated as they ascend the sides of the uterus – while the uterus is being pulled, as in AH, or pushed, as in LH, to the opposite side (Jones 2003, Reich 2007). A meta-analysis of 3 112 LAVH/LH operations and 34 studies in 1989-1995 showed relatively low incidences for ureter injuries (0.3%), while the majority (24) of these studies involved ligation of the uterine vessels laparoscopically (Meikle et al. 1997). During the corresponding period in Finland, the incidence was considerably higher (Table 2). The experience of the gynaecologist exceeding 30

hysterectomies, compared to lower experience, resulted in significantly fewer ureter (0.5% vs. 2.2%) and bladder (0.8% vs 2.0%) injuries in LH (Mäkinen et al. 2001).

In complex pelvic surgery, such as hysterectomy for endometriosis, prophylactic indwelling stents can serve to locate the ureters. Lighted stents were used in 151 difficult pelvic operations, with no injuries occurring; in addition, unsuccessful placement due to previously undiagnosed ureteral pathology occurred in 6, thus saving litigation costs. It seems that fenestrated ultra-red catheters allowing passage of urine are preferable (Redan and Mc Carus 2009). The average time required for stenting is 5 to 9 minutes (Redan and Mc Carus 2009, Tanaka et al. 2008), but a decision-tree analysis for cost-effectiveness involving AH showed routine stenting as cost-saving, if the rate of injury exceeds 3.2% (Schimpf et al. 2008).

Bladder injuries occurred of 172 344 AHs in 1 239 (0.7%), of 2 273 LHs in 39 (1.8%), and of 3 067 VHs in 52 (1.7%) (Juillard et al. 2009, Meikle et al. 1997, Mathevet et al. 2001). The incidence in Finland has varied among retrospective and prospective studies: Corresponding figures for AH were 0.1% and 0.5%, for LH 0.9% and 1.3%, and for VH 0.02% and 0.2% (Härkki-Sirén et al. 1997 and 1998, Mäkinen et al. 2001). Rarely may a bladder injury appear late-onset as a vesicovaginal fistula (VVF); many studies do not give rates for this more difficult complication separately. VVF has appeared after LH in 0.4% (Lafay-Pillet et al. 2007), and after VH in 0.1% (Mathevet et al. 2000); in a Finnish series after LH in 0.2%, after TAH in 0.1%, and after VH in 0.02% (Härkki-Sirén et al. 1998).

A history of caesarean section (CS) was associated with risk for bladder injury in VH (Mathevet et al. 2001, Boukerrou et al. 2003 and 2004, Neumann et al. 2004) and in LAVH (Soong et al. 2007, Lafay Pillet et al. 2009). With all hysterectomies analysed together, a 2- to 4-fold risk emerged (Rooney et al. 2005, David-Montefiore et al. 2007). Rooney et al. (2005) concluded that the risk increased by hysterectomy type, in AH by OR 1.3, in VH by OR 3.0, and in LAVH by OR 7.5.

Gastrointestinal injuries

Gastrointestinal injuries are severe and – particularly if not recognized at index surgery – potentially fatal complications, leading to reoperations with often a need for a colostomy. Occurring with hysterectomy, the injury may also lead to fistulas, with consequently vaginal excretion of faeces. With VH, those operated on for uterine prolapse more frequently had bowel injuries, which were mainly rectal (Mathevet et al. 2001), whereas with LH, half appeared as lesions of the small intestines (Shen et al. 2003b). The diagnosis of injuries caused by electrocoagulation is usually delayed, with a mean (range) 4.8 (1-10) days (Härkki-Sirén and Kurki 1997). The delay may cause a potentially fatal peritonitis; in that sense injuries occurring with LH can be more severe. A review of laparoscopy-induced bowel injuries reported a mortality of 3.6% (Van der Voort et al. 2004). In a meta-analysis of 3 112 LAVH/LH operations, bowel injuries occurred to 0.4% (Meikle et al. 1997). Incidences from individual studies are presented in Table 3.

Table 3. *Review of intestinal injuries in hysterectomy for benign disease.*

Study	Surgery years	AH n/N	AH %	LH n/N	LH %	VH n/N	VH %
Dicker et al. 1982	1978-1981	4/1283	0.3			3/568	0.5
Kovac 1995				0/63	0.0	3/548	0.5
Härkki-Sirén et al. 1997	1993-1994			5/1165	0.4		
Meltomaa et al. 1999	1993-1994	2/518	0.4	0/66	0.0	0/105	0.0
Hoffman et al. 1999	1987-1998					9/1163	0.8
Mathevet et al. 2001	1970-1996					16/3072	0.5
Cosson et al. 2001	1991-1998	4/166	2.4	2/190	1.1	3/1248	0.3
Mäkinen et al. 2001	1996	12/5875	0.2	9/2432	0.4	9/1801	0.5
Wattiez et al. 2002	1989-1995			1/695	0.1		
	1996-1999			0/952	0.0		
Shen et al. 2003a	10 years			11/2702	0.4		
Garry et al. 2004	1996-2000	3/292	1.0	1/584	0.2		
				0/336	0.0	0/168	0.0
Kafy et al. 2006	1997-2004	4/1349	0.3	1/223	0.4†	0/220	0.0
David-Montefiore 2007	2004	0/155	0.0	0/52	0.0	2/306	0.7
Morelli et al. 2007	2002-2004			1/200	0.5	0/200	0.0
Donnez et al. 2009*	1990-2006	2/409	0.5	1/1577	0.1	0/906	0.0
				2/1613	0.1†		
Juillard et al. 2009	1999-2003	583/172344	0.3				
Song et al 2011	2000-2008			9/2012	0.5		
Total		614/182391	0.3	43/14862	0.3	45/10305	0.4

*Donnez et al. 2009 report injuries resulting in colostomy only.
† LSH

In the Finnish national hysterectomy cohort in 1996, the experience of the gynaecologists exceeding 30, compared to less experience, resulted in significantly fewer bowel injuries in VH (0.3% vs. 1.3%) (Mäkinen et al. 2001). In 1990-1996, retrospective analyses of 68 bowel injuries in 102 812 gynaecological laparoscopies in Finland found intraoperative detection to be rare, in 18%. A trocar or Veress puncture caused 44%, whereas electrocoagulation caused 49% (Härkki-Sirén and Kurki 1997, Härkki-Sirén et al. 1999). A prospective LH survey in 1993-1994 showed all five injuries (0.4%) to be caused by electrocoagulation, and the diagnosis was intraoperative only once (Härkki-Sirén et al. 1997). A review of 430 bowel injuries in around 330 000 laparoscopies, of which 41% were gynaecological, observed trocar or Veress punctures as being the cause in 42%, and thermal injuries in 26%; as many as 62% of these injuries were detected intraoperatively (van der Voort et al. 2004). Adhesiolysis elevates the risk for bowel injury (van Goor 2007). Van der Voort et al. (2004) observed adhesions or a previous laparotomy in 69% of injury cases. One 7-year follow-up of 3 613 laparoscopic surgeries observed 21 patients with inadvertent enterotomies, of which 19 presented with a history of abdominal surgery – a trocar caused 3 injuries, and adhesiolysis, 18 (Binenbaum and Goldfarb, 2006).

Vascular injuries

Injuries of the major vessels – the aorta, the vena cava or the iliac vessels – are intraoperative haemorrhagic catastrophes needing immediate reconstructive vascular surgery. Occurring with hysterectomy for benign disease, they are virtually limited to LH. The incidence is low (0.01-0.04%), but for 71 cases in total, mortality was relatively high: 15% (Champault et al. 1996, Chapron et al. 2000). Most injuries are entry-related (Table 4); one series of 47 trocar injuries observed the first trocar as the cause of 39 (Champault et al. 1996). The iliac vessels are the injury site in 63% to 82% (Härkki-Sirén and Kurki 1997, Härkki-Sirén et al. 1999, Fruhwirth et al. 1997, Chapron et al. 2000), and within cases defined to either side, in 15 of 19, the injury occurred on the right side (Fruhwirth et al. 1997, Chapron et al. 2000). Severe entry-related vascular injuries may also involve the inferior mesenteric or the inferior epigastric arteries (Chapron et al. 2000, Härkki- Sirén 1999).

Table 4. *Moment of the major vascular injury, in gynaecologic laparoscopy.*

Study	Veress needle	Trocar	Operative phase
Chapron et al. 2000	4	15	5
Fruhwirth et al. 1997	2	5	2
Härkki-Sirén 1999	1	5*	5
Total	7 (16%)	25 (57%)	12 (27%)

*includes a case of perforation of the iliac artery with a scalpel during umbilical incision

Bleeding complications

In a Finnish study of major gynaecological surgery, postoperative haemorrhage was the most common reason for ICU care, occurring in 2.3 per 1000 (Heinonen et al. 2002). Bleeding complications are traditionally categorised by their appearance as (intra)operative or postoperative (Harris 1995). Operative bleeding complications can be defined as haemorrhage exceeding 500 ml (Rasmussen et al. 2004, Heinberg et al. 2004, Chopin et al. 2009) or 1000 ml (Hansen et al. 2008b), sometimes, just as clinically relevant haemorrhage without any arbitrary limits (David-Montefiore et al. 2007). If need for a transfusion is considered a complication, its timing, during or after surgery, is rarely defined in the literature. In the CREST study with 1 283 AHs, transfusions during surgery were administered to as many as 10%, and another 5.4% received a transfusion postoperatively. Respective rates for the 568 VHs were considerably lower, 4.9% and 3.4% (Dicker et al. 1982). The eVALuate study avoided assessing bleeding complications as intra- or postoperative, but instead described haemorrhage as major when a transfusion was required, and minor if not; in addition a haematoma was major only if it required a transfusion or drainage. A major haemorrhage occurred in AH for 2.4%, in LH for 4.6%, and in VH for 2.9%. Major haematomas occurred in around 1% of all hysterectomy types;

minor haematomas were more frequent, at around 4% with LH, and 6% with other hysterectomies (Garry et al. 2004). The Finnish national cohort in 1996 defined haemorrhage by location: wound, intra-abdominal, vaginal, or other (Mäkinen et al. 2001). Some studies record postoperative bleedings only when they require return to the operating room (Dicker et al. 1982). As the definitions vary considerably, direct comparisons are difficult.

A review of RCTs of various methods of hysterectomy concluded that blood loss and drop in haemoglobin were higher for AH than for LH, whereas no significant difference occurred in substantial bleeding or transfusions. For LH compared to VH, the odds for substantial bleeding and transfusion were more than double, but in appearance of pelvic haematomas, no differences occurred for either comparison (Nieboer et al. 2010).

Blood coagulation capacity undergoes changes as plasma concentrations of several blood coagulation factors in healthy individuals increase with age (Hamilton et al. 1974, Hager et al. 1989, Mari et al. 1995 and 2008, Luxembourg et al. 2009). The pathophysiological significance of modest changes may be uncertain, yet thrombosis associating with older age is well known (Heit et al. 2001, Pineo and Hull 2005, Geerts et al. 2008). The clinical manifestation of bleeding complications as being reduced with age was obvious in a comparison of 336 women aged under 36, with 588 women aged over 60, all undergoing VH. Differences between the young and the old in postoperative bleeding were 7.7% vs. 2.7%, for transfusions, 9.8% vs. 4.4%, for haematomas, 5.4% vs. 2.0%, and for unexplained fever, 6.5% vs. 2.2%. Retrospective statistical analysis (χ^2; conducted by the thesis author) revealed all these differences to be significant ($p<0.01$) (Pratt and Galloway 1965). A more recent study of over 37 000 hysterectomies observed the odds for severe operative complications continuously decreasing with age; the trend was evident also just for haemorrhage and visceral damage (McPherson et al. 2004). One 78 000-hysterectomy evaluation revealed a trend towards increased odds for haemorrhage in women aged less than 60, and the younger were also more likely to be readmitted due to haemorrhage (Spilsbury et al. 2008).

Obesity compared to normal weight has been associated with bleeding of 500 ml or more in LH (Heinberg et al. 2004). In another LH study, the absolute risk difference for haemorrhage of 500 ml or more was over three-fold for the obese, but with an adjusted logistic regression analysis the risk did not persist (Chopin et al. 2009). In 444 VH and 503 AH operations, bleeding of 500 ml or more occurred in 2.9% and 13.7%; in respect to those obese, in 8% and 18%; differences by BMI group were significant for VH only (Rasmussen et al. 2004). Analysing the postoperative complications, Rasmussen et al. (2004) were surprised to find in AH the incidence for a wound haematoma as significantly higher for those of normal weight (7%), and cases were sporadic for those overweight, with only a single case appearing in the 101 who were obese.

Bleeding complications in the context of thrombosis prophylaxis are assigned separately.

Venous thromboembolism

Rudolph Virschow (1854) described the contributing triad for thrombosis more than 150 years ago: increase in blood coagulability, venous stasis, and trauma to the vessel wall. When spontaneous or therapeutic lysis of a lower extremity thrombus fails to persist, embolism of single or multiple thrombi may travel into the pulmonary venous system. Venous thromboembolic events (VTE) are a single disorder: In patients diagnosed with deep venous thrombosis (DVT), asymptomatic pulmonary embolisms (PE) were radiologically detectable in nearly 40% (Moser et al. 2004). About 15% of PEs are fatal (Kearon 2003).

Table 5. *Review of deep venous thrombosis (DVT) with benign disease after major gynaecologic surgery, in patients not given thrombosis prophylaxis (TP). The data represents incidence of asymptomatic disease, diagnosed by routine postoperative daily ^{125}I-labelled fibrinogen scanning. Only in the studies by Bonnar et al., Walsh et al., and Clarke-Pearson et al was the exact localisation of the DVT verified with phlebography.*

Study	TP not given n	DVT n	%
Bonnar et al. 1972	140	15	10.7
Ballard et al. 1973	55	16	29.1
Walsh et al. 1974	217	21	9.7
Taberner et al. 1978	44	9	20.5
Turner et al. 1984	92	4	4.3
Clarke-Pearson et al. 1987	64	4	6.3
Total	612	69	11.3

In major gynaecological surgery, among 945 untreated controls in 12 trials, DVT incidence without TP was on average 16% (Geerts et al. 2001). As VTE associates with malignancy, in hysterectomy for benign disease only, incidence is lower (11%, Table 5). Only one of the studies in Table 5 analysed presence of DVT by type of hysterectomy, and observed 7% in 100 VHs, and 12% in 117 AHs (Walsh et al. 1974). These series, representing results of routine screening, ran several decades ago; current practise encourages a faster mobilisation of the patient. A register study of 13 000 cases in over 1.6 million operations in 1992-1996 revealed an overall incidence of symptomatic VTE of 0.8%; with AH, 0.3% for benign, and 1.2% for malignant disease (White et al. 2003). The frequency of TP for gynaecology went unstated, but presumably was lower than the 45% to 50% that these researchers estimated for orthopaedics. Importantly, VTEs were mostly diagnosed after discharge (56%), and occurrence as PE was high, both in those diagnosed during hospitalisation (37%), and after discharge (39%). With hysterectomy for benign disease, PEs have accounted for most VTEs: Multicentre studies observed in 1 346 surgeries 7 VTEs (0.5%), of which 5 were PEs (Garry et al. 2004), and in

9 949 hysterectomies 10 VTEs (0.1%) of which 7 were PEs (Hansen et al. 2008b); TP coverage for the first study was unknown, and for the latter 100%. Finnish prospective studies showed low VTE incidences: 0.1% and 0.2%, with 1% and 35% receiving TP (Meltomaa et al. 1999, Mäkinen et al. 2001).

Laparoscopic surgery in itself aroused suspicions, as the lower limb venous return is reduced by the pneumoperitoneum and the reverse Trendelenburg position (Jorgensen et al. 1994, Sobolewski et al. 1995, Wilson et al. 1994). It seems the risk for thrombosis due to the pneumoperitoneum itself is theoretical, with no clinical effect (Lord et al. 1998, Wazz et al. 2000). In laparoscopic surgery, symptomatic VTE is observable in 0.2% (White et al. 2003), and in most prospective reports covering various types of TP, VTE after laparoscopy is a rare event, even in routine screening (0-2%) (Geerts et al. 2008). Only a single small placebo-controlled study on TP in laparoscopic surgery exists: Among the 25 placebo-receiving cholecystectomy (LCC) patients, no VTE arose (Bounameaux et al. 1997). A larger survey on 587 LCCs reported no symptomatic VTEs, with TP given to 3% only (Blake et al. 2001). In contrast to upper abdominal surgery, in gynaecology the position of the patient should be favourable for the venous return; the Trendelenburg position somewhat counteracts the dampening effect of the pneumoperitoneum (Rosen et al. 2000). In gynaecology, an earlier evaluation of 50 247 laparoscopies reported an incidence for both symptomatic DVT and PE of only 0.02% (Chamberlain 1980), and a more recent prospective study with ultrasonography routine screening, reported no DVTs in 266 without TP (Ageno et al. 2007). Hysterectomy, in contrast to minor laparoscopy, is more time-consuming, and involves more bleeding, and theoretically more an efficient coagulation response. In Finland, with 1 165 LHs in 1993-1994, one DVT occurred with a 15% TP coverage (Härkki-Sirén et al. 1997). With a 22% coverage in 1996, 7 (0.3%) VTEs occurred among the 2 434 LHs; only two of them had received TP (previously unpublished data), and one LH patient died of a massive PE (Mäkinen et al. 2001, Härkki et al. 2001). A register-based study of over 60 000 LHs in 2003-2007 in the USA, with the majority for benign disease (96.2%), observed PEs rarely (0.07%). The incidence of DVTs, however, was relatively high (0.9%), increasing later in the study period. Pharmaceutical TP had been given to only 11.9% (Ritch et al. 2011).

Risk factors

Epidemiologic studies have showed that VTEs follow the initial theories of Virschow. Iatrogenic or accidental tissue damage activates coagulation: Both surgery and trauma are important risk factors, enhanced by immobilisation (Heit et al. 2001, Geerts et al. 2008). The importance of muscular work and tonus is demonstrated in patients with acute spinal cord injury: without TP, clinical VTE occurs in nearly half, and asymptomatic disease is detected in over 80% (Furlan and Fehlings 2007). In surgery, general anaesthesia, with its drug-induced relaxation, poses a higher risk than does regional anaesthesia (NICE 2010).

A Million Women Study linkage with National Health Service data showed a lower risk for VTE to emerge in day-case surgery: Compared with not having surgery, women aged 50 or

more were almost seventy times more likely to be readmitted with a VTE after inpatient surgery, whereas the risk was only ten-fold after day-case surgery. Importantly, the VTE risk peaked at the third postoperative week, and remained increased for up to 12 weeks (Sweetland et al. 2009). Reviews state that the risk is higher for orthopaedic and malignant disease surgery (Geerts et al. 2008). Sweetland et al. (2009) concluded also that the VTE risk at 6 weeks postoperatively for inpatient surgery was greatest for hip or knee replacements (RR 221) and surgery for cancer (RR 92), but lower for gastrointestinal surgery (RR 56); in fact, gynaecological surgery had the lowest risk (RR 23).

It is of particular importance to recognise those at risk for VTE, because unlike antibiotic prophylaxis, TP is determined by risk. The characteristics of such patients are widely described in the literature. The central risk factors are previous VTE and coagulopathy, inherited or acquired, along with cancer. Obesity (Geerts et al. 2008), and older age also induce thrombosis (Heit et al. 2001, Pineo and Hull 2005, Geerts et al. 2008). Varicose veins or varicose ulcers are possible indicators of DVTs not previously detected (Koch et al. 2001). Smoking poses a risk, particularly high with concomitant use of oral contraceptives (OC) (Pomp et al. 2008), which is an eminent risk factor (RCGP 1978, Farmer 2000). The effect of estrogen is also observed in thrombosis associating with pregnancy and the postpartum period (James et al. 2006, Marik and Plante 2008), and with hormone therapy (HT) (Cushman et al. 2004). Most coagulation factors arise from the liver, and thus patients with liver disease are at reduced risk for VTE (Heit et al. 2000). Transdermally administered estrogens, minimizing the hepatic induction of clotting factors, diminish VTE risk compared to the effect of oral estrogens (L'Hermite et al. 2008).

Thrombosis prophylaxis

Avoidance of PE, and of death induced by PE, are the main targets of prophylaxis.

Mechanical compression of the leg and its veins, by intermittent pneumatic compression devices (IPC) or simply by graduated compression stockings (GCS) is effective (Geerts et al. 2008). A meta-analysis found a 50% reduction in DVT formation with GCS alone, and efficacy was increased when combined with another TP method (Sachdeva 2010). Within the high-risk group of gynaecological oncology, for DVT prevention, IPC and pharmacological TP are of similar value (Clarke-Pearson et al. 1993, Maxwell et al. 2001), but these randomised trials have been criticised for lacking power analysis (Einstein et al. 2007). In fact, with IPC, PE occurred in 4.1% (Martino et al. 2006); a considerably higher figure than the VTE incidence of 1.2% observed for AH for cancer in a large epidemiologic study (White et al. 2003).

Heparin is nowadays called unfractionated heparin (UFH), to distinguish it from heparin fragments such as enoxaparin and dalteparin (Rang et al. 2007). Pharmacokinetic benefits of low-molecular fractionated heparin (LMWH) in comparison with UFH are renal excretion, better bioavailability, and a longer elimination half-life. Thus LMWH is superior from a practical point of view: Dosing is less frequent, dose-adjustment blood tests are unnecessary, and LMWH can be self-injected (Lassila and Leinonen 2001, Rang et al. 2007).

The landmark study on heparin TP appeared almost four decades ago. This international prospective randomised multicentre trial of over 4 000 patients resulted in a significant reduction in routinely scanned DVTs with UFH (7.7%) versus no treatment (24.6%); PEs and deaths from PEs were also significantly fewer (Kakkar et al. 1975). Evidence of UFH efficacy versus no treatment, and the equal efficacy of UFH and LMWH in prevention of VTE is apparent in numerous meta-analyses (Geerts et al. 2008), and also individually for general (Mismetti et al. 2001), colorectal (Wille-Jørgensen et al. 2003) and gynaecological surgery (Oates-Whitehead et al. 2003). For benign gynaecological disease, UFH versus no treatment reduced the incidence of routinely scanned DVT from 29-20% to 3.6-6% (Ballard et al. 1973, Taberner et al. 1975). Pooling the rates of fatal PE in prospective studies of over 7 000 gynaecologic surgeries, including malignancies, use of TP shows a 75% risk reduction (from 0.4% to 0.1%) (Geerts et al. 2001), and the clinical PE risk reduction was identical for general surgery (Mismetti et al. 2001). Preventive efforts reduce, but do not fully eradicate, this pathology: In 4 000 surgeries with 46 VTEs, most (87%) occurred with TP (Mosen et al. 2004), and in a large evaluation of PEs, of those who underwent surgery, half had received TP (Goldhaber et al. 1999).

TP is clearly a reasonable use of health care resources, even for patients with a relatively short life expectancy, such as seen in gynaecological oncology (Maxwell et al. 2000), for which the effective UFH dose is 5 000 IU three times a day; twice daily being insufficient (Clarke-Pearson et al. 1990, 1983). High- versus low-dose LMWH was the comparison in a RCT of over 1 700 abdominal surgeries, with a third involving benign disease. With dalteparin 5 000 IU versus 2 500 IU, routinely scanned DVTs were significantly fewer (6.8% vs.13.1%); the same appeared for malignant disease only (8.5% vs 14.9%). Unfortunately, for benign disease no separate results were available (Bergqvist et al. 1995). With low-dose daily enoxaparin (20 mg) in over 9 900 surgeries, of which 16% were for malignancies, and a fifth gynaecological, low rates of PE and DVT occurred (0.2% and 0.1%) (Haas and Flosbach 1994). Regrettably, this low-dose study had a follow-up covering the first postoperative week only. Therefore, in the light of the current VTE evidence stating that the majority occur after discharge (White et al. 2003, Sweetland et al. 2009), such results must be greatly underestimated.

Usually initiation of TP has been preoperative, for instance, in 55 of 59 studies reviewed for general surgery (Mismetti et al. 2001), and in all 11 reviewed for gynaecological oncology (Einstein et al. 2007). Comparisons concerning the efficacy of postoperative initiation are currently lacking for gynaecological surgery. For orthopaedic surgery, however, one review concludes that early postoperative initiation of LMWH, compared to preoperative, did not reduce antithrombotic efficacy (Raskob and Hirsh 2003).

The vast majority of studies apply a 7-day-duration of TP (Mismetti et al. 2001, Einstein et al. 2007); RCTs for a shorter duration are lacking. A 3-day TP was used in a Finnish study with 100 AH operations, of which 88 were for benign disease, with no clinical VTEs observed (Kaaja et al. 1992). An observation of 3-day vs 12-day TP comes from bariatric surgery: All clinical VTEs occurred in the 3-day group (6/132 vs. 0/159, p=0.006). The 3-day group, however, included 11 laparotomies, whereas otherwise the study involved laparoscopy only. The

investigators of these morbidly obese patients concluded that the main risk factor for VTE was conversion (Raftopoulos et al. 2008).

Extended prophylaxis for up to a month improved efficacy, according to a review of four RCTs conserning major abdominal or pelvic surgery. Two studies involved malignancy only; and for the remaining two, 60% to 69% of cases involded cancer. With routine venography or objective verification of symptomatic disease, VTE occurred in 14.3% with LMWH given for a week, versus in 6.1% with LMWH for up to a month (Rasmussen et al. 2009).

Complications related to thrombosis prophylaxis

In over 9 000 general surgeries with enoxaparin 20 mg daily, haematomas or excessive bleedings occurred in 12.4% (Haas and Flosbach, 1994). Both UFH and LMWH associate with bleeding complications, and in a comparison of the two in abdominal or pelvic surgery, the risk seems to be equal (Heilmann et al. 1989, Steiner et al. 1989, Borstad et al. 1992, Bergqvist et al. 1997, Baykal et al. 2001, Mismetti et al. 2001), or in favour of LMWH (Kakkar et al. 1993). LMWH, versus placebo or no treatment, more than doubled the risk for total and major haemorrhagic complications in a large meta-analysis on general surgery, and the risk for wound haematomas and transfusions also increased (Mismetti et al. 2001). In gynaecologic oncology, however, a recent meta-analysis observed no increased risk for bleeding complications with pharmaceutical TP (Einstein et al 2007), even with daily high-dose LMWH no increase occurred versus IPC (Maxwell et al. 2001). In a meta-analysis of RCTs involving abdominal and pelvic surgery mostly for cancer, no significant difference appeared in hemorrhagic events with prolonged one-month LMWH compared to one-week use, 4.1% vs. 3.7% (Rasmussen et al. 2009).

It seems that risk for bleeding is affected by risk for thrombosis: High-dose dalteparin compared with low-dose, given on the evening before the operation, elevated the risk for bleeding in particular for those without a single risk factor for thrombosis (Flordal et al. 1996). Another study observed the risk for bleeding with high-dose compared to low-dose as 5-fold (5.0% vs. 0.9%), while with malignant disease the difference was non-significant (4.6% vs 3.6%) (Bergqvist et al.1995). Moreover, in two studies of gynaecologic surgery only, bleeding with LMWH seemed to be dose-dependent: Daily high-dose dalteparin, but not low-dose dalteparin led to increased haematomas and transfusions in comparisons to the same UFH dose; only 6% to 7% were undergoing surgery for cancer (Borstad et al. 1988, 1992).

A meta-analysis concerning the timing of TP in orthopaedic surgery concluded that initiation within 2 h of surgery associated with increased major bleeding, but at 6 h postoperatively did not (Raskob and Hirsh 2003). Evaluation of over 9 000 hysterectomies for benign disease observed postoperative bleeding with TP in 7%, and that when both operative and postoperative bleeding complications were analysed together, postoperative initiation was safer than preoperative. Type or dose of heparin was unknown (Hansen et al. 2008b).

Use of LMWH in patients with epidural or spinal regional anaesthesia has resulted in neuraxial haematomas resulting in long-term permanent paralysis (FDA 1997). Prior to a neuraxial blockade, LMWH should be discontinued for at least 18 hours after once daily high-dose, and for 8-12 hours after twice daily low-dose; catheters should be removed during the minimum level of the anticoagulant effect, just before the next scheduled dose (Geerts et al. 2008).

Heparin-induced thrombocytopenia (HIT) is less frequent with LMWH than with UFH, but is gaining in importance due to the current evidence in favour of extended prophylaxis (Rasmussen et al. 2009). HIT appears within 2 weeks of treatment (Prandoni et al. 2005). The risk factors are female sex and prophylaxis for surgical patients compared to medical patients (Warkentin et al. 2006). The immunologic pathophysiology involves injury to the vascular endothelium, subsequently inducing thrombosis and stroke (Warkenin et al. 2008, Koskinen et al. 2010). For over 1 700 LMWH users, the rate was 0.8%, but as high as 1.7% for those exposed to LMWH or UFH earlier in life (Prandoni et al. 2005). Diagnosis is established with a platelet drop of at least 50%, and the presence of heparin-dependent IgG antibodies; LMWH should be discontinued and a haematologist consulted (Warketin et al. 2008, Koskinen et al. 2010).

Prophylaxis guidelines

The task for the gynaecologist is to identify those at risk. Patient database-linked computerized alerts are effective reminders (Mosen et al. 2004), and can even reduce VTEs in high-risk patients (Kucher et al. 2005). Relying on conventional methods, TP can either be individually prescribed, or simplifications attempted, based on guidelines. The American College of Chest Physicians (ACCP) has a nearly 20-year history of such thorough reviews (Clagett et al. 1995). The American College of Obstetricians and Gynaecologists 2007 guidelines (ACOG 2007) seem to be a modification of the 7th edition of the ACCP guidelines (Geerts et al. 2004), with an additional arbitrary cut-off for the duration of surgery (Table 6). Considering ACOG recommendations for those in moderate risk for VTE, doses of dalteparin and enoxaparin seem not to be equivalent (Table 6). The 8th edition of the ACCP guidelines (Geerts et al. 2008) abandoned all arbitrary limits (Table 6) earlier applied in respect to age. Routine TP is recommended with all major gynaecologic surgery, referred to as open surgery (Table 6). LMWH dosage outlines are broad: Initiation is unguided, dose is referred to as “at recommended doses”, and duration is “until discharge”. Specifically, duration is dealt with cancer surgery or those with previous VTE (Geerts et al. 2008).

The National Institute for Health and Clinical Excellence (NICE) guidelines omit from their routine consideration of TP only procedures with local infiltration anaesthesia. Importantly, these UK guidelines also cover day-case surgery. To reduce risk for VTE, regional, instead of general anaesthesia should be chosen when possible. In addition, these guidelines are simplified, without any risk categories, and the recommendations for gynaecological, gastrointestinal, thoracic, and urological surgery are identical: Routine TP for those at increased risk only (Table 6), but guidance on initiation and dose for LMWH are lacking. NICE also recommends that all

patients should be advised to consider stopping estrogen containing OC, or HT, 4 weeks before surgery (NICE 2010).

Table 6. *Examples of prophylactic strategies for VTE prevention in gynaecological surgery (ACCP specifically for laparoscopy, see text.).*

Risk category	Definition of risk			Prophylaxis recommendation		
	ACOG 2007	ACCP 2008	NICE 2010	ACOG 2007	ACCP 2008	NICE 2010
Low	Duration < 30 min and age < 40, with no ARF	Minor surgery in mobile patients	No specific risk categories. Increased risk includes: Cancer Age over 60 Dehydration Thrombophilia BMI over 30 Significant medical comorbidity † VTE history or with a first-degree relative HT or OC use Varicose veins with phlebitis Pregnancy and postpartum 6 weeks ‡	No, but early and "aggressive" mobilization	No, but early and "aggressive" mobilization	Mechanical prophylaxis begun at admission, LMWH / UFH added for patients at a low risk for major bleeding, taking into account individual factors and according to clinical judgement. ‡ Consider to always combine LMWH / UFH. UFH preferable with renal failure Duration: until mobility no longer reduced, generally for 5-7 days. Major cancer of the abdomen or pelvis: one month.
Moderate	Duration < 30 min with ARF Duration < 30 min and age 40-60, with no ARF Major surgery with age < 40, with no ARF	Most general, open gynaecologic or urologic surgery patients		UFH 5000 IU x2, LMWH (dalteparin 2500 IU or enoxaparine 40 mg), GCS or IPC.	LMWH (at recommended doses), UFH x2 or x3, fondaparinoux*	
High	Duration < 30 min with age > 60 or with ARF Major surgery and age > 40 or with ARF	Hip or knee arthroplasty, hip-fracture surgery, major trauma, spinal-cord injury		UFH 5000 IU x3, LMWH (dalteparin 5000 IU or enoxaparine 40 mg), or IPC.	LMWH (at recommended doses), fondaparinoux, oral vitamin K antagonist*	
Highest	Major surgery with age > 60 and prior VTE, cancer, or coagulopathy			Consider continuing prophylaxis for 2-4 weeks after discharge	Cancer surgery or previous VTE: consider duration up to a month for selected high-risk patients	

* IPC (intermittent pneumatic calf compression) and / or GCS (graduated compression stockings) with high risk for bleeding, but consider switching to anticoagulant thrombosis prophylaxis when high bleeding risk decreases.
† For example heart disease; metabolic, endocrine, or respiratory pathologies; acute infectious diseases; inflammatory conditions.

ARF, additional risk factors; HT, hormone therapy; OC, oral contraceptives; UFH, unfractionated heparin; LMWH, low-molecular fractionated heparin

Importantly, ACOG and NICE give no recommendations for laparoscopic surgery. The ACCP guidelines are against TP for procedures "entirely laparoscopic" in gynaecologic patients who are without additional VTE risk factors (Geerts et al. 2008). With additional risk factors, TP in laparoscopic surgery should be by LMWH, UFH, IPC, or GCS (one or more). For major gynaecologic surgery for benign disease, TP is recommended even without additional risk factors and by the same selection of methods, except not GCS alone. Thus, it seems that laparoscopic surgery is considered somewhat the opposite of major surgery. These guidelines do not define "major surgery", and regarding hysterectomy they are somewhat ambiguous, as any vaginally performed surgery is given no consideration at all. Also whether LH is "entirely laparoscopic", when concomitant vaginal surgery is performed, is unclear. The recent LH results of Ritch et al. (2011) may influence future guidelines.

The ENDORSE survey conducted in 358 hospitals in 32 countries analysed over 18 000 patients undergoing major surgeries: 93% were at risk for VTE, but 62% only received TP. Corresponding rates for gynaecologic and urologic surgeries together were 88% at risk, but 54% given TP (Kakkar et al. 2010). In Finland, a multicentre study stated that 73% of patients at risk received TP; and 47% of those with pharmaceutical TP, also had GCS. IPC was sporadic only, and GCS alone was rare (10%). Various surgical departments participated and in the three departments representing gynaecology, TP for those at risk was given least often (for 43%) (Virtanen et al. 2010). Both studies, by Virtanen et al (2010) and Kakkar et al (2010), analysed TP coverage guided by the same 7thACCP recommendations (Geerts et al. 2004).

Postoperative infections

Infectious morbidity is the single most common postoperative complication of hysterectomy. Surgical-site infection (SSI) rates vary considerably, even with adequate means of prevention in use, i.e. antibiotic prophylaxis (AP) for the majority. Generally the lowest incidences appear in retrospective studies, with no follow-up after discharge, and the highest in prospective settings including either routine follow-up or patient questionnaires. Epidemiological data from Scotland reveal active postdischarge surveillance as nearly doubling the SSI rate for AH, and in CS the effect was more than 10-fold (Reilly et al. 2006). A national Danish hysterectomy database reported postoperative infections in 2004 occurring in 4%, and in 2006 in 2% (Hansen et al. 2008a), which are suspiciously low rates considering that over 60% underwent laparotomy. The Swedish National Register for Gynecologic Surgery in 2000-2003 observed postoperative infections with AH in 12.0%, with LH in 15.0%, and with VH in 9.9%; questionnaires were collected from both doctors and patients. Patients reporting pelvic infection or abscess, wound infection, or sepsis were included, but urinary tract infections (UTI) or fever alone were not recorded (Löfgren et al. 2004). In 2000-2007, for AH, the same register observed postoperative infections in 11.2% with UTI not included; but with UTI included, in 14.7% (Kjølhede et al. 2009), and with LAVH and VH operations together, subsequent rates were 9.5% and 13.3% (Kjølhede et al. 2011). The prospective multicentre eVALuate study involved follow-up by a routine 6-week visit, and reported infections for AH in 16.1%, for LH in 13.3%, and for VH in 14.3%. Rates are percentages of patients (with one or several infections), and the definition was

all-inclusive: SSI, fever, or UTI (Garry et al. 2004). Likewise, FINHYST in 1996 included all of these; the rate for AH was 10.5%, for LH 9.0%, and for VH 13.0% - the latter burdened with a quantity of UTIs (7.3%) (Mäkinen et al. 2001).

SSIs after hysterectomy include infections of the incisional wound in the skin, plus vaginal or pelvic infections. Infections of the vaginal cuff are either plain cellulitis-type or infected cuff haematomas or abscesses (Hager 2003), which are mainly defined separately into two groups called vaginal cuff infection and pelvic infection (Dicker et al. 1982, Harris 1995). The term "organ-space SSI" is also used for hysterectomy (Olsen et al. 2009). A major textbook claims that septic pelvic thrombophlebitis (SPT) complicates gynaecologic surgery in up to 0.5% of cases (Hager 2003), but such a figure may possibly arise from an era of less frequent TP. Gynaecologic cases represent the minority of SPT, which after CS occurs in 1 of 800 (Garcia et al. 2006). A case with LH operated on benign disease has been published on a single occasion (Nezhat et al. 2009).

One gynaecologic surgery review listed 32 definitions for postoperative febrile morbidity: 38º C on two occasions at least 4 hours apart and over 24 h after surgery was most common (Hemsell 1991). Excluding gynaecological surgeries with a high risk for infection, such as concomitant colorectal procedures or patients with recent chemotherapy, fever occurred in up to 16% (37 of 228), but only 6 developed an actual infection requiring antibiotics (Kendrick et al. 2008). Unexplained fever in most AH studies has occurred in 10% to 20%, and in VH studies in 5% to 8%, with a considerable variation in definitions, subjective diagnoses, other concomitant infections, and use of prophylactic antibiotics (Harris 1995). In larger studies involving around 1 000 LH operations or more, incidences have ranged from 0.76% to 5.1% (Wattiez et al. 2002, Garry et al. 2004, Donnez et al. 2009); in Finland from 1.6% to 3.2% (Härkki-Siren et al. 1997, Mäkinen et al. 2001).

Microbes responsible for infections

Posthysterectomy infectious morbidity arises mostly from the polymicrobial vaginal flora, in which apathogenic lactobacilli dominate, but anaerobes also are normally present. Moreover, up to 40% of asymptomatic women carry *Gardnerella vaginalis* (Eschenbach 2003). Prehysterectomy cultures revealed a growth of six or more different bacterial species for the majority, from a variety of over 40 species in total (Ohm and Galask 1975, 1976).

The "golden-staph", *Staphylococcus aureus,* is the most important pathogen of wound infections, among other normal flora bacteria of the skin and vagina such as the Streptococci and coagulase-negative Staphylococci frequent in plain cellulitis-type wound infections (Brook and Frazier 1990, Hager 2003, Valtonen and Rantala 2010). In addition, *Escherichia coli* is commonly isolated from wounds of the trunk and the lower part of the body (Brook and Frazier 1990). Deep infections, unlike the superficial, often involve anaerobes. Anaerobes play an important part in postoperative pelvic infections, of which the polymicrobial content is aerobic Gram-positive cocci and Gram-negative rods in around 40%, and anaerobes in 60% (Hager

2003); the three typical pathogens complicating gynaecological surgery are Enterococci, *E.coli*, and Bacteroides species (De Lalla 2002). In gynaecological infections, *Prevotella bivia* and *Prevotella disiens* – formerly part of the Bacteroides genus – are the most important anaerobes, and *Bacteroides fragilis* is commonly responsible for abscesses (Murray et al. 2009); all three produce β-lactamases (Rang et al. 2007). Anaerobes of a less virulent type may also cause severe infections: Septic shock is described in a patient with a postoperative pelvic abscess caused by *G. vaginalis* and *Peptostreptococcus* (Datcu et al. 2009).

Anaerobic infections are opportunistic from the normal flora, and a synergistic interaction is part of their pathogenesis: Anaerobes require the presence of other bacteria to initiate infection (McDonald and O'Loughlin 1993, Jousimies-Somer 2003, Brooks et al. 2007). A weakening of the immune response caused by hypoxia, trauma or disturbance of the normal flora is usually involved (Jousimies-Somer 2003). Hysterectomy itself, without any AP, causes a change in the vaginal flora: The vaginal cultures on the fifth postoperative day of those given placebo in both VH and AH resulted in significantly fewer cultures of aerobic gram-positive rods such as Lactobacilli and Difteroides, and more frequent cultures of *E. coli* and anaerobes, mainly Bacteroides species (Ohm and Galask 1975, 1976). Similar results appeared in a later study with less frequent Lactobacilli, and more frequent Coliforms, Enterococci, and Bacteroides species at a mean of 3.9 days, in comparison with preoperative cultures – but Candida was similar (Vincelette et al. 1983).

Risk factors

In AH, preparation of the vagina with povidone-iodine gel randomised against no cleansing resulted in no significant differences in overall infectious morbidity, but no pelvic abscesses occurred in the antisepsis group (Eason et al. 2004). Similarly with chlorhexidin compared to no cleansing, intra-abdominal infections in AH were reduced, but no preventive effect occurred on other infections or on overall infectious morbidity in either AH, or VH (Kjølhede et al. 2009 and 2011). Importantly, Kjølhede et al. (2009 and 2011) observed vaginal cleansing with saline to more than double the odds for overall infection morbidity at discharge for both hysterectomy types; the odds also increased for vaginal-cuff infection in AH, and for UTI in both.

Anaesthetic muscle relaxation impairs physiological warming balance, normally maintained by muscle work and tonus. This can be counteracted by forced-air blankets: Pre- and perioperative warming more than halves surgical-site infections (Kutz et al. 1996, Melling et al. 2001, Wong et al. 2007).

Febrile morbidity evidently associates with larger tissue damage: In two studies representing all three hysterectomy types, febrile events associated with AH, irrespective of antibiotic prophylaxis (Peipert et al. 2004, DiLuigi et al. 2004). A systematic review of RCTs observed "febrile episodes or unspecified infections" as significantly reduced for all minimally invasive methods in comparison to AH: An OR of 0.55 was observed for LH(a), OR 0.28 for LAVH, and OR 0.42 for VH (Nieboer et al. 2010). Febrile morbidity and also infections overall are

increased with TAH compared to SAH, in which the vagina is not opened (Löfgren et al. 2004, Lethaby et al. 2006). In an adjusted logistic regression analysis, the risk for SSI with AH, in comparison with VH, was more than double (Shapiro et al. 1982).

When 13 hospitals with high SSI rates were compared to 20 hospitals with low SSI rates: mean operation duration was significantly longer (mean difference 25 min) (Campbell et al. 2008). Shapiro et al. (1982) built a model to explore the association of SSI with duration of hysterectomy: Probability of infection increased with duration, for both those receiving and those not receiving cefazolin prophylaxis. With the former, risk equalled no prophylaxis at 3 h 20 min. A more recent evaluation of AH observed operation time had been significantly longer for those suffering from incisional SSI (Olsen et al. 2009).

SSI associated also with increasing blood loss (Shapiro et al. 1982). A nation-wide Swedish cohort showed more postoperative infections occurring with operative bleeding of 1000 ml or more (Persson et al. 1996); a threshold of 750 ml has also been associated with febrile morbidity (Peipert et al. 2004). A transfusion was a significant risk factor for SSI in a logistic regression model with over 113 000 operations analysed (OR 1.37) (Campbell et al. 2008), and similarly in one evaluation of only AH operations, risk for wound infections increased (OR 2.40) (Olsen et al. 2009). It is hypothesized the transfusion of red cells transiently affects immunosuppression by impairing clearance of bacteria by the phagocytic cells (Houbiers et al. 1997). In gynaecologic oncology with bleeding of 1500 ml or more the serum concentrations of prophylactic antibiotics were significantly lowered at 1 to 2 hours, in comparison to less bleeding, but tissue levels remained sufficient. Irrespective of bleeding, concentrations were insufficient after 3 hours (van Lindert et al. 1990).

A large register study analysing all hysterectomy types together showed obesity (BMI > 28) as being an independent risk factor for postoperative infection morbidity (OR 1.34), in up to 13.5% of the obese (Löfgren et al. 2004). For both AH (OR 1.59) and VH (OR 1.29) separately, similar results arose with BMI > 30 (Kjølhede et al. 2011 and 2009), whereas no significant difference was observable in LH (Heinberg et al. 2004, Chopin et al. 2009). Morbid obesity (BMI > 35) raised the odds for SSI in AH to nearly six-fold (Olsen et al. 2009). No wound was infected with a subcutaneous tissue thinner than 3 cm, and in those with infected wounds, subcutaneous tissue was significantly thicker, a mean 5.1 cm. In this logistic regression analysis, not BMI but rather the depth of the subcutaneous tissue in AH was the significant risk factor (Soper et al. 1995).

Smokers have significantly increased rates of overall SSI (Campbell et al. 2008), and also organ-space SSI after hysterectomy (Olsen et al. 2009).

The elderly undergoing hysterectomy seem not to be at higher risk for complications. In fact, the opposite is evident: Younger women are at risk for infections (Shapiro et al. 1982, Hemsell et al. 1995, Löfgren et al. 2004, Spilsbury et al. 2008, Olsen et al. 2009, Kjølhede et al. 2011). The national register of Kjølhede et al. (2011) combined LAVH and VH operations, Hemsell et al. (1995) studied AH, and the other evaluations were of all types of hysterectomies. The group with increased risk is most commonly defined as those aged under 40. Two reviews covered

together 12 publications in between 1955 and 1982, in which the risk factor for VH pelvic infection was premenopausal age (Hamod et al. 1982, Hemsell 1991). The reason why the younger are more at risk is unclear (Hager 2003).

When the vaginal flora in bacterial vaginosis (BV) is altered, with increasing concentrations of *G. vaginalis* and anaerobes, the risk for cuff cellulitis or abscess in AH with no AP is over three-fold (Soper et al. 1990), but BV had no effect on risk for wound or urinary tract infections. Similarly in a national Swedish study, BV was a risk factor for overall postoperative infections (Persson et al. 1996). Women with BV undergoing AH benefited from 1 g rectal metronidazole as a 5-day treatment initiated on the preoperative day: Cuff infections were nonexistent with metronidazole, in comparison to 27% without treatment – no difference arose with wound or urinary tract infections, or in the cuff infections of those with lactobacilli florae (Larsson and Carlsson 2002).

Antibiotic prophylaxis

The number of antibiotic-resistant bacterial strains has been correlated with the number of kilograms of antibiotics used in hospitals (Cobb et al. 2002). Antibiotic prophylaxis (AP) combats the endogenous organisms inoculating the surgical site. Surgical classifications are clean, clean-contaminated, contaminated, and dirty wounds, but in the latter two, antibiotics are already part of the treatment. Prophylactic use is indicated by increased risk or difficult consequences of infection; such as when the respiratory, gastrointestinal, or genitourinary tract is opened, or when foreign endoprothesis materials are placed in clean surgery (Valtonen and Rantala 2010). In colorectal surgery, AP is recommended to include additional anaerobic coverage (Nelson et al. 2009); in comparison to AH, after colon procedures, the rate of complex SSI (deep incisional, or organ-space infections) is over four-fold (Anderson et al. 2008).

Accurate AP timing was first understood when the greatest effect against postoperative infections in an animal model was obtained with AP given before the bacteria gained access to the tissues (Burke 1961). The optimal AP tissue level should be reached by the time of contamination (Hager 2003). Against wound infections, a preoperative period of 2 h prior to incision was the most effective timing, with the risk being increased for earlier pre-, intra-, or postoperative administration (Classen et al. 1992). In colorectal surgery, intra- or postoperative doses given additionally may elevate the risk for resistant organisms and the appearance of *Clostridium difficile* colitis (Nelson et al. 2009). Likewise, with hysterectomy, single-dose prophylactic efficacy was significantly better, or the same as with multiple doses (Tanos and Rojansky 1994, Chang et al. 2008). Evidence in support of multiple doses is indirect only: Cefazolin tissue concentrations were reduced in one study of 11 patients undergoing surgery of 3 to 8 h in duration. Additional doses were suggested to be administered if the operation excees 3 h or if blood loss is greater than 1500 ml (Swoboda et al 1996).

The first evidence of benefits from AP in hysterectomy arose with VH (Duff and Park 1980), whereas early reviews of AH presented controversial results (Hirsch 1985, Cartwright 1984).

The high incidences particularly for pelvic infection if no AP is given (17%-64%) may have enhanced the supportive evidence for VH (Duff and Park 1980, Hamod et al. 1982). With AH, the reduction is less: One review observed pelvic infections with VH in 25%, with AH in 10%, but with AP administrated in both, they fell to 5% (Hirsch 1985). In AH (and LH), the vagina is opened at the end of the procedure, and the period of exposure to vaginal bacteria is brief in comparison with VH. A prospective single-centre evaluation in Finland observed postoperative infections in 39% of VHs, with AP given to 31%, whereas in AH infections occurred in 24%, and in LH in 3%, with AP given to 22% and 100% (Meltomaa et al. 1999). Subsequently, a later meta-analysis observed AP as beneficial also with AH: Overall infections (21%) were more than halved (9%) (Mittendorf et al.1993).

Cephalosporins

Cephalosporins, first isolated from the Cephalosporium fungus, are categorised in generations by time of introduction and by their antimicrobial spectrum, widening towards the gram-negative, as generations increase (Rang et al. 2007, Brooks et al. 2007). Cefalexin and cefazolin are examples of first-generation drugs, cefuroxime, cefoxitin, and cefotetan of the second, and ceftriaxone of the third. The first generation cefazolin is effective against common pathogens in most clean-contaminated procedures, but agents with better gram-negative and anaerobic activity, such as cefoxitin and cefotetan, may be preferred in colorectal, obstetric, and gynaecological procedures (Cobb et al. 2002, De Lalla 2002). In Finland, cefuroxime AP in surgery has had a dominant position (Rantala and Huotari, 2010). The owners of the marketing authorisations for cefazolin and cefoxitin cancelled their authorisations from Finland in 1985 and in 2002, and cefotetan has never had a marketing authorisation (Fimea, 2011). A meta-analysis of placebo-controlled and comparative AP studies analysed 19 and 21 studies with AH and 18 and 34 with VH: A prophylactic regime with 1 or 2 g IV cefazolin was proposed, with identical recommendations for both hysterectomy types (Hemsell 1991).

In the literature in English, only eight relatively small studies on cefuroxime were identified; Wijma et al. (1987) and Boodt et al. (1990) demonstrate yet again the excess of operative-site infections in VH with no AP given (Table 7). Nor were studies of cefuroxime involved in a meta-analysis on AH pooling cephalosporins by first, second, and third generation: overall infection rates were 10.8%, 9.7%, and 7.4%, and a significant infection reduction against placebo occurred with all. Febrile morbidity, however, was effectively prevented by first-, but not by some second- (cefamandole) or third-generation (cefotaxime) drugs (Tanos and Rojansky, 1994). Single-dose third-generation ceftriaxone had an efficacy similar to that of three doses of cefazolin (Hemsell et al. 1984, Stiver et al. 1990). The second-generation cefotetan, however, is superior to cefazolin: A single-dose comparison produced no difference in wound infections, but against pelvic infections, cefotetan had better efficacy (Hemsell et al. 1995). Cefuroxime has never been studied in comparison to either cefazolin or to cefotetan (Table 7). Cefotetan has lower activity against Staphylococci and Streptococci than do other second-generation drugs in general, but better activity against anaerobes (personal communication with Dr Kari Sammalkorpi 2011). Importantly, its elimination half-life (T ½) is long, from 3 h up to 4.6 h (Hemsell et al. 1995, Druglib.com 2011), whereas the T ½ of

cefazolin is 1 h 50 min, and of cefuroxime around 1 h 30 min (Rang et al. 2007, Druglib.com 2011).

Table 7. *A review of studies involving cefuroxime AP with hysterectomy. Infections refer to operative site infection (in Wilma et al. to vaginal cuff abscess), except in Kauer et al. and Friese et al. to a need for postoperative antibiotics, and in Brouwer et al. and Eckenhausen et al. to febrile morbidity. VH&C, vaginal hysterectomy with colporrhaphy*

Study, hysterectomy	Antibiotics	Infections n / N (%)	Significance
1. Scarpignato et al. 1980, AH	Cefuroxime (1 day) Ampicillin + oxacillin (5 days)	0 / 21 0 / 26	
2. Wijma et al. 1987, AH	Cefuroxime + metronidazole (3 doses) Cuff drainage tube (3 days)	0 / 27 2 / 30 (7)	NS
2. Wijma et al. 1987, VH	Cefuroxime + metronidazole (3 doses) Cuff drainage tube (3 days)	0 / 21 8 / 27 (30)	P < 0.05
3. Friese et al. 1989, AH	Cefuroxime + metronidazole Amoxycillin + clavulanate	3 / 37 (8) 1 / 44 (2)	NS
3. Friese et al. 1989, VH	Cefuroxime + metronidazole Amoxycillin + clavulanate	5 / 66 (8) 2 / 67 (3)	NS
3. Friese et al. 1989, VH&C	Cefuroxime + metronidazole Amoxycillin + clavulanate	2 / 49 (4) 6 / 67 (9)	NS
4. Boodt et al. 1990, AH	Cefuroxime + metronidazole Placebo	2 / 113 (2) 2 / 97 (2)	NS
4. Boodt et al. 1990, VH	Cefuroxime + metronidazole Placebo	1 / 63 (2) 13 / 56 (23)	P < 0.001
4. Boodt et al. 1990, VH&C	Cefuroxime + metronidazole Placebo	0 / 39 7 / 38 (18)	P < 0.05
5. Eckenhausen et al. 1990, AH	Cefuroxime + metronidazole (1 dose) Cefuroxime + metronidazole (3 doses)	33 / 84 (39) 27 / 75 (36)	NS
6. Kauer et al. 1990, VH	A. Cefuroxime B. Cefuroxime + metronidazole C. Metronidazole	0 / 23 0 / 23 9 / 22 (41)	A vs C, P < 0.05 B vs C, P < 0.05 A vs B, NS
7. Brouwer et al. 1990, VH	Cefuroxime + metronidazole (3 doses) Placebo	0 / 27 13 / 26 (50)	P < 0.001
7. Brouwer et al. 1990, VH	Cefuroxime + metronidazole (3 doses) Ciprofloxacin (1 dose)	0 / 58 3 / 54 (6)	NS
8. Brouwer et al. 1995, VH	Cefuroxime + metronidazole (1 dose) Ceftriaxone (1 dose)	3 / 114 (3) 5 / 112 (5)	NS

Cefuroxime has a spectrum from gram-positive cocci – with the exception of enterococci and methicillin-resistant staphylococci (MRSA) – to gram-negative rods such as *E. coli* (Brooks et al. 2007). In addition, cefuroxime, unlike first-generation drugs, shows activity against some anaerobes: Gram-positive cocci such as Peptococcus and Peptostreptococcus species, gram-positive rods including Clostridium species (not *C. Difficile*), and gram-negative rods, including Fusobacterium and some Bacteroides species, with the exception of *B. fragilis* (Rang et al. 2007, Murray et al. 2009, Druglib.com 2011). Anaerobic Mobiluncus rods, abundant in women with BV (Eschenbach 2003, Paavonen 2011), are susceptible to cefoxitin, and also to other betalactams (Bahar et al. 2005, Rautio 2010). Similarly, the aerobic *G. vaginalis* is suspectible to cefuroxime (Martens et al. 1991, personal communication with Dr Martti Vaara in 2011).

Nitroimidazoles

Metronidazole was first introduced as an antiprotozoal agent effective against amoebas and against flagellates such as *Giardia Lamblia* and *Trichomonas vaginalis* (Rang et al. 2007). Trichomoniasis, like BV, predisposes for pelvic infection after AH (Soper et al. 1990). Metronidazole is a good option in treating infections caused by important anaerobic opportunists such as *B. fragilis* (Jousimies-Somer 2003, Brooks et al. 2007). Metronidazole is also important in the treatment of antibiotic-associated *C. difficile* colitis (Kelly and LaMont 2008). Because of the relatively narrow spectrum delimiting most aerobic bacteria other than *G. vaginalis*, metronidazole is an option against BV.

In Finland, metronidazole in the context of hysterectomy AP has had history of success, from an AH trial randomised against placebo: The 58 receiving metronidazole had no operative-site infections (Kauppila et al. 1983). Another Finnish trial enrolling 146 AH operations showed tinidazole as being effective in prevention of abscesses with an absolute risk reduction of 7.8% (Karhunen et al. 1980). Nowadays the only nitroimidazole with a marketing authorisation in Finland is metronidazole; authorisation for the last product containing tinidazole was annulled in 1998 (Fimea).

Four large reviews evaluating over 200 studies (Duff and Park, 1980, Cartwright 1984, Hemsell 1991, Mittendorf et al. 1993) showed metronidazole as involved in only eight studies, with a beneficial effect in three (Appelbaum et al. 1978, Kauppila et al.1983, Poulsen et al. 1984); all were AH studies versus placebo. The AH meta-analysis with a mean infection rate of 21% with placebo involved five studies with metronidazole, for which the overall infection rate was lower (6.3%) (Mittendorf et al.1993). Only a single large placebo-controlled study has appeared since: 258 AHs were enrolled with postoperative wound infections reduced from 12% to 6% (Henriksson et al. 1998). Metronidazole may be more effective than placebo, but from comparative AP studies, support for the superiority of metronidazole is lacking (Hamod et al. 1980, Houag et al. 1984, for Kauer et al. 1990, see Table 7).

Prophylaxis guidelines

Establishment of a preoperative policy has been shown to improve AP coverage with hysterectomy (DiLuigi et al. 2004). In Sweden in 1998, AP was not used prior to hysterectomy (Henriksson et al. 1998), but already in 2000-2003 as many as 74.5% received AP; the range between hospitals was wide, 28% to 96% (Löfgren et al. 2004). Similarly in Denmark, AP use ranged from 32% to 100% in 2004, but already in 2006, increased awareness resulting from the ongoing Danish hysterectomy database (DHD) resulted in 99% coverage (Hansen et al. 2008a). Nowadays in Sweden, a national recommendation pro AP exists, but recommends no particular regime (personal communication with Dr Preben Kjølhede, 2011). In Denmark and Norway, recommendations are similar (Table 8); for example in Oslo, cefalotin 2 g plus metronidazole 1.5 g IV is used for total hysterectomy, but no AP for subtotals (personal communication with Dr Anton Langebrekke, Ullevål University hospital, 2011).

The UK guidelines identify only one meta-analysis (Tanos and Rojansky, 1994), in which cephalosporins significantly reduced infections, but surprisingly the evidence statement concludes: "There is insufficient evidence available (owing to poor reporting) to determine the effect on wound infection in abdominal hysterectomy of antibiotic prophylaxis compared with placebo or no prophylaxis"; furthermore, "There is insufficient evidence that prophylactic administration of antibiotics results in fewer SSIs compared with no other antibiotic treatment or with placebo, in abdominal hysterectomy" (NICE 2008). Although not stated, the UK guidelines may have been influenced by results from the VALUE cohort, which observed no difference in severe postoperative complications with AP (McPherson et al. 2004). Another UK guideline, by The Scottish Intercollegiate Guidelines Network (SIGN) recommends AP, but does not specify which one (SIGN 2008), (Table 8).

The Society of Gynaecological Surgery in Finland released its recommendation in 2007. Preoperative AP should be given in the period of 1 h prior to incision, preferably as a cephalosporin such as the second generation cefuroxime IV at a dosage of 1.5 g to 3 g depending on patient weight. The first alternative for those with a betalactam-allergy is clindamycin 600 mg IV. Extra dosage is recommended, if the operation exceeds 3 h, or if haemorrhage exceeds 1500 ml (GKS 2007). Because of lack of controlled studies, the recommendations in the context of extended prophylaxis are possibly a result of indirect support (Shapiro et al. 1982, van Lindert et al.1990, Swoboda et al. 1996).

Table 8. *Prophylactic antimicrobial regimens in hysterectomy by various national guidelines*

Society / Reference	Year	Country	Hysterectomy type	Recommendation for AP
ASHP	1999	USA	AH, VH, and radical hysterectomy	cefazolin 1 g IV, cefotetan 1 g IV, or cefoxitin 1 g IV
ACOG	2006	USA	AH, LH and VH	cefazolin 1 g or 2 g IV, or cefoxitin 2 g IV with hypersensitity to penicillin: metronidazole 1 g IV or per oral tinidazole 2 g
Hansen et al. 2008 (DHD study)	2006	Denmark		cefuroxime plus metronidazole
NICE	2008	UK	AH	evidence insufficient for AP
SIGN	2008	Scotland, UK	AH and VH	AP recommended, not specified
NGF	2009	Norway	any hysterectomy	cefalotin 2 g IV or cefuroxime 1,5 g IV, consider combining metronidazole 1,5 g IV
ACOG	2009	USA	any hysterectomy, also LSH	cefazolin 1 g or 2 g IV with hypersensitity to penicillin: clindamycin 600 mg IV or metronidazole 0.5 g IV, plus gentamycin 1.5 mg/kg IV or quinolone 400 mg IV

ASHP, The American Society of Health-System Pharmacists; ACOG, The American College of Obstetricians and Gynaecologists; DHD, Danish hysterectomy database; SIGN, The Scottish Intercollegiate Guidelines Network; NGF, Norsk gynekologisk forening; LSH, laparoscopic subtotal hysterectomy.

AIMS OF THE STUDY

The aim of this thesis was to evaluate hysterectomy for benign disease in Finland, both retrospectively from registers, and in a prospective one-year setting of operations at the national level (the FINHYST study in 2006).

The specific aims were to evaluate

1. hysterectomy methods and surgery-related outcome (I, II)

2. incidence of complications (I, III, IV, V)

3. various risk factors for these complications (III, IV, V)

4. use of pharmaceutical thrombosis prophylaxis, and other factors associated with bleeding (IV)

5. effects of antibiotic prophylaxis (V)

SUBJECTS AND METHODS

Registers

Study I

The Hospital Discharge Register (HDR) of the National Institute for Health and Welfare in Finland (THL), prior to 2009 called the National Research and Development Centre for Welfare and Health (STAKES) were requested to provide the numbers of hysterectomies for benign disease (NCSP codes for AH LCD00 and LCC10, for VH LCD10 and LEF13; and for LH LCD04, LCD01, LCD 11, LCC 11). Operations performed for malignant indications were excluded, based on the International Classification of Diseases (ICD-10) codes related to cancer (Chapter C). The Patient Insurance Centre registers were first used to analyse reported major complications of any LH operation for benign disease performed during 2000-2005. The incidence of each complication was calculated per year, and for the study period as a whole, based on the LH numbers obtained from the HDR: 13 942 LH operations (all NCSP codes for LH) in total for benign disease were performed during 2000-2005. The previously reported data for 1992-1999 (Härkki et al. 2001) were compared to the 2000-2005 results; then all data in together were used in order to create the national learning curve of LH, introduced in Finland in 1992.

Studies II to V

The HDR was used to evaluate hysterectomy numbers, specifically coverage of the prospective FINHYST for hysterectomy for benign disease in Finland in 2006. The register of the Patient Insurance Centre was analysed for major complications during any hysterectomy for benign disease in 2006, serving also as a patient-provided verification of major complications for the prospective FINHYST study in 2006.

Study IV evaluated VTEs retrospectively not only from the Patient Insurance Centre, but also from the HDR for all hysterectomies performed in 2006. Analysis of all discharge diagnoses of various events of thromboses (ICD-10 codes I80, I82, I26) were requested within a postoperative range of 3 months. Data came both from inpatient and out-patient care visits at public hospitals (HILMO register), thus comprising both emergency room and hospital ward treatment involving the ICD codes for VTEs. From the HDR data, which provided date of operation, age, ICD-10 code, and type of hysterectomy, a search for matches was performed in the FINHYST 2006 data.

Subjects

Studies II to V

Data on women undergoing hysterectomy for benign cause in Finland were prospectively collected from 1 January to 31 December 2006. All 46 public hospitals (100%) where hysterectomies are performed collaborated, comprising 5 university clinics (Helsinki, Turku, Tampere, Kuopio and Oulu; the one in Helsinki containing 3 different units), 16 central hospitals, and 23 local hospitals. In addition, 9 private clinics (90%) agreed to participate, and patients were recruited from 7. For numbers of patients per clinic, see Appendix 1.

A one-month pilot study in April 2005 was performed in Helsinki University Central Hospital to test the feasibility of the study form (Appendix 2) completed by the performing gynaecological surgeons, who identified themselves as either specialists or residents. They indicated their prior experience in the particular approach for hysterectomy as below 10, 10 to 30, or over 30 operations ever performed. The number of patients recruited (forms accompanied by written patient consents) was 5 324, of which 45 were excluded: one underwent no surgery during 2006, one did not undergo hysterectomy but a colpoperineoplasty only, two patients made contact afterwards and wished to withdraw from the survey, six forms directly indicated a malignancy, 21 indicated that the final diagnosis had altered after the histology (ICD-10 code for a malignant disease). In addition, 14 patients indicated (patient questionnaire, response rate 75%) that their final diagnosis had been malignant; which was verified from their patient files. In total 5 279 hysterectomies were included, representing 79.4% (of 6 645, HDR) of the hysterectomies for benign disease in 2006.

Patient-related variables included height, weight, and date of birth, from which body mass index (kg/m^2), and age (with no decimals) at date of surgery were calculated. The gynaecological surgeons were requested to report a single main preoperative indication for hysterectomy, defined as myoma, menorrhagia, dysmenorrhea, endometriosis, uterine prolapse, adnexal mass, or other, with a description, and ICD-10 code. Surgery-related variables included the main approaches as abdominal (TAH or SAH), laparoscopic (LH(a), LAVH or LSH) or vaginal; and any conversions. Concomitant procedures were defined as uni- or bilateral salpingo-oophorectomy (BSO), vaginal procedures as anterior or posterior colporrhaphy or both, repair of enterocele, and urinary incontinence operations. BSO was further analysed by age (Study II). In addition, other concomitant procedures with description and adhesiolysis were noted. Operation time (min) was defined from the first incision to the final suture. The uterus was weighed postoperatively without any adnexa. Haemorrhage (ml) was estimated by standard operating room routines: usage of suction and surgical sponges. Antibiotic prophylaxis (AP) was defined as no prophylaxis, cefuroxime or metronidazole or both, or other antibiotic (with description) alone, or combined. Thrombosis prophylaxis (TP) was defined as pharmaceutical only. If no TP was indicated on the form, TP was considered as not given. TP was defined as low-molecular-weight heparin (LMWH), or other, with description. After surgery, the gynaecological surgeons rated the difficulty of the operation on a verbal five-point scale: very easy, easy, ordinary,

difficult, or very difficult. Postoperative hospital stay was ascertained in fractions of days, based on date of surgery and date of discharge. Sick-leave was reported as the number of sick-leave days for women employed at time of discharge from the hospital.

Definitions of complications

Complications were categorized by the time of their appearance: Intraoperatively detected or postoperative. Late-onset postoperative complications, detected after discharge when a patient visited an out-patient clinic or was readmitted to the hospital, were collected on another specific form (Appendix 2, p.119). In the absence of such a form, the patient was assumed not to have a late complication. Conversions to laparotomy were not calculated as complications, whereas complications responsible for conversions were (such as haemorrhage or organ injuries).

Intraoperative complications were defined as haemorrhage of 1000 ml or more, bladder, ureter, or bowel injuries, vascular injuries (epigastric vessels and major vessels such as the aorta, vena cava or iliac vessels), or other complications (with description) resulting in additive procedures or treatment during surgery. Postoperative complications were defined as haemorrhage or haematoma, wound infection, urinary tract infection (UTI), febrile event, deep vein thrombosis (DVT), pulmonary embolism (PE), ileus, hernia (with description), and other complications (with description). The causes of each reoperation were collected. Organ injuries were classified by detection as intraoperative or postoperative. Wound infection was defined as antibiotic treatment or drainage needed, UTI as a single bacterial growth exceeding 10^5/ml, and febrile event as clinically relevant fever for unknown reason with axillary temperature of 38.0 ºC or more. Late-onset postoperative complications on the additional form were defined similarly to those detected during the initial hospitalization, adding pelvic infection, defined as haematoma or abscess. The need for and duration of readmittance to hospital, as well as reoperations occurring, and data on other types of treatment were collected.

Transfusions, preoperative, intraoperative, and postoperative were also collected, but not categorised as complications. Data on red blood cell (RBC) transfusions showed that 16% occurred prior to the operation. Intraoperatively transfused patients, with a bleeding less than 1000 ml, had a haemorrhage equal to or lower than 300 ml in 44%; thus the need for transfusion indicated a preoperative anaemia rather than uncontrollable bleeding. Regarding operative bleeding, a complication was thus simply defined as haemorrhage of 1000 ml or more. This decision was strengthened by information on severe blood-product transfusion reactions: Generally the incidence in Finland in 2006 was 12 per 100 000. The rate limited to only RBC transfusions was even lower; 6 per 100 000 (Finnish Red Cross, personal communication with blood security coordinator Sanna Makkonen). We limited the definition of complication related to transfusion to those late-onset situations when a patient was readmitted to the hospital with a need for transfusion as the sole reason.

Major complications

Major complications from the FINHYST database were calculated, comprising intra- and postoperative complications with definitions such as PE or DVT, all injuries to bladder, ureter, or bowel, or to major vascular structures such as the aorta, vena cava, or iliac vessels, or any other necessary reoperations occurring either during the initial hospitalisation, or at a readmission. Or possible surgery-related death.

Ethics

The FINHYST 2006 study plan was approved by the Ministry of Social Affairs and Health in Finland, and the Helsinki University Hospital Ethics committee, i.e. the Institutional Review Board (IRB) in 2004 (Dnro 457/E8/04); by these decisions, the study was directly approved in all hospitals involved, except in four clinics (Espoo, Hyvinkää, Seinäjoki, and Lahti) which re-evaluated and approved the plan in their local IRBs. Each patient received the study information in writing, and gave a written consent. Data were collected by the operating gynaecological surgeons anonymously, with no economic compensation. The study was included in the ClinicalTrials.gov protocol (NCT00744172).

All patients in Finland are insured during their hospitalisation; this insurance covers bodily injuries that patients may have sustained. Any patient may file a claim of unsatisfactory treatment during Finnish health care to the Patient Insurance Centre free of charge. The Patient Insurance Centre handles and decides on possible financial compensations. The study plan in order to investigate registers of the Patient Insurance Centre complication was approved by the Ministry of Social Affairs and Health in Finland in 2004. An extended request was approved in 2006 to analyse filed claims until 31st of December 2008.

Statistics

Statistical calculations were performed with SPSS (15.0-17.0). Categorical data were analysed by χ^2-test or Fisher's exact probability test, continuous variables by univariate analysis of variance (ANOVA), with post hoc testing by Tukey (Study II). Pair-testing used the t-test for normally distributed variables. The LH learning curve was performed with the Generalized Linear Modelling technique. The response function indicating the number of complications follows binomial probability distribution; results were reported based on the logistic model.

The correlations in order to investigate associations with operative haemorrhage were calculated as Spearman's rank correlation coefficient rho (ρ), 2-tailed, and all results presented were significant at the p=0.01 level. Rho (ρ) can vary between -1.00 and 1.00: Verbal interpretations for positive correlations were categorised as 'small' with ρ ranging between 0.10 and 0.29, as 'medium' with ρ between 0.30 and 0.49, and as 'large' with ρ between 0.50 and 1.00 (Perrera et

al. 2008). The same ranges with negative values of ρ were applied in inverse relationships emerging as negative correlations.

Univariate data analysis preceded logistic regression; the choice of control variables was guided by clinical interests and by prior research on risk factors. Logistic regression served for analysis of associations of risk for complications. A level of $p<0.05$ was considered statistically significant, and adjusted odds ratios (exponential of B-coefficient) were presented with 95% confidence intervals. Risk factors were analysed for each complication individually, and in addition by categorising complications into three larger groups: Major complications, infections, and total (overall) complications, with the latter expressing the risk for appearance of any complication. Risk factors for complications or groups of complications were analysed by all hysterectomies together, and by type of hysterectomy.

In Study III, risk factors for each complication or group of complications were analysed for all hysterectomies together; the comparison of the three approaches was performed first with AH as the reference, then VH, in order to represent all pairs. Furthermore, risk factors were analysed separately inside each type of hysterectomy. The prior experience of the gynaecological surgeon of 30 operations or fewer ever performed of that particular type of hysterectomy was compared to experience exceeding 30. Patient age was classified to match the pre-, peri-, and postmenopausal age-groups of under 45, 45 to 54, and 55 or over, with the youngest age group as the reference. A standard classification of body mass index (BMI; kg/m^2) classed patients as overweight (25.0 to 29.9), obese (30.0 to 34.9), or extremely obese (35.0 or over), with normal weight (under 24.9) as the reference. The model was adjusted for the main indications myomas, menorrhagia, dysmenorrhea, endometriosis, uterine prolapse, adnexal mass, or other, with myomas as the reference, except for VH, for which the reference was uterine prolapse (61% of VHs). A large uterus was classified with a chosen cut-off point of 500 g, with a large uterus of 500 g or over compared to the uterus weighing less than 500 g, or unknown. Prior caesarean section (CS), prior laparotomy (other than CS), prior laparoscopy, adhesiolysis, any concomitant surgery (other than adhesiolysis), and antibiotic and thrombosis prophylaxis were applied as categorical variables (yes or no). In addition, the model was adjusted for hospital type: university, central, local, or private hospital, with university hospital as the reference. With VH, where adnexal mass as an indication was nonexistent, the three patients with the indication endometriosis were excluded, as was a single patient undergoing AH for uterine prolapse. Within certain rare complications, no events appeared in the context of some of the variables. When this occurred for a certain indication, a forced exclusion of cases with such an indication was necessary; otherwise a covariate with no effect was simply not applied in to the model. The configuration of each analysis is presented within the tables (Study III).

In Study IV, all uses of TP irrespective of product or dosage were analysed together. Initiation time of TP was unknown. For analysis with postoperative haemorrhage or haematoma, categorizing by BMI groups was impossible, as no complications in AH arose for the extremely obese. Likewise, categorizing by age with VH performed for indications other than prolapse failed for haemorrhage of 1000 ml or more and for postoperative transfusions, because in the age-group 55 or older, no cases arose. To achieve coherent and comparable results, the same

model was applied for all dependent variables, with all hysterectomy types; therefore, age and BMI both were applied as linear. The control variables in the analyses were otherwise similar to those of Study III; except uterine size was also applied as linear (g), in addition, to haemorrhage (ml). In analysing operative bleeding complications, haemorrhage was not applied, for the obvious reason of its use as the dependent variable.

In Study V, the control variables in the analyses were otherwise similar to those in Study IV, except that duration of operation (min) was included among control variables. Infections and hysterectomies in total were analysed for AP use (any), in comparison with no AP. Due to the non-randomised character of the study, the sample sizes of different groups could not be affected, and statistical power could thus not be calculated specifically beforehand. No AP accounted for 2.5% hysterectomies only, and to detect the actual differences occurring, or a 5% difference, analyses of any AP vs. no AP were underpowered for hysterectomy subgroups (AH and LH). When the separate and interactive effects of cefuroxime and metronidazole were studied, this model was adjusted for the use of other miscellaneous antibiotics. Those with unknown AP were excluded. Furthermore, for the categorised individual infections, an analysis was performed with cefuroxime or metronidazole antibiotics given alone compared to the use of their combination; with exclusion of those given other miscellaneous antibiotics. The use of cefuroxime irrespective of dosage, and of metronidazole irrespective of dosage and route were analysed as yes/no-type indicator variables. The effect of LH duration on risk for infection is presented for cefuroxime, for metronidazole, and for both given in combination (Study V). In this model, other antibiotics were applied as null. The curve was illustrated in order to present a common LH case, with mean values and the most common categorical variable responses applied. The graph presents a duration range of 23 to 305 min, covering all except a single extreme duration involving an iliac vessel injury.

Essential unknown data were always omitted from the hospital files, such as type of hysterectomy, or indication for surgery; less essential data were not requested in retrospect. Age was always known, BMI was unknown for 166 (3.1%) of the 5 279, and experience of the surgeon for 195 (3.7%). Control variables of unknown BMI and unknown experience of the surgeon were used to allow accurate categorisation (Study III). Uterine weight was unknown for 246 (4.7%). A uterus weighing 500 g or more, however, is uncommon and also more likely to be reported, thus in the model for Study III, unknown uterine weight was assumed to be under 500 g. Operative haemorrhage was unknown for 113 (2.1%), and duration of the operation for 162 (3.1%). No specific variables for unknown data in Studies IV and V were constructed, as there were relatively rare (always under 5%).

Specifically, dosages of AP and TP were often left unreported, possibly due to the poor design of the form for these data (Appendix 2). With LMWH, the dose was unreported for 46%, and its duration for 56%. The exact dose of cefuroxime AP went unreported for 62%, and of metronidazole, for 76%. Consequently, as explained above, prophylaxis was applied as a categorical variable (yes/no); all, irrespective of dosage, were analysed together.

RESULTS

Hysterectomy methods

In Finland, hysterectomies for benign indication declined from 2002 to 2006 by 34%. The abdominal route has become least common, as VH exceeded it in 2002 and LH in 2005. Since 2007, the number of hysterectomies for benign disease has been relatively stable (Figure 6). The number in 2010 was 5 930.

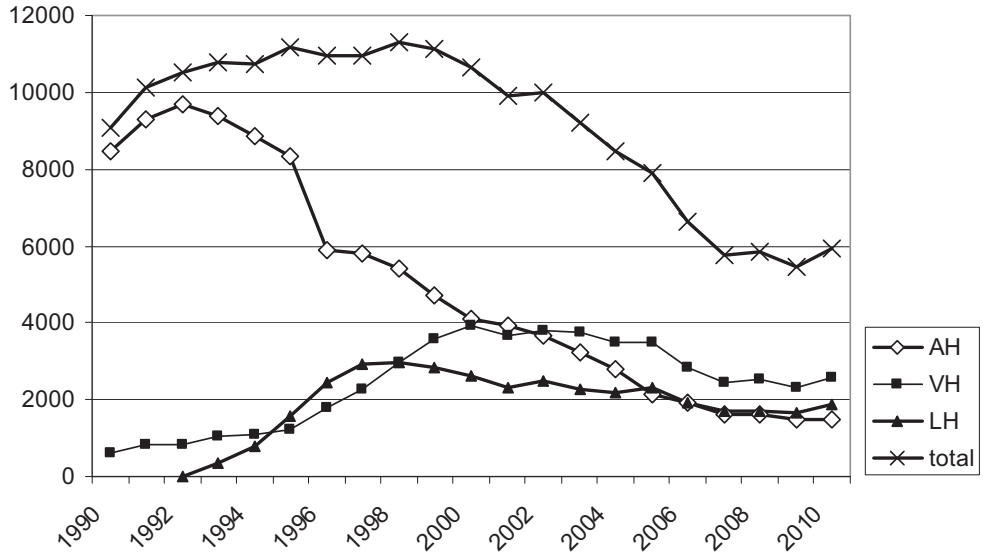

Figure 6 *Number of hysterectomies for benign disease in Finland in 1990-2010 (Source:HDR)*

FINHYST covered 79.4% of the annual 6 645 hysterectomies for benign disease in 2006; 5 279 patients in total were recruited. The three main hysterectomy methods were distributed thus: 44% VHs (2 345), 32% LHs (1 679), and 24% AHs (1 255). Subtotal hysterectomy was rare (1.7%). The majority of LHs (76.8%) involved laparoscopic coagulation of the uterine vessels (Table 9). The three main hysterectomy methods also involve subtotal procedures under AH and LH, and conversions to laparotomy under LH and VH (Table 9); the intention-to-treat strategy was chosen in order to analyse actual complications of LH and VH. No significant differences as indicators of selection bias were apparent in the proportions of LH or VH, but the AH rate in FINHYST 2006 compared to the national rate based on the HDR was significantly smaller (Table 10, *in italics*).

Table 9. *Hysterectomy methods in FINHYST in 2006.*

Main method	AH		LH			VH		
n (%)	1255 (23.8)		1679 (31.8%)			2345 (44.4%)		
Specific method	TAH	SAH	LH(a)	LAVH	LSH	LH conversion	VH for prolapse	VH other	VH conversion
n	1170	85	1289	300	3	87	1431*	900*	14
% of main method	93.2	6.8	76.8	17.9	0.2	5.2†	61.0	38.4	0.6†

*VH other refers to indications other than prolapse. The actual n (%) when categorising solely by indication are 1433 (61.1) for prolapse, and 912 (38.9) for other indications; 2 conversions occurred with patients operated on for prolapse.
† Conversion rate of LH vs VH, p <0.001.

Abbreviations: TAH, total abdominal hysterectomy; SAH, subtotal abdominal hysterectomy; LH(a), laparoscopic hysterectomy with laparoscopic division of the uterine arteries; LAVH, laparoscopically assisted vaginal hysterectomy; LSH, laparoscopic subtotal hysterectomy.

Table 10. *Number of hysterectomies annually for benign indication from the Hospital Discharge Register (HDR) in comparison with FINHYST in 2006, by type of hysterectomy. The feasible comparisons in italics. The intention-to-treat approach in FINHYST included laparoconversions in the group for hysterectomy initially chosen; thus, direct comparisons to evaluate selection bias were not viable. In order to perform this comparison, conversions of FINHYST were summed up to the AH group, similar to the way they are registered in HDR.*

Hysterectomy	FINHYST 2006 n (%)		HDR 2006 n (%)		P
total	5279		6645		
AH	1255	(23.8)	1913	(28.8)	<0.001
AH including conversions	*1356*	*(25.7)*			*<0.001*
LH	1679	(31.8)	1899	(28.6)	<0.001
LH excluding conversion	*1592*	*(30.2)*			*0.060*
VH	2345	(44.4)	2833	(42.6)	0.050
VH excluding conversion	*2331*	*(44.2)*			*0.096*

Patient characteristics and convalescence

The women in FINHYST in 2006 underwent hysterectomy at a mean (SD) age of 52.1 (10.5); their ages ranged from 21 to 94. Their mean (SD) BMI was 26.5 (4.7), and 2 917 (55.3%) were overweight (BMI ≥ 25.0), and 1 056 (20.0%) were obese (BMI ≥ 30.0). The postoperative hospital stay and sick leave were significantly shorter, in LH vs. AH, likewise in LH vs. VH (both p<0.001). Compared to VH not related to prolapse (Table 11), sick-leave was significantly shorter with LH(a), mean (SD) 20.9 (5.8) days (p<0.001), but mean hospital stay was the same for both, 1.8 days.

Table 11. *Patient characteristics and their postoperative hospital stay and sick leave by type of hysterectomy in FINHYST in 2006. Numbers are means (SD).*

Hysterectomy	Age	BMI	Postop hospital stay, days	Sick-leave days
AH	50.1 (8.8)	27.2 (5.4)	3.8 (1.8)	32.2 (4.6)
LH	49.2 (8.6)	26.1 (4.6)	2.0 (1.4)	22.0 (6.2)
VH	55.0 (11.8)	26.5 (4.4)	2.3 (1.5)	29.4 (8.0)
VH for prolapse*	60.2 (11.4)	26.5 (4.0)	2.7 (1.6)	34.2 (7.3)
VH, other indications *	46.9 (6.8)	26.4 (5.0)	1.8 (1.1)	25.0 (5.9)

*conversions excluded
Each category, between the three main hysterectomy groups AH, LH, and VH, resulted in significant differences in ANOVA (post hoc testing: age in LH vs. AH p=0.046; other pairs, p<0.001); except for BMI with LH vs. VH (p=0.057).

Indications

While hysterectomies for benign indications have declined since 1998, the proportion of malignant indications increased from 8.8% in 1997, to 14.8% in 2007. In 2010, the rate declined to 13.2% (Figure 7).

In 2006, the main indications involving benign disease, all hysterectomy methods combined, were 1 751 patients operated on for myomas (32.9%), 1 486 for uterine prolapse (28.0%), 1 113 for menorrhagia (20.9%), 294 for adnexal mass (5.5%), 145 for dysmenorrhea (2.7%), 130 for endometriosis (2.4%) and 369 for other indications (7.5%). The other indications included 167 for endometrial hyperplasia (3.1%), 95 for cervical premalignancy (1.8%), 28 for abdominal pain (0.5%), 22 for familial history of cancer (0.4%), and 15 for other sporadic indications numbering less than 20 (each under 0.4%). The main indication for VH was unrelated to uterine

prolapse in 39%. While uterine prolapse with 61%, was the most common indication for VH, myomas were the most common indications for AH and LH, by 58% and 39%.

Indication influenced age for undergoing hysterectomy: endometriosis at a mean (SD) 41.9 (6.7) years, dysmenorrhea 43.1 (5.2), menorrhagia 46.0 (5.9), myomas 49.2 (6.2), adnexal mass 57.8 (10.2), endometrial hyperplasia 58.1 (9.0), and uterine prolapse 60.2 (11.4). Women operated on for endometrial hyperplasia had a mean (SD) BMI of 28.5 (6.3), ranging between 18.5 and 50.2. Their BMI was significantly higher than that of women operated on for other indications combined (BMI 26.4, $p<0.001$). No such significant difference by BMI occurred with any other indication.

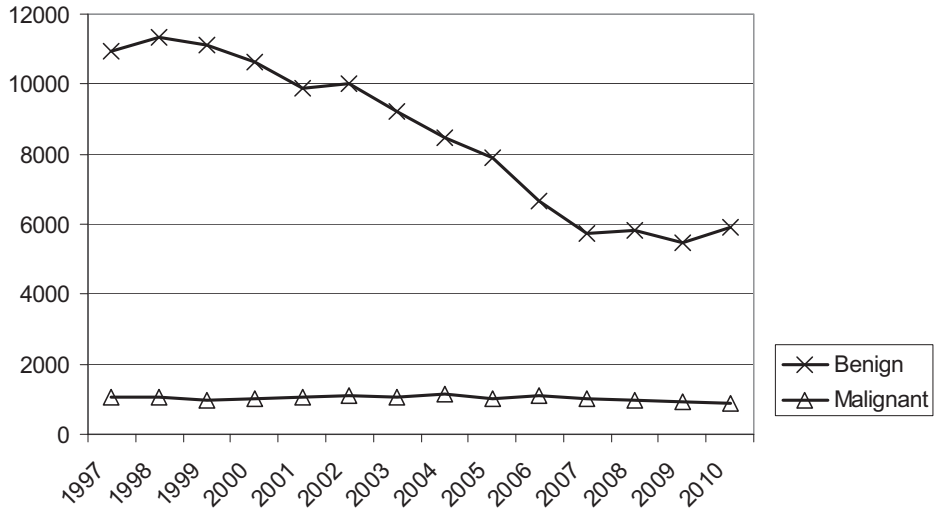

Figure 7 *Number of hysterectomies in Finland 1997-2010, by benign and malignant disease. (Hysterectomy for malignant disease categorised by ICD codes for malignancy involved with the various NCSP codes for hysterectomy.HDR 2011).*

Hospitals and gynaecological surgeons

The majority of hysterectomies took place in central hospitals (Table 12). All three methods were performed in all university hospitals, and VH was performed in each public hospital. LH was performed in 15 of 16 central, and in 17 of 23 local hospitals. Numbers for each hospital individually are presented in Appendix 1. LH was the most common method in university hospitals, and VH in local and central hospitals. Data are illustrated in contrast to results from a decade ago, when AH was the main method in all hospital types (Figure 8).

Table 12. *Hysterectomies in FINHYST in 2006, per type of hospital .Mean and SD for AH, LH, and VH calculated excluding the hospitals with null operations (0).*

Hospital type	Public hospitals			Private hospitals
	University	Central	Local	
Number of hospitals	7*	16	23	7
Hysterectomies (%)	1930 (36.6)	2057 (39.0)	1243 (23.5)	49 (0.9)
Hysterectomies in total, mean (SD) range	276 (112) 156-442	129 (62) 34-235	54 (38) 4-158	7 (7) 2-22
AH operations, mean (SD) range	52 (36) 24-115	36 (26) 9-97	14 (11) 0-42	2 (1) 0-3
LH operations, mean (SD) range	121 (76) 32-240	35 (37) 0-153	17 (16) 0-59	7 (9) 0-20
VH operations, mean (SD) range	103 (38) 66-183	60 (37) 20-158	28 (27) 1-127	2 (2) 1-6

*University hospitals are situated in 5 areas, with one containing 3 different units (Appendix 1).

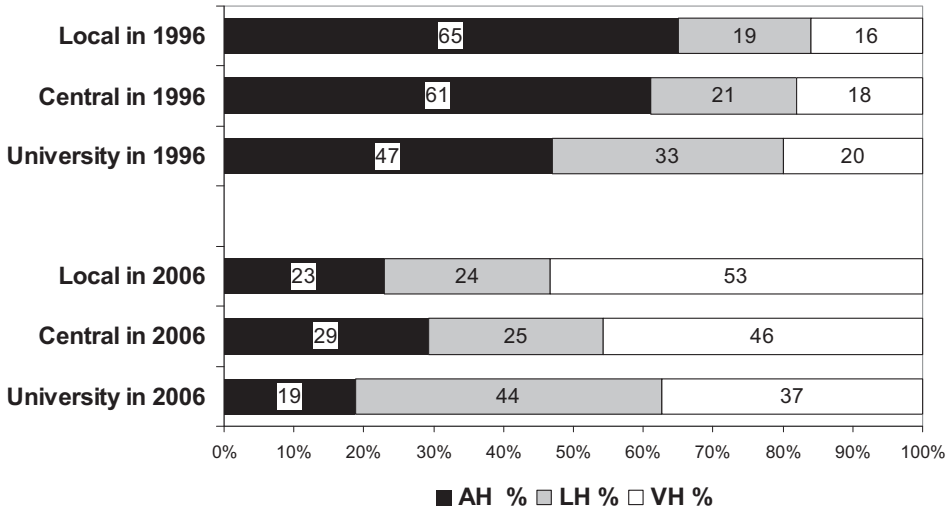

Figure 8 *FINHYST hysterectomy methods in 1996 and in 2006 by type of public hospital (university, central, or local hospital).Overall in 1996, AH was performed for 58%, LH for 24%, and VH for 18%. Corresponding data from a decade earlier published with the permission of the guarantor of the study (Mäkinen et al. 2001).*

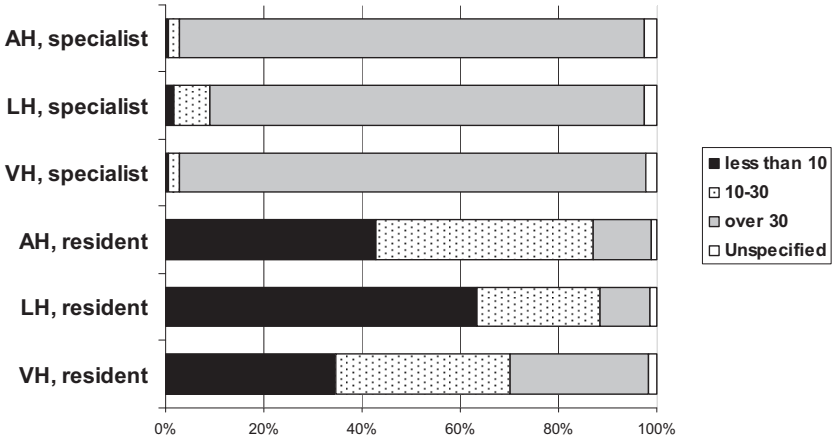

Figure 9 *Prior experience identified by specialist and resident gynaecological surgeons in FINHYST in 2006 with categories as under 10, 10 to 30, or more than 30 operations of that particular type of hysterectomy (AH, LH, or VH) ever performed.*

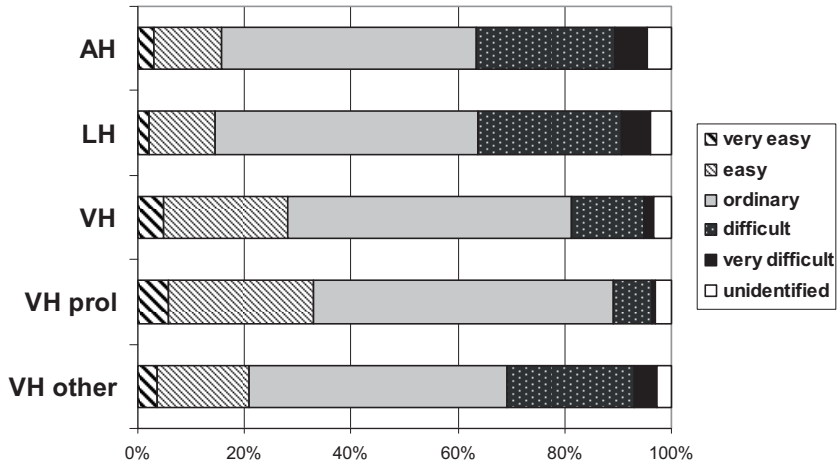

Figure 10 *Difficulty of operation by type of hysterectomy in FINHYST in 2006, identified by gynaecological surgeons on a verbal 5-point scale: very easy, easy, ordinary, difficult, or very difficult. VH prol= VH for the main indication prolapse. VH other= all other indications together.*

In FINHYST in 2006, 1 145 (21.7%) of hysterectomies were performed by residents, 3 832 (72.6%) by gynaecologists qualified as specialists, and 302 (5.7%) were left unidentified. Of the three methods, LH was least often performed by a resident: 285 (17%) of LHs. Residents were also least experienced with LH (Figure 9). Specialists with experience fewer than 30 operations ever performed were rare. University hospitals were the main teaching hospitals for residents, as 37.6% of hysterectomies performed were by a resident, whereas this was 17.8% in central and 10.4% in local hospitals. Data on the presence, experience, or qualification of the assistant gynaecologist was absent.

The gynaecologists were asked their subjective opinion as to the difficulty of the operation. For VH, it was identified as easy or very easy to perform by 29.1%, with VH for prolapse by 34.0%. For AH and LH, such operations were 16.4% and 15.2% only. If the non-prolapsed uterus was the main indication, however, scales for all three hysterectomy types were alike (Figure 10)

Surgery-related outcome

Mean operation time was shortest for VH, 30 mins less than for LH and 15 mins less than for AH. Similarly, mean haemorrhage rate and mean weight of the uterus were lowest in VH (Table 13). LH(a) compared to LAVH was significantly faster to perform (mean duration 103 min vs. 122 min, $p<0.001$) and resulted in less bleeding (mean haemorrhage 222 ml vs. 303 ml, $p<0.001$), yet with no significant difference between uterine weights. In a comparison of LH(a) vs. VH not related to prolapse, non-significant differences appeared in the mean haemorrhage and in uterine weight, but VH was significantly faster to perform (69 min vs. 103 min, $p<0.001$).

Table 13. *Surgery-related outcome, mean values (SD). Per hysterectomy type, the current outcome of 2006 is compared to results in 1996 (Mäkinen et al. 2001): All pairs p<0.001, except LH for haemorrhage p=0.603.*

Hysterectomy type, year	Operation time min	(SD)	Haemorrhage ml	(SD)	Uterine weight g	(SD)
AH 2006	93*	(37)	355*	(360)	433*	(425)
AH 1996	86	(31)	305	(312)	290	(302)
LH 2006	108*	(43)	270*†	(669)†	210*	(146)
LH 1996	124	(48)	262	(271)	195	(108)
VH 2006	78*	(34)	203*	(269)	131*	(110)
VH 1996	88	(32)	342	(353)	109	(84)

*All surgery-related outcome in 2006 between the three hysterectomy types resulted in significant differences in ANOVA and in post hoc testing of all hysterectomy pairs ($p<0.001$). † Excluding a single case of 25 000 ml bleeding, mean (SD) haemorrhage was 255 (274) ml.

The uteruses weighed 500 g or more in 365 AHs (29.1%), in 80 LHs (4.8%), and in 40 VHs (1.7%), and no laparoconversion was necessary with LH in 67, and with VH in 38. The weight exceeded 1000 g in 86 (17.7%) uteruses of 500 g or more. The largest uterus successfully removed by LH weighed 1 100 g, by VH 1 070 g, but by AH 3 720 g.

Operative haemorrhage was highest with AH (Table 13). While both increasing BMI and uterus size correlated with increasing haemorrhage, the effect was strongest with uterine size (Table 14, Table 15). This correlation was smaller for AH than for other types of hysterectomies; in AH uteruses were larger, and the overall bleeding was more pronounced, also from the incision itself. An inverse relationship (negative correlation) appeared also with age and haemorrhage (Table 14). Among the three main hysterectomy types, the relationship of age and decreasing mean operative haemorrhage (Figure 10) was similar.

Table 14. *Correlations related to operative haemorrhage (ml), with body mass index (BMI, kg/m²), age, and uterus size (g), Uteruses tend to be smaller in those older; correlation of age with uterus size is presented to express the magnitude of other correlations. Spearman's correlation coefficients ρ (rho) are preceded by their verbal interpretation: Small, medium, or large correlation.*

Hysterectomy	Haemorrhage and BMI	Haemorrhage and age	Haemorrhage and uterus size	Age and uterus size
AH	small (0.175)	small (-0.127)	small (0.221)	small (-0.148)
LH	small (0.136)	small (-0.145)	medium (0.372)	minimal (-0.090)
VH all	small (0.110)	small (-0.212)	medium (0.352)	large (-0.597)
VH for prolapse	small (0.122)	small (-0.234)	medium (0.352)	large (-0.555)
VH for other	small (0.112)	no (-0.033)	medium (0.379)	no (0.075)

ρ can range from -1.00 (perfect negative association) to 1.00 (perfect positive association). Negative ρ indicates an inverse relationship, a positive direct relationship.

Table 15. *Mean operative haemorrhage (ml) by body mass index (kg/m²).*

	Normal weight < 25.0	Overweight 25.0-29.9	Obese 30.0-34.9	Extremely Obese ≥ 35	P
AH	311	356	394	435	0.006
LH	235	254	296*	319	0.006
VH	180	201	239	344	<0.001
VH for prolapse	161	190	204	333	<0.001
VH for other	206	224	310	351	<0.001

* A single disrupting case of 25 000 ml excluded. Otherwise, the mean haemorrhage for the obese resulted 397 ml (Anova p=0.010).

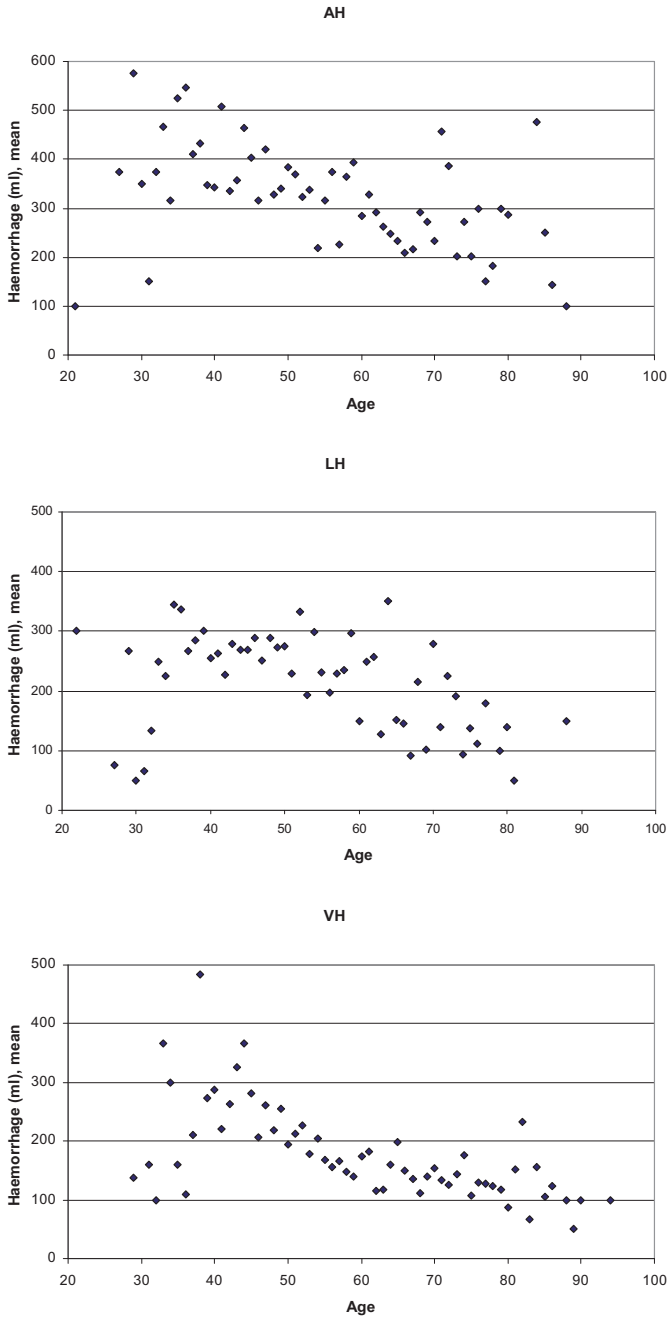

Figure 11 *Mean operative haemorrhage (ml) according to age, in AH, LH, and VH. Haemorrhage data were available for 1 227 AH, 1 643 LH, and 2 296 VH operations. With LH, an outlier of 25 000 ml is excluded from these graphics.*

Problems with instrumentation were reported in 25 (1.5%) of LH, and 5 (0.2%) of VH, whereas in AH these were absent. The haemostatic-method ultrasound scalpel (ULS) was used in 584 LHs (35%), and as a single haemostatic method alone in 335 (20%); the Ligasure® was involved in 61 (3.6%). The Ligasure® was somewhat more commonly used in AH, in 68 (5.4%) and in VH, in 174 (7.4%); alone in 77 (3.3%). The LH haemostasis-related data were analysed in comparison with usage of bipolar alone versus ULS alone: No difference was observable in operation time or uterine weight, but mean operative haemorrhage differed: 226 ml with bipolar, versus 270 ml with ULS (p=0.012).

Conversions to laparotomy occurred in LH in 5.2%, and VH in 0.6% (Table 9). Conversions in LH were most commonly performed due to adhesions, 30 of 87. Of the 87 conversions, 52 were during LH(a) and 16 during LAVH; 19 were indicated to be performed as early conversions after a laparoscopy only. In VH, in addition to the 14 actual laparotomy conversions, three laparoscopies were performed to secure haemostasis, and one due to a bladder perforation. Mean haemorrhage in LH conversions was 859 ml and in VH conversions 1 492 ml, but if the conversion was performed to secure haemostasis, mean haemorrhage in LH was 3 657 ml and in VH 2 950 ml. When the conversion was reported to be due to uterus volume, the mean weight of the uterus in LH was 522 g (SD 179 g) and in VH 532 g (SD 313 g). The experience of the surgeon or the gynaecologic surgeon as being a resident or specialist was of no statistical significance regarding a conversion. The risk factors for conversion in LH were a large uterus, adhesions, and obesity (Table 16).

Table 16. *Factors associated with laparoconversion of LH; results of logistic regression analysis with conversion as the dependent variable.*

	n / N (%)	Adjusted OR	95 % CI		P
Operative haemorrhage 1000 ml or more	17 / 50 (34.0)	8.75	4.36	17.59	<0.001
Uterine size 500 g or more	13 / 80 (16.3)	2.57	1.25	5.30	0.011
Adhesiolysis	13 / 99 (13.1)	2.83	1.27	6.30	0.011
Normal weight (under 25.0)	29 / 737 (3.9)	1.00 (reference)			
Overweight (25.0-29.9)	29 / 569 (5.1)	1.45	0.83	2.54	0.195
Obese (30.0-34.9)	23 / 247 (9.3)	2.36	1.26	4.43	0.007
Extremely Obese (35.0 or over)	5 / 68 (7.4)	1.86	0.64	5.37	0.251

Conversion rates were 5.2% for haemorrhage less than 1000 ml, 4.6% for uterus size less than 500 g, and 4.7% with no adhesiolysis.

Analysis adjusted for hospital type, surgeon's experience, patients' age, indication for hysterectomy, prior cesarean section, prior laparotomy, prior laparoscopy, concomitant surgery (any), and antibiotic and thrombosis prophylaxis.

Concomitant surgery

Concomitant surgery is usually planned in advance, and means procedures performed during the same operation as hysterectomy. Concomitant procedures (one or several) were performed to 633 (50.4%) patients undergoing AH, on 747 (44.5%) undergoing LH, and on 1379 (58.8%) undergoing VH. Advanced surgery related to endometriosis was infrequent; resections of the adjacent organs were performed on 13 patients in total (Table 17). Bowel resections for pathology other than endometriosis were performed due to a bowel perforation once; otherwise for a benign tumor of the appendix or for diverticulosis (Table 17). Incontinence surgery comprises all operations with Tension-free Vaginal Tape (TVT), Trans-Obturator Tape (TOT) and Tension-free Vaginal Tape Obturator (TVT-O) together; Burch procedures were none. The most common concomitant procedure was anterior colporrhaphy (AC) performed to 1 145 in total. Posterior colporrhaphy (PC) was performed on 830; in VH, AC and PC were performed on 1 087 and 768, and AC alone on 466, PC alone on 147, and both on 621. Colpoperineoplasties in Table 17 comprise AC and PC procedures, enterocele repair and pelvic floor repair with some newer means: Prolift® mesh had been inserted in 24 concomitant to VH. With VH for prolapse, 1 171 (82.1%) underwent some type of colpoperineoplasty.

Table 17. *Concomitant surgeries in the 5 279 FINHYST hysterectomies. Many with multiple concomitant procedures.*

	AH		LH		VH	
	n	%	n	%	n	%
Adnexal surgery, any	646	51.5	728	43.4	115	4.9
Colpoperineoplasty, any	17	1.4	87	5.2	1281	54.6
Sacrospinousfixation	-	0.0	2	0.1	35	1.5
Incontinence surgery	4	0.3	9	0.5	50	2.1
Appendectomy	47	3.7	3	0.2	-	0.0
Bowel resection	3	0.2	-	0.0	-	0.0
Cholecystectomy	2	0.2	-	0.0	-	0.0
Hernia repair (inguinal/umbilical)	4	0.3	3	0.2	2	0.1
Vulva procedure	1	0.1	6	0.4	11	0.5
Other	9	0.7	2	0.1	1	0.04
Endometriosis related:						
Bowel resection due to endometriosis	8	0.6	3	0.2	-	0.0
Ureter resection and reanastomosis	1	0.1	-	0.0	-	0.0
Bladder resection due to endometriosis	-	0.0	1	0.1	-	0.0
Retrocervical endometriosis resection	2	0.3	2	0.3	-	0.0
Endometriosis foci resection	10	0.8	10	0.6	-	0.0

Adnexal surgery comprises uni- and bilateral salpingectomies, salpingo-oophorectomies, ovarian resections, ovarian cyst aspirations, and parovarian cyst removals (Table 17). Bilateral salpingo-oophorectomy (BSO) was performed on 1 049 (19.8%) in total. When obvious reasons for oophorectomy were excluded (Figure 12), the rate for cancer prophylactic BSO was 30.3% with AH, 26.5% with LH, and 2.2% with VH. Unilateral salpingo-oophorectomies (USOs) were performed on 312 (5.9%) but no data on history of USO were available; thus enquiry as to neither ovary conserved with USO was impossible.

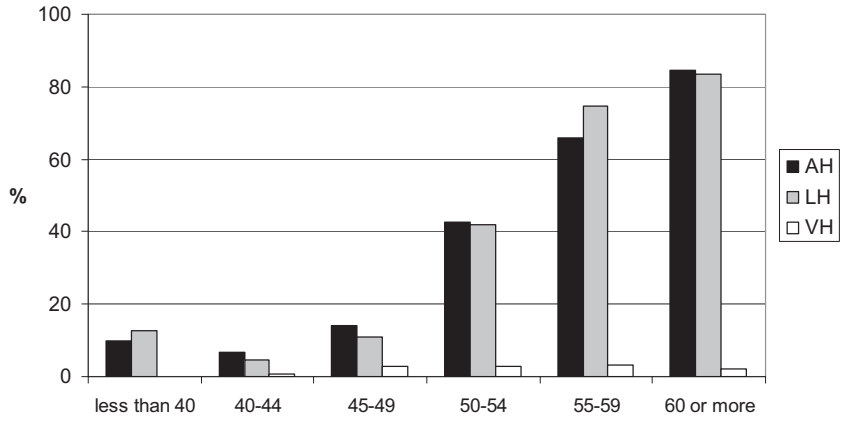

Figure 12 *Prophylactic BSO % by age-group and hysterectomy type.* *Indications adnexal mass, prior breast cancer, familial history of cancer, and transsexualism excluded from analysis.*

In addition to the concomitant procedures, adhesiolysis had been necessary in AH for 83 (6.6%) and in LH for 99 (5.9%), but rarely in VH, with 14 (0.6%). Endometriosis was the indication for hysterectomy in patients with adhesions in 32 (24.6%) in total; in 18 AH and 14 LH operations. In analysis of adhesiolysis as the dependent variable, endometriosis was a risk factor (OR 4.33, 95% CI 2.51-7.47, p<0.001), as were prior caesarean sections and other laparotomies (OR 1.79, 95% CI 1.26-2.54, p=0.001 and OR 2.85, 95% CI 2.10-3.86, p<0.001). Prior laparoscopies had no effect (OR 0.93, 95% CI 0.69-1.32, p=0.685). Among those with adhesiolysis performed, 40 (20.4%) had neither endometriosis nor any surgery in their past.

Major complications

The definition of major complications comprises organ injuries or reoperations for any other cause, VTEs, and possible surgery-related death. Major complications of LH, the newest of the hysterectomy types, were analysed from the Patient Insurance Centre registers. The yearly numbers of the Patient Insurance Centre for major complications of LH in 2000-2006 are in Table 18. During that 7-year period, 2000-2006, the overall incidence of major complications was 9.7 per 1000 operations; a result significantly lower than the corresponding figure (17.6)

from the era right after LH introduction in the 1990's (Table 19). The incidence of major complications has been reasonably steady in this century, indicating that a national learning curve plateau has been reached (Figure 13).

Table 18. *Major complications of laparoscopic hysterectomy 2000-2006 in Finland.* *Source: Patient Insurance Centre.*

Year	2000		2001		2002		2003		2004		2005		2006	
LH	2 608		2 240		2 485		2 226		2 150		2 233		1 899	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Ureter injury	8	0.31	10	0.45	7	0.28	7	0.31	6	0.28	9	0.40	5	0.26
Bladder injury	3	0.12	3	0.13	5	0.20	3	0.13	5	0.23	4	0.18	1	0.05
VVF	6	0.23	4	0.18	2	0.08	4	0.18	3	0.14	3	0.13	2	0.11
Bowel injury	2	0.08	1	0.04	1	0.04	1	0.04	1	0.05	6	0.27	3	0.16
Reoperation, other	8	0.31	2	0.09	3	0.12	1	0.04	6	0.28	5	0.22	8	0.42
Thrombosis	1	0.04	-	0.00	-	0.00	-	0.00	2	0.09	2	0.09	1	0.05

Table 19. *Major complications of laparoscopic hysterectomy (LH) 1992-1999 vs 2000-2006.* *(Source: Patient Insurance Centre.)*

Numbers of LH	1992-1999 13 885		2000-2006 15 841		
	n	%	n	%	P
Ureteral injury	125	0.90	52	0.33	<0.001
Bladder injury and VVFs	68	0.49	48	0.30	0.010
Bowel injury	20	0.14	15	0.09	0.216
Major vascular injury	2	0.01	1	0.01	0.602
Death	1	0.01	-	0.00	
Other	29	0.21	39	0.25	0.501
Total	245	1.76	154	0.97	<0.001

VVF, vesicovaginal fistula

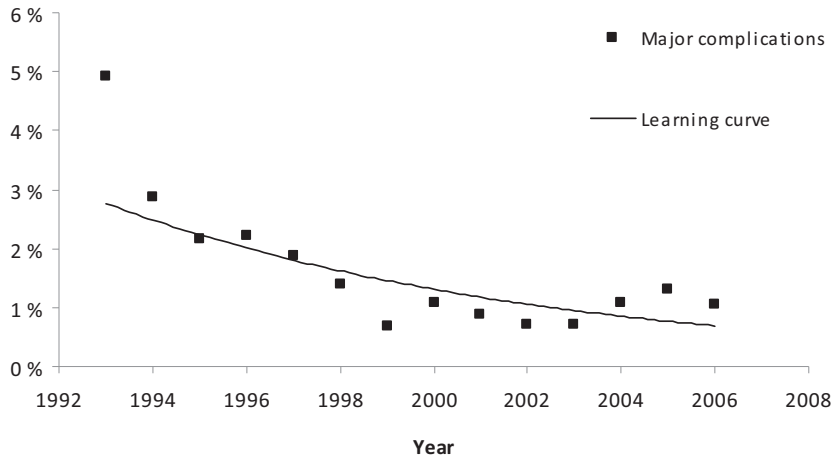

Figure 13 *National LH learning curve (1993-2006) based on major complications reported to the Patient Insurance Centre.* *The likelihood ratio test for the model is statistically significant ($\chi 2=55.84$, $p<0.001$).*

Among those recruited to FINHYST in 2006, no severe complications were left unreported when verified from the Patient Insurance Centre files; a single exception was one DVT occurring after an iliac vessel injury. The major vessel injury itself was reported, so the occurrence of a major complication with this patient was known. FINHYST covered 79.4% of annual hysterectomies in 2006, and 84.3% of major complications reported to the Centre. Differences between rates of complications according to the Patient Insurance Centre, within and outside the FINHYST recruits, were non-significant, indicating no selection bias (Table 20).

Table 20. *Major complications reported to the Patient Insurance Center of hysterectomy for benign disease occurring in 2006, by their appearance in FINHYST 2006 (representing 79.4% of annual hysterectomies).*

Complications, Patient Insurance Centre n / N, %		In FINHYST n / N, %	Not in FINHYST n / N, %	P
Total	51 / 6 645, 0.8	43 / 5 279, 0.8	8 / 1 366, 0.6	0.388
AH	19 / 1 913, 1.0	16 / 1 255, 1.3	3 / 658, 0.5	0.095
LH	20 / 1 899, 1.1	16 / 1 679, 1.0	4 / 220, 1.8	0.278
VH	12 / 2 833, 0.4	11 / 2 345, 0.5	1 / 488, 0.2	0.704

Major complications reported to FINHYST in 2006 are presented in Table 21. By indication, major complications were most common with endometriosis in LH (12.2%), with adnexal mass in AH (7.2%), and with menorrhagia in VH (5.3%). In the adjusted logistic regression model, no type of hysterectomy was independently associated with any organ injuries or major complications overall.

Table 21. *Major complications of FINHYST by type of hysterectomy*

	AH	LH	VH
Intraoperative complications			
Death	-	-	-
Bladder injury	9	14	14
Ureter injury	1	-	-
Bowel injury	3	5	2
Major vessel	-	1	-
Postoperative complications			
Early			
Death	-	-	-
Pulmonary embolism	1	-	1
Bladder injury	-	2	-
Ureter injury	2	-	1
Bowel injury	-	2	-
Reoperation: Haemorrhage or haematoma	21	25	35
Reoperation: Other †	4	2	-
Late (after discharge)			
Death	-	-	-
Pulmonary embolism	-	-	-
Bladder injury	2*	1	-
Ureter injury	1	5	-
Bowel injury	-	-	-
Reoperation: Pelvic infection (haematoma or abscess)	5	7	9
Reoperation: Wound infection	1	-	-
Reoperation: Vaginal haemorrhage	-	9	1
Reoperation: Other ‡	1	-	-
Total, major complications	51	73	63
Patients with major complication(s) occurring (%)	50 (4.0)	72 (4.3)	61 (2.6)

*Both are vesicovaginal fistulas

†A case of retained drainage tube in AH, and suspicion of haemorrhage in LH. Otherwise all are cases of laparotomy wound dehiscence.

‡A case of retained sponge.

Major complications occurred more frequently in hysterectomies with adhesiolysis: of 99 LHs, in 10 (10.1%), and of 83 AHs, in 11 (13.3%). Analysing all hysterectomies together, adhesiolysis (OR 2.41, 95% CI 1.38-4.21, p=0.002), and the indication adnexal mass (OR 2.30, 95% CI 1.25-4.22, p=0.007) were associated with appearance of major complications. By type of hysterectomy, adhesiolysis was associated significantly in AH only (OR 4.02, 95% CI 1.63-9.94, p=0.003). In LH, an indirect relationship with adhesions was evident with endometriosis being a risk factor (OR 2.87, 95% CI 1.02-8.03, p=0.045) when adhesiolysis was removed from the model.

Major complications occurred among 721 VHs performed in university hospitals in 23 (4.4%), but in central hospitals of 942 in 16 (1.7%), and in local hospitals of 665 in 13 (2.0%); the adjusted odds for major complication was significantly reduced for both central and local hospitals (OR 0.37, 95% CI 0.19-0.70, p=0.002; OR 0.46, 95% CI 0.22-0.94, p=0.032, respectively), compared to university clinics.

Urinary tract injuries

For urinary tract injuries occurring with LH, a reduction in 2000-2006 compared to 1992-1999 occurred in bladder injuries and vesicovaginal fistulas (VVF) combined, and specifically in ureter injuries (Table 19). In LH, the overall incidence of urinary tract injuries was relatively stable (0.6-0.8%) during 2000-2005, suggesting that a plateau had been reached. In 2006, urinary tract injuries of the Patient Insurance Centre amounted to 0.4%.

In 2006, in the prospective FINHYST, bladder injuries during LH were 17 (1.0%), during AH 11 (0.9%) and during VH 14 (0.6%). It seems that the intraoperative detection rate of bladder injuries reduced eagerness to seek compensation from the Patient Insurance Centre. In FINHYST, of 42 bladder injuries, 37 (88%) in total were recognised and repaired at index surgery (Table 21). Only four simple bladder injuries were reported to the Patient Insurance Centre; one of which occurred with LH (Table 18). No VVF occurred with VH. Both VVFs in FINHYST occurred with AH (Table 21), and were present also in the Patient Insurance Centre files. Both VVFs with LH (Table 18) occurred outside the FINHYST cohort (Table 20).

In analysis of all hysterectomies, uterine size of 500 g or more (OR 2.88, 95% CI 1.05-7.90, p=0.040) and a history of a CS (OR 4.01, 95% CI 2.06-7.83, p<0.001) were the independent risk factors for bladder injury. In LH 2.6% (7 of 272), and in VH 2.9% (6 of 207) with a history of CS suffered a bladder injury; with no CS, incidences were 0.7% and 0.4% (respective logistic regression results; OR 5.39, 95% CI 1.87-15.55, p<0.002 and OR 7.89, 95% CI 2.50-24.85, p<0.001).

In FINHYST, ureter injuries in LH were 5 (0.3%), in AH 4 (0.3%), and in VH 1 (0.04%) (Table 21). All 10 cases appeared in the Patient Insurance Centre files, of which, 9 were not recognised until postoperatively; moreover, 6 had already been discharged from the hospital (Table 21), including all 5 cases with LH. The diagnostic delay was 2 weeks on average, ranging from 6 to 22 days. In total, ureter injuries in LH during 2000-2006 according to the Patient Insurance

Centre were 52; all went unrecognised at index surgery. The LH incidence of ureter injuries was reasonably steady in 2000-2006 (0.33% in average), indicating that a national learning curve plateau had been reached (Table 18, Figure 14).

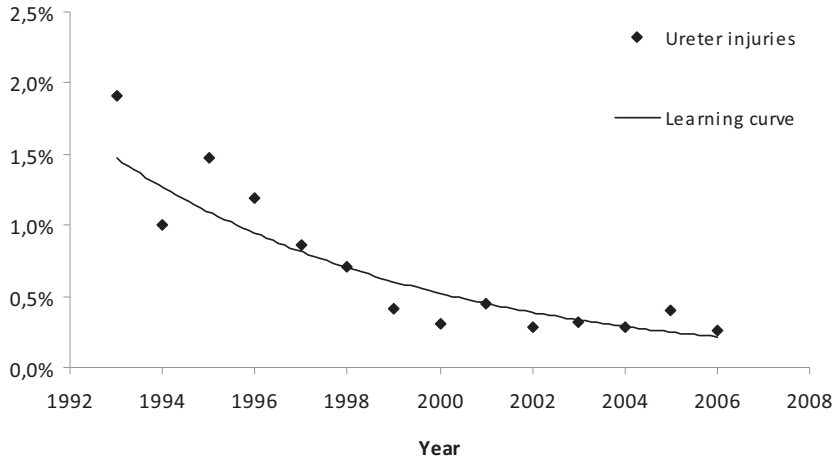

Figure 14 *National LH learning curve (1993-2006) based on ureter injuries reported to the Patient Insurance Centre.* *The likelihood ratio test for the model is statistically significant ($\chi 2=49.68$, $p<0.001$).*

Gastrointestinal injuries

According to the Patient Insurance Centre data, for the bowel injuries in LH, no significant reduction was observable between 1992-1999 and 2000-2006 (0.1% for both, Table 19). The bowel injuries in LH from the Patient Insurance Centre in 2000-2006 were 15, in 14 patients: Only one patient had a small-intestine injury recognised intraoperatively, but she later underwent a reoperation with a Hartmann procedure, due to an unrecognised perforation of the sigmoid colon. Of the 15, small-intestine injuries were seven, large-intestine injuries were eight, and five of them were complicated with fistulation presenting with vaginal faecal excretion. Reoperations to repair small-intestine injury occurred on the median third postoperative day (range 1-9). One case of a rectovaginal fistula was not diagnosed until 3 months postoperatively; otherwise reoperations to repair large intestine injury occurred on the median fourth postoperative day (range 3-17).

All intraoperatively recognised bowel injuries of FINHYST in 2006 were left unreported to the Patient Insurance Centre, whereas the postoperatively diagnosed bowel injuries, both occurring with LH, were present there (Table 21). In FINHYST, of 12 injuries, a total of 10 (83%) were recognised intraoperatively (Table 21), and no stoma surgery was necessary. In one case occurring with AH, a resection of the injured cecum was performed concomitant to appendectomy. Bowel injuries of LH not reported to the Patient Insurance Centre totalled five;

laparoconversion for suturing of the lesion had been necessary twice, two cases were sutured laparoscopically, and once no specific treatment was needed for a serosa lesion. The two postoperatively detected bowel injuries in LH were both perforations of the rectosigmoid colon, with sigmoideostomy performed on the fourth postoperative day. One had a Hartmann operation with stoma reversal within 3 months. The other case with deep endometriosis was complicated by a rectovaginal fistula. An attempt to close the sigmoideostomy at 3 months was unsuccessful, resulting in resection of the rectosigmoid. Furthermore, due to an infection, after 9 days a third reoperation was performed resulting in a transversotomy; finally, stoma reversal at 7 months was successful.

In the logistic regression model analysing all hysterectomies together, adhesiolysis appeared as a significant risk factor for bowel injury (OR 29.07, 95% CI 7.17-117.88, $p<0.001$). In LH, of 99 with adhesiolysis, injuries occurred in 5 (5.1%; OR 56.45, 95% CI 5.96-534.82, $p<0.001$), whereas in those without adhesions, cases were 2 (0.1%).

Venous thromboembolism

No DVTs were reported to FINHYST in 2006. Only two cases of PE were reported; both diagnosed prior to discharge (Table 21). A third actual case, also diagnosed at index hospitalisation, occurred after an injury to the iliac vessels; this case emerged from the Patient Insurance Centre files (Table 18).

Because of concern over missing cases, VTEs were requested from the HDR in THL for ICD-10 codes I80, I82, and I26 within the postoperative range of 3 months involving hysterectomies performed in 2006. With hysterectomy for benign disease, VTEs requiring hospital ward treatment were nine in total: six PEs and three DVTs. Four of the PEs occurred with AH, and two with VH; of these, both VH cases and half of those with AH appeared within FINHYST recruits. One of the three DVTs occurred with VH, and two with LH; both were in FINHYST. Hence six of the nine VTE cases in HDR occurred in women recruited to FINHYST, representing 79.4% of national operations.

In addition, with hysterectomies for benign indications, the HDR out-patient data revealed seven cases (ICD-10 codes) of VTE without any hospital ward treatment for VTE (cases from the emergency room only). Six of the seven were FINHYST recruits, and verification from hospital files showed that in reality all had been at the level of suspicion only, with negative ultrasonography or spiral CT examinations. Thus, including the inpatient i.e. hospital ward discharge data only, the register-based national one-year incidence of VTE after hysterectomy for benign disease was 0.1% (9 / 6 645). In comparison with this 0.1%, the HDR inpatient VTE incidence of hysterectomy for gynaecologic malignancies in 2006 was over ten-fold: 1.3% (15 / 1 112, $p<0.001$).

All six FINHYST VTE cases had some or several predisposing factors: Age of 60 or over, obesity, prolonged bedrest, thrombophilia, or excessive surgery; a case of iliac vein injury

developed a DVT on the injured side. All six had received LMWH, some of them for a very short period only.

Major vascular injury

The Patient Insurance Centre data on major complications of LH in 2000-2006 provided only a single major vascular injury, occurring within FINHYST in 2006 (Tables 19 and 21). This entry-related injury was preceded by multiple attempts to place the Veress needle and the umbilical trocar; the conventional instruments had been replaced with longer ones. Both the left common iliac artery and vein were punctured, and the estimated bleeding in the 8-hour 10-min laparotomy operation was 25 000 ml. In particular, from the venous side bleeding was severe; use of haemostatic patches and agents and multiple sutures were necessary. A venous thrombosis at the popliteal level was diagnosed prior to discharge. When this 54-year old patient was readmitted after a month with symptoms of ileus, a CT scan showed iliac and femoral veins being obliterated with thrombosis, despite warfarin treatment. The venous return of the lower extremity was suspected to be permanently impaired.

Bleeding complications

Operative bleeding complications

In contrast to that major vascular injury reported also to the Patient Insurance Centre (Tables 19 and 21), operative bleeding complications in FINHYST include other (minor) vascular injuries, and operative haemorrhage of 1000 ml or more. Four injuries of the epigastric inferior arteries appeared with LH (0.2%). With VH, two unintended unilateral salpingo-oophorectomies due to bleeding were reported.

Operative haemorrhage of 1000 ml or more occurred in AH for 72 (5.7%), in LH for 50 (3.0%), and in VH for 37 (1.6%). Differences between hysterectomies evened out with the adjusted analysis; the lowered results for the less invasive methods were non-significant. Overall, uterine size of 500 g or more was a risk factor (OR 2.93, 95% CI 1.88-4.58, $p<0.001$). In AH, 37 (10.2%) cases of operative haemorrhage of 1000 ml or more occurred in university hospitals, but 25 (4.1%) in central and 10 (3.5%) in local hospitals (OR 0.42, 95% CI 0.24-0.74, $p=0.003$ and OR 0.31, 95% CI 0.41-0.71, $p=0.006$, respectively). The uteruses removed in university clinics were larger than were those removed in other hospitals (mean weight 479 g vs. 413 g, $p=0.016$).

Similar to that observed for haemorrhage as a general phenomenon (Figure 11), fewer cases of operative haemorrhage of 1000 ml or more occurred in older age, except in LH (Table 22). In VH, the trend was similar both for those operated on for prolapse and for others. Taking all

hysterectomies together, risk for operative haemorrhage of 1000 ml or more in comparison to risk in those aged less than 45 was reduced for both the older age-groups (age 45-54; OR 0.52, 95% CI 0.35-0.76, p=0.001, and age 55 or more; OR 0.31, 95% CI 0.17-0.56, p<0.001). With LH and VH, the more overweight the patients, the higher the incidence of operative haemorrhage of 1000 ml or more. In AH, however, operative haemorrhage of 1000 ml or more was similarly frequent in those of normal weight.

Thrombosis prophylaxis had no significant effect on operative bleeding complications, but timing of prophylaxis initiation (pre- or postoperative) was unknown.

Table 22. *Operative haemorrhage of 1000 ml or more by patient characteristics uterine size 500g or more, age and BMI. (Statistically significant in bold.)*

	AH n / N	%	LH n / N	%	VH n / N	%
Uterine size 500 g or more	34 / 365	9.3	11 / 80	13.8	2 / 40	5.0
Adjusted OR (95% CI)	**2.76 (1.52-5.02)**		**5.47 (2.51-11.95)**		1.91 (0.38-9.57)	
P	**<0.001**		**<0.001**		0.043	
Age						
Under 45	30 / 289	10.4	39 / 470	2.3	20 / 471	4.2
45 to 54	31 / 682	4.5	62 / 850	3.5	14 / 810	1.7
55 or over	11 / 284	3.9	12 / 359	2.5	3 / 1064	0.3
Adjusted OR (95% CI)*	0.96 (0.92-1.00)		0.99 (0.95-1.04)		**0.90 (0.86-0.95)**	
P	0.058		0.830		**<0.001**	
Body mass index (BMI)						
Normal weight (under 25.0)	23 / 476	4.8	20 / 737	2.7	11 / 983	1.1
Overweight (25.0-29.9)	25 / 427	5.9	11 / 569	1.9	12 / 865	1.4
Obese (30.0-34.9)	12 / 203	5.9	13 / 247	5.3	8 / 339	2.4
Extremely Obese (35.0 or over)	6 / 108	5.6	4 / 68	5.9	6 / 91	6.6
Adjusted OR (95% CI)*	1.02 (0.97-1.07)		**1.06 (1.00-1.13)**		**1.09 (1.03-1.16)**	
P	0.408		**0.038**		**0.003**	

*Results of logistic regression analysis below each frequency table are based on the original values, not on the categorized values, of the variables. In the logistic regression model age and BMI were applied linear, thus, results are presented as average adjusted odds ratio for one year increase in age, and as average adjusted odds ratio for one unit increase in BMI.

Postoperative bleeding complications

With LH in 2000-2006, most of the reoperations occurring for cause other than organ injury were due to postoperative haemorrhage: 24 of 33 (Table 18). In FINHYST in 2006, as well,

postoperative haemorrhage was the single most common reason for a reoperation (Table 21). No significant differences appeared in postoperative bleeding complications by type of hysterectomy (Table 23), but haematomas discovered after discharge were not collected as distinguished from abscesses, as the definition of pelvic infections included both. For appearance of pelvic infections, those undergoing LH and VH were at risk, in comparison to AH (see Infections; Table 26). By indication for hysterectomy, actual postoperative haemorrhage or haematomas occurred in LH for adnexal mass in 6.4% (OR 4.76, 1.52-14.91, p=0.007) and in VH for menorrhagia in 5.2% (OR 3.97, 1.37-11.56, p=0.011). In VH, 39 cases of postoperative haemorrhage or haematoma occurred in university hospitals (5.4%), but 13 in both central (1.4%), and local (2.0%) hospitals (OR 0.22, 95% CI 0.11-0.43, p<0.001, and OR 0.33, 95% CI 0.17-0.65, p=0.001).

Table 23. *Postoperative haemorrhage complications occurring in FINHYST in 2006; logistic regression for comparison of hysterectomy methods.*

	Major	Minor	Total		AH as reference group for LH and VH				VH as reference group for LH and AH			
	n	n	n	%	Adjusted OR	95% CI		P	Adjusted OR	95% CI		P
Early-onset postoperative haemorrhage or haematoma (any location, at index hospitalisation)												
AH	21	12	33	2.6	1.00				0.79	0.44	1.40	0.413
LH	25	20	45	2.7	0.87	0.52	1.44	0.577	0.68	0.42	1.10	0.118
VH	35	30	65	2.8	1.27	0.72	2.26	0.413	1.00			
Late-onset postoperative haemorrhage (vaginal, after discharge)*												
AH	-	-	-	0.0								
LH	9	5	14	0.8								
VH	1	4	5	0.2								
Total of early- and late-onset												
AH			33	2.6	1.00				0.81	0.46	1.43	0.469
LH			59	3.5	1.12	0.69	1.82	0.657	0.91	0.58	1.42	0.670
VH			68†	2.9	1.23	0.70	2.17	0.469	1.00			

"Major" refers to operatively treated cases.

* derived from the form for late-onset complications, "complication other, with description"

† In two patients, bleeding occurred twice

Patient characteristics, too, affected occurrence of postoperative haemorrhage or haematoma. Analysing all hysterectomies together, those aged 55 or more had half the risk of those aged less than 45 (OR 0.49, 95% CI 0.26-0.89, p=0.020). Results by type of hysterectomy are presented in

Table 24. In VH for indications other than prolapse, for the youngest the incidence was highest (under 45; 5.6%; 45 to 54; 3.0%; 55 or over; 1.0%), and the risk rose on average by 8.8% per year (2.0-15.1%, p=0.012), (Study IV).

In AH, those overweight and obese had fewer postoperative haemorrhages or haematomas; the extremely obese had none. A one-unit rise in BMI reduced this risk on average by 17.0% (8.3-25.0%), (Table 24).

Table 24. *Postoperative haemorrhage or haematoma (early-onset) occurrence by patient characteristics: descriptive data categorised by age and BMI. Results from logistic regression presented as average adjusted odds ratio for one year increase in age, and as average odds ratio for one unit increase in BMI. (Statistically significant in bold.)*

	AH n / N	%	LH n / N	%	VH n / N	%
Age						
Under 45	3 / 289	1.0	17 / 470	3.6	22 / 471	4.7
45 to 54	24 / 682	3.5	21 / 850	2.5	27 / 810	3.3
55 or over	6 / 284	2.1	7 / 359	1.9	6 / 1064	1.5
Adjusted OR (95% CI)	1.00 (0.95-1.05)		0.97 (0.92-1.01)		**0.97 (0.94-1.00)**	
P	0.919		0.180		**0.044**	
Body mass index (BMI)						
Normal weight (under 25.0)	23 / 476	4.8	26 / 737	3.5	36 / 983	3.7
Overweight (25.0-29.9)	8 / 427	1.9	13 / 569	2.3	18 / 865	2.1
Obese (30.0-34.9)	2 / 203	1.0	2 / 247	0.8	8 / 339	2.4
Extremely obese (35.0 or over)	0 / 108	0.0	2 / 68	2.9	3 / 91	3.3
Adjusted OR (95% CI)	**0.83 (0.75-0.92)**		0.95 (0.88-1.02)		0.97 (0.91-1.03)	
P	**<0.001**		0.161		0.256	

In the logistic regression model age and BMI were applied linear. Results of logistic regression analysis below each frequency table are based on these original values, not on the categorized values, of the variables.

Thrombosis prophylaxis

Thrombosis prophylaxis (TP) was defined as pharmaceutical only. TP was given to 64.8% in total (3420 of 5279, Table 25), and identified as LMWH in 97% (3313); 3% (107) left unidentified. Exact drug and dosage were indicated for 54% (1792) of those given LMWH. Enoxaparine (1097, 61%) was more frequently used than dalteparine (695, 39%). A majority of 57% (1023) received a lower daily dose equivalent (enoxaparine 20 mg or dalteparine 2500 international units, IU), higher doses (40 mg or 5000 IU) were given to 41% (742). Even higher doses or combinations of varying daily doses were reported for 27. Among those receiving the

higher daily dose, a minority of 115 (15%) had received it divided into 12-h intervals; most (13%) on the day of surgery only. Specifically the initiation, pre- or postoperative, was not recorded on the study form. Thus, results on use of TP not affecting operative bleeding complications should be interpreted with caution (Study IV); although most seem to have received a lower dose, postoperative initiation may well predominate. Duration was reported for 44% (1445), among whom extended duration – LMWH continued after discharge – applied to 172 (5.2% of the 3313 given LMWH). TP use increased with age. With those aged over 60, in AH and in VH, 88.5% and 80.5% received TP, but in LH, 66.8%. A similar trend appeared for the obese: the higher the BMI, more frequent the use of TP (Study IV).

All use of TP was analysed as a whole (categorical variable, given vs. not given), irrespective of LMWH product or dosage. Among all hysterectomies, postoperative haemorrhage or haematoma associated significantly with use of TP (OR 2.00, 95% CI 1.34-3.00, p<0.001). By type of hysterectomy, this appeared with AH, but not with LH, or with VH (all indications), for which the result was only close to significance (Table 25). With VH for prolapse, TP raised significantly the odds for postoperative haemorrhage. With all hysterectomies together, appearance of a postoperative transfusion, not listed as an actual complication, was associated independently with TP (OR 1.74, 95% CI 1.16-2.59, p=0.007), by type of hysterectomy in AH only (OR 3.34, 95% CI 1.41-7.88, p=0.006).

Table 25. *Pharmaceutical thrombosis prophylaxis (TP) and logistic regression analysis results for associations of TP and early-onset postoperative haemorrhage or haematoma.*

	AH	LH	VH	VH prolapse	VH other
TP given n (%)	902 (71.9)	998 (59.4)	1520 (64.8)	1049 (73.2)	471 (51.6)
Days on TP, mean (SD), maximum	4.3 (2.8), 30	3.0 (2.8), 35	3.2 (2.9), 30	3.3 (2.7), 30	2.9 (3.2), 30
Postoperative haemorrhage or haematoma					
n (%)	33 (2.6)	45 (2.7)	65 (2.8)	31 (2.2)	34 (3.7)
in TP given n/N (%)	28 / 902 (3.1)	30 / 998 (3.0)	45 / 1520 (3.0)	28 / 1049 (2.7)	17 / 471 (3.6)
in TP not given n/N (%)	5 / 353 (1.4)	15 / 681 (2.2)	20 / 825 (2.4)	3 / 384 (0.8)	17 / 441 (3.9)
Adjusted OR	**2.87**	1.67	1.81	**4.82**	1.11
(95% CI)	**(1.03-7.98)**	(0.82-3.40)	(0.99-3.29)	**(1.38-16.83)**	(0.50-2.46)
P	**0.043**	0.157	0.053	**0.014**	0.798

Infections

Infections comprise postoperative infections occurring at index hospitalisation, and late-onset infections occurring after discharge that are diagnosed and treated at the outpatient clinics of hospitals. Most wound infections were late-onset (63%), as were 20% of urinary tract infections (UTI), and 22% of febrile events. Pelvic infections represent complications diagnosed only after discharge (100%). Results for risk factors are adjusted for various control variables such as use of antibiotic prophylaxis. Women who underwent AH were at higher risk for wound infections than were those who underwent LH or VH (Table 26). None of the 20 wound infections among the 2 345 VHs arose from conversions. As infections involving the site of the surgical closure in the vagina (the vaginal cuff) were not collected separately, some were apparently reported as wound infections instead of pelvic infections. To distinguish similarly cuff infections from wound infections of the skin for hysterectomy types other than VH would have been impossible; thus results are reported as is (Table 26).

Table 26. *Infections categorised; logistic regression for comparison of methods. (Statistically significant in bold.)*

Complication		n	%	AH as the reference group to LH and VH				VH as the reference group to LH and AH			
				Adjusted OR	95% CI		P	Adjusted OR	95% CI		P
Urinary infection	AH	28	2.2	1.00				1.47	0.66	3.27	0.345
	LH	11	0.7	**0.33**	**0.15**	**0.70**	**0.004**	0.48	0.21	1.12	0.090
	VH	36	1.5	0.68	0.31	1.51	0.345	1.00			
Wound infection	AH	30	2.4	1.00				**3.81**	**1.60**	**9.10**	**0.003**
	LH	25	1.5	**0.46**	**0.25**	**0.86**	**0.014**	1.77	0.78	4.03	0.172
	VH	20	0.9	**0.26**	**0.11**	**0.63**	**0.003**	1.00			
Febrile event	AH	32	2.5	1.00				1.51	0.74	3.07	0.258
	LH	23	1.4	**0.50**	**0.27**	**0.91**	**0.023**	0.75	0.38	1.49	0.407
	VH	22	0.9	0.66	0.33	1.35	0.258	1.00			
Pelvic infection (haematoma or abcess)	AH	10	0.8	1.00				**0.19**	**0.08**	**0.41**	**<0.001**
	LH	54	3.2	**5.08**	**2.45**	**10.54**	**<0.001**	0.94	0.59	1.50	0.799
	VH	51	2.2	**5.40**	**2.46**	**11.89**	**<0.001**	1.00			
Infections total*	AH	97	7.7	1.00				1.14	0.78	1.66	0.493
	LH	113	6.7	0.84	0.61	1.16	0.287	0.96	0.69	1.34	0.812
	VH	122	5.2	0.88	0.60	1.28	0.493	1.00			

* A patient may have had more than one complication. Infections total comprise urinary infections, wound infections, febrile events for unknown reason, and pelvic infections, or a combination of these. Data include both early- and late-onset infectious morbidity.

Undergoing AH was also an independent risk factor for febrile events and UTIs, in comparison with LH. No significant differences in any complication arose between LH and VH. The only category, in which the minimally invasive methods of LH and VH presented a higher risk than did AH, was pelvic infection (Table 26). Half of the pelvic infections of AH required a reoperation, but in LH and VH, only 13.0% and 17.6%. Thus, the incidence of pelvic infection in need of surgical treatment was the same with all hysterectomy types: 0.4%.

The characteristics of the patients affected occurrence of infections: Particularly the young and the obese had higher rates (Table 27). In VH, pelvic infection occurred less commonly with uterine prolapse, in comparison with all other indications together (1.2% vs 3.7%, p<0.001; adjusted for uterine weight in linear OR 0.31, 95% CI 0.14-0.70, p=0.004). A descending trend for pelvic infection by the pre-, peri-, and postmenopausal age categories of the study were observable in LH (4.5% - 3.6% - 0.6%) and in VH (4.0% - 2.3% - 1.2%). In LH, total infections were not affected (Table 27), but febrile events, occurring in 0.4% for those normal weight, were significantly increased for the overweight and the obese (2.1% and 2.4%; OR 5.49, 95% CI 1.51-19.91, p=0.010 and OR 7.70, 95% CI 1.83-32.43, p=0.005).

Table 27. *Total infections by patient characteristics. Results for logistic regression with characteristics categorised, for AH, LH, and VH separately.* *(Statistically significant in bold.)*

	AH n / N	%	LH n / N	%	VH n / N	%
Age						
Under 45	20 / 289	6.9	39 / 470	8.3	36 / 471	7.6
45 to 54	52 / 682	7.6	62 / 850	7.3	45 / 810	5.6
Adjusted OR (95% CI)	0.93 (0.51-1.68)		0.97 (0.62-1.53)		0.79 (0.49-1.28)	
55 or over	25 / 284	8.8	12 / 359	3.3	41 / 1064	3.9
Adjusted OR (95% CI)	0.85 (0.40-1.78)		0.57 (0.26-1.24)		0.57 (0.32-1.04)	
Body mass index (BMI)						
Normal weight (under 25.0)	21 / 476	4.4	44 / 737	6.0	40 / 983	4.1
Overweight (25.0-29.9)	45 / 427	10.5	41 / 569	7.2	47 / 865	5.4
Adjusted OR (95% CI)	**2.79 (1.61-4.81)**		1.29 (0.82-2.00)		1.50 (0.97-2.33)	
Obese (30.0-34.9)	21 / 203	10.3	17 / 247	6.9	22 / 339	6.5
Adjusted OR (95% CI)	**2.41 (1.27-4.56)**		1.22 (0.68-2.21)		**1.77 (1.03-3.05)**	
Extremely Obese (35.0 or over)	9 / 108	8.3	4 / 68	5.9	10 / 91	11.0
Adjusted OR (95% CI)	1.84 (0.80-4.24)		1.17 (0.40-3.45)		**2.68 (1.26-5.71)**	

Taking all hysterectomies and infections together, patients aged 55 or older were at a lowered risk compared to those aged less than 45 (OR 0.66, 95% CI 0.47-0.79, p<0.001). For each BMI group, the risk gradually increased (Study III), and was nearly doubled for the extremely obese (OR 1.82, 95% CI 1.13-2.95, p=0.014). Particularly wound infections in AH were observed more often in women with a BMI other than normal: of the 427 overweight in 15 (3.5%) (OR 5.49, 95% CI 1.74-17.30, p=0.004) and of the 309 obese in 8 (3.9%) (OR 5.04, 95% CI 1.44-17.64, p=0.011), compared to 4 (0.8%), of the 517 of normal weight. In AH, infections associated significantly also with adhesiolysis and with concomitant surgery (Study III), and occurred more frequently in university hospitals (9.1%, 33 of 363) than in central (7.6%, 46 of 603; OR 0.59, 95% CI 0.35-0.99, p=0.045), or local hospitals (6.0%, 17 of 283; OR 0.47, 95% CI 0.24-0.91, p=0.025). For wound infections, results in favour of other than university clinics were similar.

Febrile events more commonly involved gynaecological surgeons with experience less than 30 LHs (2.4%, 9 of 382, OR 2.66, 95% CI 1.06-6.69, p=0.038), compared to those with experience of more than 30 LHs (1.1%, 13 of 1230). This was the only study outcome in which experience less than 30 hysterectomies of a particular type was associated with a complication. Operation time was faster for the more experienced LH surgeons (101 vs. 130 min, p<0.001). Duration of the operation was not included in the conventional model used in analysis of all complications, including intraoperative ones. A model in the context of antibiotic prophylaxis specifically analysed duration (Study V), and in LH its increase was associated with appearance of infections overall; the association was strongest for the febrile events.

Antibiotic prophylaxis

Antibiotic prophylaxis (AP) was given to 97.5% (5 111 of 5 240); with AH to 96.3%, LH to 98.3%, and VH to 97.7% (Figure 15, flowchart of AP). In the subtotal AH, AP was used less often, for 92.9% (79 of 85). Infections in total were fewer in those given AP (6.1%, 311 of 5 111), compared to those not given AP (11.6%, 15 of 129, p=0.010). The number needed to treat (NNT) was 19. With logistic regression adjusted for the control variables, and also duration of operation, the risk for infection with all hysterectomies together with any AP fell to less than one half (adjusted OR 0.41, 95% CI 0.23 – 0.73, p=0.002).

Exact cefuroxime dosage was reported for a total of 38% of those receiving it (1 647 of 4 301). The vast majority reported cefuroxime preoperatively at induction as a single 1.5-g IV dose. Extended prophylaxis (in 3 cases one, in 11 cases two extra doses) and miscellaneous dosages of 750 mg, 1 g, or 2 g (8 in total) were rare. Exact metronidazole dosage was reported for a total of 24% of those given it (680 of 2 855), usually 0.5 g IV at induction; 8 had received a 1-g IV dose. Per oral and vaginal administration was rare, in 2.2% (64) and 1.5% (42), usually at doses of 2 g and 0.5 g. The group “other antibiotic” of 180 patients comprised 18 different antimicrobial drugs, used alone or in combination; clindamycin (52), and per oral cefalexin (38) most commonly.

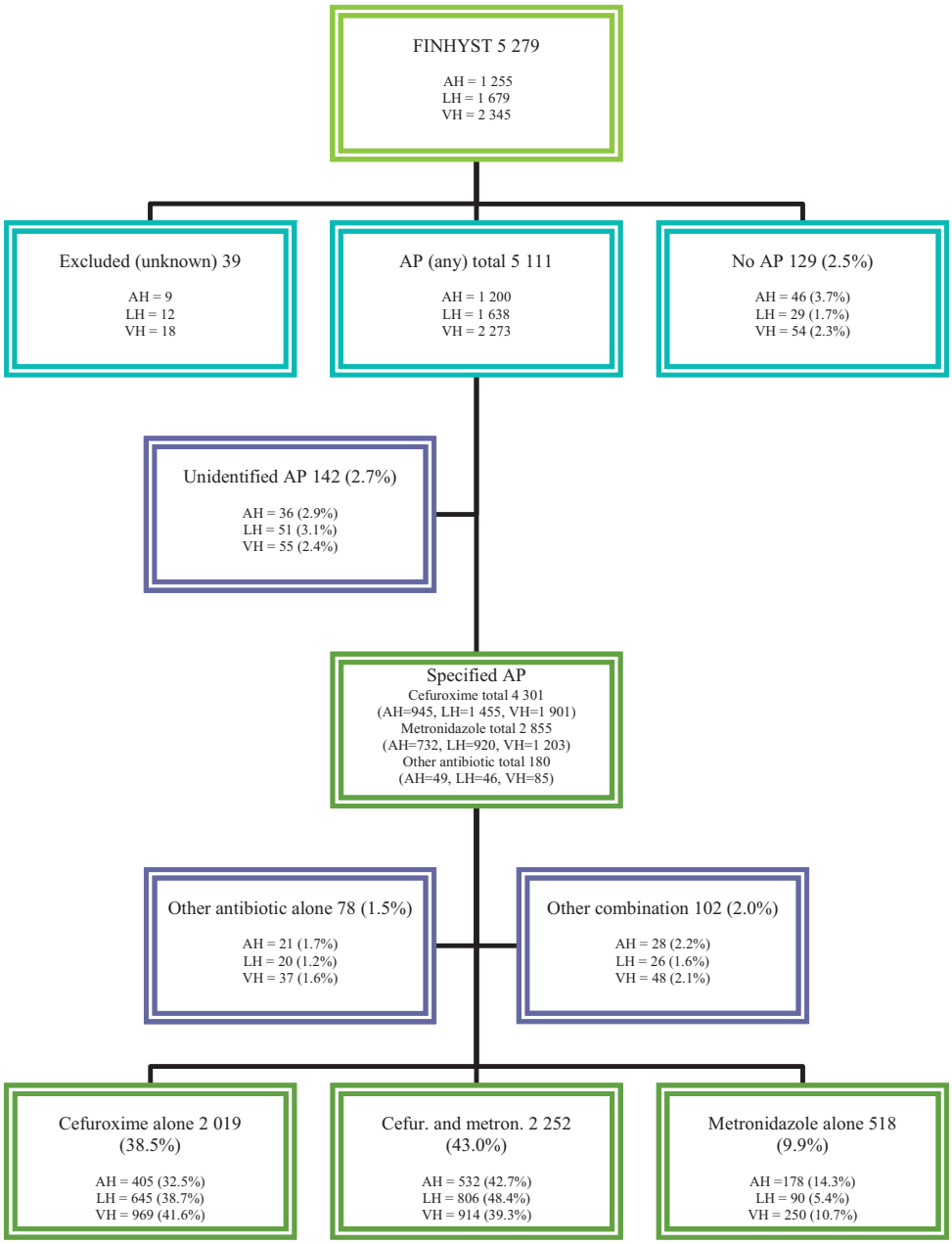

Figure 15 *Flowchart of antibiotic prophylaxis (AP) with numbers (%) indicated for all hysterectomies, then per type of hysterectomy (AH, LH, VH).*

Table 28. *Infection complications by antibiotic prophylaxis.* (*For values for cefuroxime alone, metronidazole alone, or their combination, use of other miscellaneous antibiotics was excluded.)*

	Total	Infections, total*		Febrile event		Wound infection		Pelvic infection		UTI	
	N	n	%	n	%	n	%	n	%	n	%
AH											
Antibiotic, any	1200	94	7.8	31	2.6	28	2.3	10	0.8	28	2.3
No antibiotic	46	3	6.5	1	2.2	2	4.3	-	0.0	-	0.0
Metronidazole alone	178	27	15.2	9	5.1	10	5.6	2	1.1	7	3.9
Cefuroxime alone	405	28	6.9	6	1.5	7	1.7	6	1.5	10	2.5
Combination of cefur. and metron.	532	31	5.8	14	2.6	6	1.1	2	0.4	10	1.9
LH											
Antibiotic, any	1638	106	6.5	22	1.3	23	1.4	52	3.2	9	0.5
No antibiotic	29	3	10.3	-	0.0	2	6.9	-	0.0	1	3.4
Metronidazole alone	90	13	14.4	6	6.7	1	1.1	4	4.4	2	2.2
Cefuroxime alone	645	37	5.7	6	0.9	7	1.1	22	3.4	2	0.3
Combination of cefur. and metron.	806	50	6.2	8	1.0	15	1.9	22	2.7	5	0.6
VH											
Antibiotic, any	2273	111	4.9	19	0.8	17	0.7	47	2.1	35	1.5
No antibiotic	54	9	16.7	2	3.7	3	5.6	4	7.4	-	0.0
Metronidazole alone	250	31	12.4	9	3.6	3	1.2	15	6.0	6	2.4
Cefuroxime alone	969	38	3.9	5	0.5	8	0.8	15	1.5	12	1.2
Combination of cefur. and metron.	914	35	3.8	4	0.4	5	0.5	13	1.4	14	1.5

* A patient may have had more than one complication. Infections total comprise urinary infections, wound infections, febrile events for unknown reason, and pelvic infections, or a combination of these. Data include both early- and late-onset infectious morbidity.

Cefuroxime had a risk-reducing effect for total infections with all hysterectomy methods (Table 29), whereas the independent effect of metronidazole, or the interaction effect of cefuroxime and metronidazole were both non-significant. Hence although the lowest absolute rate of infections occurred with a combination of cefuroxime and metronidazole for AH and VH (Table 29), no statistically significant additional risk-reducing effect with metronidazole occurred.

Subgroup analyses for individual infection complications were performed for those given the two main antibiotics only, with miscellaneous other antibiotics excluded from analyses. Cefuroxime alone or metronidazole alone was compared to their combined use: For all types of

infections, the effect of cefuroxime alone was non-significantly different from that of cefuroxime and metronidazole in combination. In contrast, metronidazole given alone compared to its use in combination with cefuroxime led to an increased risk for total infections in AH (adjusted OR 3.63, 95% CI 1.99-6.65), in LH (OR 3.53, 95% CI 1.74-7.18), and in VH (OR 4.05, 95% CI 2.30-7.13), similarly for febrile events (OR 2.86, 95% CI 1.09-7.46; OR 13.19, 95% CI 3.66-47.49 and OR 12.74, 95% CI 3.01-53.95, respectively), for wound infections in AH (OR 6.88, 95% CI 1.09-7.49), and pelvic infections in VH (OR 4.26, 95% CI 1.76-10.31).

Table 29. *Independent effect of categorised antibiotic prophylaxis for total infections. (Statistically significant in bold.)*

	AH		LH		VH		ALL	
	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Cefuroxime	**0.33**	**0.20 - 0.56**	**0.34**	**0.19 - 0.63**	**0.21**	**0.13 - 0.33**	**0.29**	**0.22 - 0.39**
Metronidazole	0.97	0.58 - 1.62	1.21	0.73 - 1.99	0.75	0.47 - 1.19	0.95	0.72 - 1.24
Other, miscellaneous	0.89	0.31 - 2.45	0.60	0.18 - 1.97	**0.26**	**0.08 - 0.87**	**0.53**	**0.28 - 0.99**

The interaction of cefuroxime and metronidazole was non-significant for all analyses.

Duration of surgery was associated independently with the appearance of infections: The odds for wound infection in AH rose by an average of 13.3% per 10 min (95% CI 0.1-28.3%, p=0.048). In LH, the risk for total infections rose by 6.1% per 10 min (95% CI 0.4-12.1%, p=0.042) with the strongest effect emerging for febrile events: by 12.5% per 10 min (95% CI 0.4-26.0%, p=0.042). The estimated probabilities for appearance of infections in total are presented graphically for cefuroxime and metronidazole (Figure 16). LH mean duration was 1 h 48 min (Table 13). With cefuroxime, compared to the infection rate estimated for the mean duration (6.3%), at 3 h, the estimated rate was 1.5-fold (9.4%) (Figure 16).

A comparison of AP in 2006 to that in a similar national study a decade previously (Mäkinen et al 2001) showed AP overall had become more common, as the coverage increased from 82.1% to 97.5%. Moreover, the predominance of metronidazole in 1996 shifted to cefuroxime in 2006 (Figure 17).

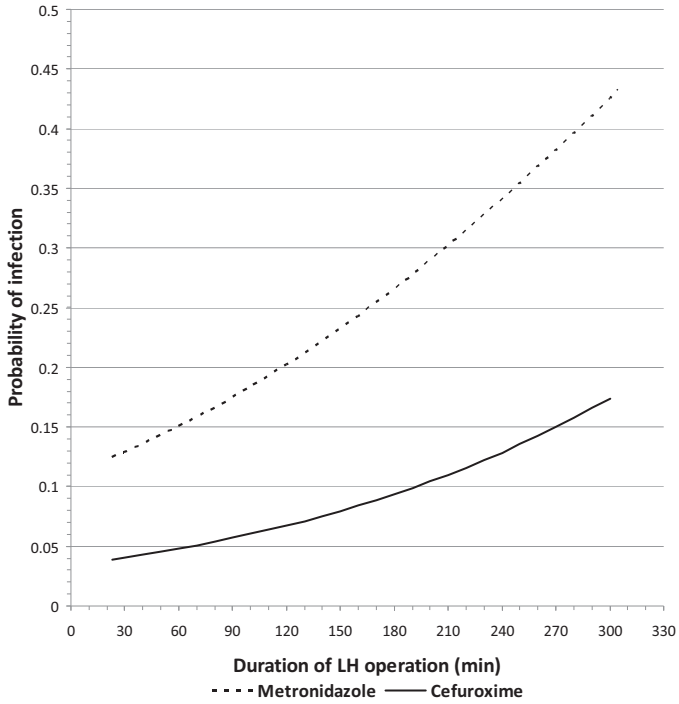

Figure 16 *Estimated probabilities of infection associated independently with the effect of cefuroxime and metronidazole, as a function of duration of the laparoscopic hysterectomy (LH), in a logistic regression analysis adjusted for confounders.*

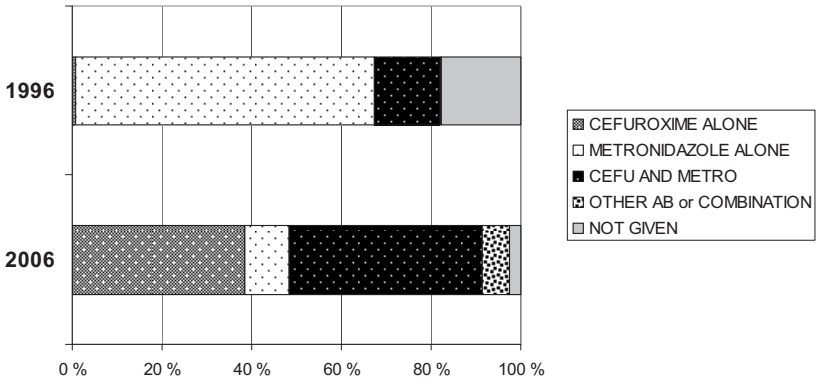

Figure 17 *Antibiotic prophylaxis in 2006 compared to rates in 1996. (Previously unpublished data, printed with permission of the guarantor of the study (Mäkinen et al 2001). In fact, in 1996, instead of "metronidazole", the data were collected as "a nitroimidazole antibiotic".)*

Summary of complications

Overall, in FINHYST in 2006, complications occurred in AH for 241 women (19.2%), in LH for 258 (15.4%), and in VH for 275 (11.7%). Different complications in total were 270 with AH, 288 with LH, and 316 with VH. Complications comprise intraoperative, or postoperative early and late complications – major complications, haemorrhagic events, and infections are presented separately (see Contents). Apart from these, ileus occurred most frequently in AH (1.1%) and urinary retention in VH (1.6%) (Study III). Sporadic postoperative complications reported were for example angina pectoris, nerve distension of the upper extremity, pneumonia, and postdural puncture headache; such miscellaneous complications are all included under total complications.

In analysis of total complications with logistic regression, no statistically significant differences emerged between the three hysterectomy methods. Complications were associated with adhesiolysis, uterine size of 500 g or more, concomitant surgery, and thrombosis prophylaxis. Age over 55 reduced risk for a complication compared to age under 45 (Table 30).

Analysis by type of hysterectomy showed that in LH the risk factors for complications overall were adhesiolysis and uterine size of 500 g or more (Table 31).

In AH, complications were associated with adhesiolysis, large uterine size, thrombosis prophylaxis (Table 32), and concomitant surgery (Study III). In addition, complications were fewer for local and central hospitals, compared to university hospitals. The uteruses removed abdominally in university clinics were larger than uteruses removed in other than university hospitals (mean weight 479 g vs. 413 g, p=0.016).

In VH, patient characteristics significantly associating with complications were age of 45 or less, and extreme obesity. Complications were significantly reduced for local hospitals, compared to university hospitals (Table 33). No significant difference appeared in the mean weight of the uteruses removed vaginally as regards university clinics vs. other hospitals (134 g vs.129 g, p=0.338), or between local hospitals vs. other hospitals (131 g vs. 131 g, p=0.939). Antibiotic prophylaxis (AP) was related to reduced total complications; outcome specifically for infections and for type of AP is presented separately (Study V).

Because concomitant surgery differed considerably by type of hysterectomy (Table 17), it was handled as a categorical variable (yes/no), meaning one or several procedures performed, irrespective of which. Similarly as in AH, concomitant surgery was associated with total complications of VH (Study III). In VH, if AC and PC both were performed, a complication occurred in 12.4% (77 of 621); when PC was performed alone in 14.0% (22 of 147), but with AC alone in 8.8% (41 of 466). In a model adjusted for AC, enterocele repair, surgery for urinary incontinence, and concomitant procedures as “other”, overall complications of VH associated with PC (OR 1.50, 95% CI 1.08-2.09. p=0.015).

Table 30. *Predisposing factors for occurrence of complications overall: logistic regression model with all FINHYST hysterectomies together.* *See next page. (Statistically significant in bold. The model was also adjusted for indications, for which results were non-significant.)*

Table 30.	Adjusted OR	95% CI		P
Type of hospital				
University	1.00			
Central	0.86	0.71	1.03	0.109
Local	0.83	0.67	1.03	0.095
Private	0.65	0.25	1.67	0.373
Experience of the gynaecological surgeon				
More than 30 operations ever performed	1.00			
Less or equal to 30 operations ever performed	0.81	0.55	1.19	0.284
Patient age				
Under 45	1.00			
45 to 54	0.84	0.69	1.03	0.088
55 or over	**0.61**	**0.47**	**0.79**	**<0.001**
Body mass index				
Normal weight (under 25.0)	1.00			
Overweight (25.0-29.9)	1.10	0.92	1.32	0.304
Obese (30.0-34.9)	1.18	0.94	1.49	0.153
Extremely obese (35.0 or over)	1.38	0.99	1.92	0.060
Prior caesarean sections (CS)				
None	1.00			
One or more	0.93	0.74	1.17	0.554
Prior laparotomy (other than CS)				
None	1.00			
One or more	1.04	0.87	1.25	0.662
Prior laparoscopy				
None	1.00			
One or more	0.97	0.80	1.17	0.716
Adhesiolysis				
No	1.00			
Yes	**2.48**	**1.75**	**3.52**	**<0.001**
Concomittant surgery				
No	1.00			
Yes	**1.28**	**1.05**	**1.56**	**0.014**
Uterine size				
Under 500 g	1.00			
500 g or more	**1.60**	**1.12**	**2.28**	**0.009**
Antibiotic prophylaxis				
No	1.00			
Yes	0.67	0.45	1.01	0.057
Thrombosis prophylaxis				
No	1.00			
Yes	**1.25**	**1.04**	**1.49**	**0.015**
Type of hysterectomy*				
VH	1.00			
AH	1.20	0.92	1.57	0.179
LH	1.03	0.81	1.31	0.799

*With AH as reference (OR 1.00), LH was non-significant (OR 0.86 95% 0.69-1.07 p=0.169).

Table 31. *Risk factors in LH for complications overall; logistic regression model derived from total complications occurring with LH.*

	n/N	%	Adjusted OR	95% CI		P
LH complications, total	258 / 1679	15.4				
Uterine size 500 g or more						
No	238 / 1599	14.9	1.00			
Yes	20 / 80	25.0	1.83	1.06	3.16	0.030
Adhesiolysis						
No	233 / 1580	14.7	1.00			
Yes	25 / 99	25.3	1.69	1.00	2.84	0.049

Table 32. *Risk factors in AH for complications overall; logistic regression model derived from total complications occurring with AH.*

	n/N	%	Adjusted OR	95% CI		P
AH complications, total	241 / 1255	19.2				
Type of hospital						
University	80 / 363	22.0	1.00			
Central	112 / 603	16.0	0.67	0.47	0.96	0.028
Local	48 / 283	17.0	0.63	0.41	0.98	0.038
Private	1 / 6	16.7	0.90	0.10	8.09	0.923
Adhesiolysis						
No	207 / 1172	17.7	1.00			
Yes	34 / 83	41.0	4.45	2.58	7.67	<0.001
Uterine size 500 g or more						
No	160 / 890	18.0	1.00			
Yes	81 / 365	22.2	1.60	1.12	2.28	0.009
Thrombosis prophylaxis						
No	54 / 353	15.3	1.00			
Yes	187 / 902	20.7	1.50	1.05	2.16	0.026

Table 33. *Risk factors in VH for complications overall; logistic regression model derived from total complications occurring with VH.*

	n/N	%	Adjusted OR	95% CI		P
VH complications, total	275 / 2345	11.7				
Type of hospital						
University	95 / 721	13.2	1.00			
Central	106 / 942	11.3	0.77	0.56	1.05	0.097
Local	73 / 665	11.0	0.69	0.48	0.97	0.036
Private	1 / 17	5.9	0.39	0.05	3.11	0.377
Patient age						
Under 45	79 / 471	16.8	1.00			
45 to 54	97 / 810	12.0	0.66	0.47	0.93	0.017
55 or over	99 / 1064	9.3	0.45	0.30	0.68	<0.001
Body mass index *						
Normal weight (under 25.0)	105 / 983	10.7	1.00			
Overweight (25.0-29.9)	98 / 865	11.3	1.15	0.85	1.55	0.357
Obese (30.0-34.9)	44 / 339	13.0	1.28	0.87	1.87	0.209
Extremely obese (35.0 or over)	20 / 91	22.0	2.12	1.22	3.70	0.008
Antibiotic prophylaxis*						
No	11 / 54	20.4	1.00			
Yes	261 / 2273	11.5	0.46	0.24	0.86	0.016

*Sums may not be coherent with the total on the uppermost line, due to missing data.

In conclusion, results from the retrospective Patient Insurance Centre register were considerably lower than from the prospective FINHYST in 2006 (Table 34). In Finland, ureter injuries in LH were significantly reduced, and comparison to the study conducted a decade earlier showed a similar positive development also for bowel injuries in VH (Table 34). Antibiotic prophylaxis increased and generally was realised with a wider antimicrobial spectrum (Figure 20); consequently, infections were reduced, in VH in particular they were more than halved. In AH, overall complications increased. For LH, organ injuries in total were reduced, but reduction in overall complications was non-significant. For VH, in 2006 the rate of total complications was nearly half that of 1996 (Table 34).

Table 34. *Summary of results on complications (%). FINHYST in 2006 compared to a national prospective cohort on hysterectomies for benign disease in 1996 (Mäkinen et al. 2001, analysed and published with permission of the corresponding author).*

		Patient Insurance Centre		FINHYST	Mäkinen et al.	P
Year(s)		2000-2005	2006	2006	1996	1996 vs. 2006
Bladder injury, including VVF	AH		0.2	0.9	0.5	0.099
	LH	0.3	0.2	1.0	1.3	0.443
	VH		0.1	0.6	0.2	0.094
Ureter injury	AH		0.2	0.3	0.2	0.263
	LH	0.3	0.3	0.3	1.1	**0.003**
	VH		0.04	0.04	0.0	1.000
Bowel injury	AH		0.0	0.2	0.2	0.737
	LH	0.1	0.2	0.4	0.4	0.811
	VH		0.0	0.1	0.5	**0.013**
Organ injury total	AH		0.4	1.4	0.9	0.054
	LH	0.8	0.6	1.7	2.8	**0.032**
	VH		0.1	0.7	0.7	0.991
Major complications total	AH		1.0	4.0		
	LH	1.0	1.1	4.3		
	VH		0.4	2.6		
Infections total	AH			7.7	9.9*	**0.016**
	LH			6.7	8.3*	0.070
	VH			5.2	12.3*	**<0.001**
Complications total	AH			19.2	16.2*	**0.010**
	LH			15.4	17.0*	0.172
	VH			11.7	22.2*	**<0.001**

* Totals in 1996 given, parallel to the 2006 data, as rate of women with any complication (a patient may have had more than one complication; previously unpublished data).

DISCUSSION

Numbers of hysterectomies for benign disease in Finland have declined considerably. Up until 2002, annual numbers exceeded 10 000; only cataract surgeries and cesarean sections were more commonly performed on women. Since 2002, and up until 2007, hysterectomies declined gradually, but during the 4-year period 2007-2010, hysterectomies for benign disease remained stable at an average 5 750 per year. In 2010, hysterectomies overall still outnumbered mammary gland surgeries (partial excisions and mastectomies), and cholecystectomies performed on women, but no longer outnumbered some orthopaedic procedures: knee arthroscopic procedures (over 8 000), and prosthetic replacements of the hip or the knee joint (each over 7 000) (HDR 2011). The high hysterectomy rates were already attracting concern in the late 1980s, when regional variations as high as three-fold were observable in Finland (Keskimäki et al. 1994). The reduction most likely originates from the indications being considered more carefully, plus other treatment modalities, conservative and operative, that may have replaced the need for hysterectomies. A third possibility is that the actual need, the prevalence of the disease, has declined. Recent epidemiologic age-adjusted data comparing the Nordic countries in 2008 showed the rate of hysterectomies per 10 000 women in Finland to be currently similar to that of those other countries, being however, still the highest: 22.1, compared to 20.6 in Iceland, 20.9 in Denmark, 19.5 in Norway, and 16.9 in Sweden (NOMESCO 2010).

Interestingly, in most other Nordic countries, hysterectomy rates have remained relatively stable. Since the millennium, only the UK, Australia, and the Netherlands showed a trend similar to that of Finland, but their reduction has been less steep (Chapman and Magos 2006, Hill et al. 2010, Hanstede et al 2012). Finnish national guidelines for hysterectomies for the indications myomas, endometriosis, and menorrhagia were first released in 2005 (Ministry of Social Affairs and Health, Finland, 2010), but already prior to this, between 2000 and 2005, hysterectomies for benign disease declined by 26%. Compared to the national survey of 10 110 hysterectomies in 1996 (Mäkinen et al. 2001), in the current study, uteruses were larger in size with all hysterectomy methods, reflecting more careful consideration of surgical treatment. Simultaneously, the proportion of hysterectomies for prolapse increased to 28% in 2006, from a previous 8-17% (Table 1). Myomas as an indication declined from 55% in 1996 (Mäkinen et al. 2001), to 33% in 2006, but rates are not directly comparable due to differences in study design: In 1996, all pathology involved was reported with overlapping diagnoses, whereas in 2006 a single main indication was requested. Presumably myomas in FINHYST 2006 represent more those with bulk symptoms, whereas cases with predominant bleeding symptoms have mostly been included under the indication menorrhagia; yet dysfunctional uterine bleeding was not recorded in separate. Menorrhagia as indication, presumably more comparable between the decades, was considerably less common (21% in 2006 vs. 31% in 1996) and the actual number of hysterectomies for menorrhagia or dysfunctional bleeding declined by 64%: from 3 076 in 1996 to 1 113 in 2006. Excluding all 5 555 with myomas, in 1996 the number of patients operated on for menorrhagia or dysfunctional bleeding was 1 532 (unpublished data). For treatment of menorrhagia, data in support of LNG-UIS were already published four years prior the 2005 Current Care guideline (Hurskainen et al. 2001, The Current Care editorial office 2005). Such good results must have had an instant effect on hysterectomy numbers, declining

since 2002. LNG-IUS received marketing authorization in Finland as early as in 1990 (Fimea 2009). Apparently this treatment modality has gained wide interest: Sales, any indication included, increased from 1996 to 2006 by 74% (Bayer Schering Pharma Finland, personal communication with Leena Kaikkonen 2008).

Moreover, alternative surgical treatments must have had an effect. In Finland, embolization treatment for myomas has not yet gained popularity, and sporadic procedures most probably have had no noticeable effect on hysterectomy numbers. Endometrial destruction and myomectomy operations are more common, but numbers for these procedures have remained relatively stable. The great increase has occurred with operative hysteroscopy procedures (Figure 5), performed to remove pathology bulging into the uterine cavity: endometrial polyps and submucosal myomas. In 1997, operative hysteroscopies in Finland were less than 700, but a three-fold increase has occurred: Since 2002, the yearly average has been around 2 100 procedures. This trend has possibly been promoted by better routine ultrasonography diagnostics for pathology of the uterine cavity.

In Finland between 1987 and 1992 hysterectomies increased, particularly in the postmenopausal age-groups, and the cause was suspected to be use of hormone therapy which had increased rapidly during the previous decade (Topo et al. 1995, Vuorma et al. 1998). Not only is the endometrium affected by estrogens, a throphic effect also occurs in the myometrium, particularly for myomas (Lumsden 1992). More recently, use of hormone therapy has been affected by results from the Women's Health Initiative study (WHI), initially released in 2002 (Rossouw et al. 2002): In Finland use of HT between 2000 and 2005 decreased by 26% (Salmi et al. 2006); simultaneously with the number of hysterectomies. Nevertheless, direct causality cannot be drawn. For instance, in Norway, during the same period, HT decreased by 45% (Rønning 2006), but hysterectomy rates remained stable (Figure 1, NOMESCO database).

Women with a higher education have fewer hysterectomies than do women with less education, a trend observed in Finland, in the UK, in Australia, and in Sweden (Luoto et al. 1992, Byles et al. 2000, Ceausu et al. 2006, Cooper et al. 2008a). The reason why hysterectomy rates have been higher in the USA and in Finland may not be related to any lower educational level; more likely the phenomenon may be connected to the burden of obesity. In Finland the prevalence of obesity is high and increasing: in 2000-2001, 24.1% of women aged over 30 were obese, but 20 years previously, only 17.9%. This trend is similar in women with a high and a low education (Lahti-Koski et al. 2010). In the USA, in 2003-2004, 33.2% of women were obese (Ogden et al. 2006). In surveys conducted from 2000 onwards, the prevalence in most Western European countries has been lower: in the Netherlands 10%, in France 11%, in Sweden 16%, in Norway 21%, and in the UK 23% (Berghöfer et al. 2008). Hysterectomy risk and obesity are associated: In the UK population, from age 36 onwards, overweight women have higher hysterectomy rates than do those of normal weight, their risk for hysterectomy being 1.5-fold. The results were not explained by parity, age at menarche, or socio-economic position (Cooper et al. 2008b). Higher BMI has been associated with hysterectomy in Sweden, irrespective of educational level (Ceausu et al. 2006). In Finland in 1989, for women aged 45 to 64, the BMI of those who had undergone hysterectomy was significantly higher than for those with no hysterectomy (Luoto

1995). In the current study, the majority of patients were overweight at the time of surgery, and particularly those with endometrial hyperplasia were burdened with obesity.

Hysterectomy methods and surgery-related outcome

In Finland, among methods of hysterectomy for benign disease, annual numbers of VH exceeded AH in 2002, and LH exceeded AH for the first time in 2005. AH nowadays is reserved for larger uteruses; compared to the prospective national hysterectomy study in 1996 (Mäkinen et al. 2001), in a decade the mean weight of the abdominally removed uterus has increased by 50%. One review of RCTs with 4 495 women and 34 studies in total, comparing methods for hysterectomy for benign disease states VH should be performed in preference to AH when possible, and if VH is not possible, LH may avoid the need for AH (Nieboer et al. 2010). If these recommendations guided the national distribution of methods, in a way where VH should be most commonly performed, followed by LH – it seems Finland is the only country in the world to match these aims, as do the University clinics of Paris (David-Montefiore et al. 2007). Since the millennium, published data on national distribution of hysterectomy methods for benign disease are available for the Nordic countries, the USA, Australia, the Netherlands, Germany, and Taiwan. Although VH has gained popularity worldwide, The Netherlands and Germany, along with Finland, are the only countries in which VH is more commonly performed than AH (Stang et al. 2011, Hanstede et al 2012). Recent register data from the Nordic countries show that Finland continues to predominate in LH: The proportion of LHs in 2008 was 36% in Finland, whereas in Sweden 4%, in Denmark 5%, and in Norway 19% (NOMESCO 2010). For the latter, LSH is the preferred type (Lieng et al. 2010). In 2006, only 1.7% of hysterectomies in FINHYST were subtotal, but already a decade ago, the interest in cervical preservation was low (7.2%), (Mäkinen et al. 2001).

As hysterectomy is a common operation, the development towards greater popularity of minimally invasive methods has an important influence on society, as thousands of women after surgery recover and become active more quickly. The hospital stay after AH is longer. Moreover, the mean difference in return to normal activities after AH vs. LH was 15.2 days shorter in favour of LH. Likewise, after VH, return to normal activities was 9.5 days shorter than in AH (Nieboer et al. 2010). Similarly in FINHYST, in comparison with AH, mean sick leave for LH was 10.2 days shorter, and for VH for the non-prolapsed uterus, 7.2 days shorter. Comparing LH and VH, in the meta-analysis of RCTs, no difference occurred in hospital stay or in return to normal activities (Nieboer et al. 2010), but in FINHYST the average sick-leave was shorter for LH. Not only short-term surgical outcome should be considered; choice of method can also have long-term adverse effects. Adhesions are more common after laparotomy than after laparoscopy: After a history of only a single operation, adhesion incidences were 9.0% vs. 1.6% (Dubuisson et al. 2010), with the number of laparotomy procedures leading to increased appearance of adhesions (Dubuisson et al. 2010, Robertson et al. 2010). Not only do adhesions complicate future surgery, they also can be its cause: In one multicentre 7-year observation that excluded cases with malignancies, the gynaecological operations, particularly AH, were the main cause of small-bowel obstruction in women. After AH, the incidence was 1.4%, and the

median interval between AH and small-bowel obstruction was 4 years (Al-Sunaidi and Tulandi, 2006).

FINHYST represented 79.4% of the annual hysterectomies for benign indications registered in the HDR. In the HDR, the proportions for AH and LH were each 29%, whereas in FINHYST these were a respective 24% and 32%. An intention to perform minimally invasive surgery may lead to conversions. The intention-to-treat design was applied in FINHYST in order to evaluate actual complications by type of hysterectomy. When the conversions were summed up to AH operations in FINHYST, similar to the way they appear in the HDR, differences between the HDR and FINHYST in proportions of LH and VH were non-significant. Selection bias had occurred, however, in less eager recruitement of those planned for AH. Other reasons for why a fifth of annual hysterectomies failed to be recruited are unknown, as no registers for patients unwilling to participate were collected. Forcing hundreds of gynaecologist in the 53 collaborating clinics to recruit each patient was impossible. A nearly 80% national coverage can be considered fairly good.

The most common approach to LH was LH(a) with 77%, and unlike in the meta-analysis of RCTs (Nieboer et al. 2010), in FINHYST, duration of surgery was not longer for LH(a) than for LAVH. Excluding VHs for prolapse, non-significant differences appeared between VH and LH(a) in mean haemorrhage and uterine weight, but VH was half an hour faster to perform. The eVALuate study, an important large randomized trial comprising 1 346 hysterectomies from 30 centres, also concluded that LH was more time-consuming than was AH; and as in FINHYST, VH was fastest (Garry et al. 2004). In contrast to FINHYST, in the eVALuate study, the conversion rate in LH was lower (3.5%) and the mean operation time for all approaches considerably shorter: 55 min in AH, 86 min in LH, and 47 min in VH, meaning that FINHYST operations were 69%, 26%, and 47% longer in duration; the comparison for VH was for indications other than prolapse. These differences may result from the eVALuate exclusion criteria of large myomas and major prolapses, due to randomisation. Moreover, all performing gynaecologists in the eVALuate were specialists, whereas in Finland 22% of operations were performed by residents. FINHYST is a nationwide study of unselected cases, representing a real-life view of hysterectomy outcome. Development in Finland since the unselected cohort a decade ago has been positive: While less invasive hysterectomy methods have become dominant, simultaneously their mean operation times have decreased.

In Denmark, fast-track hysterectomy has gained popularity (Møller et al. 2001 and 2002, Hansen et al. 2008a). This means abdominally operated patients are discharged faster; with postoperative hospitalisation of 2 days as a median. In Denmark in 2004, with AH as their main approach at 63%, readmittance occurred for 7% (Hansen et al. 2008a). In FINHYST in 2006, readmittance after AH and VH occurred for 1.8%, and in LH for 3.6%. Thus the current hospitalisation period in Finland, reduced since 1996 (Mäkinen et al. 2001), seems quite optimal.

BSO in the USA in 2005 was performed for 21% of VHs (Jacoby et al. 2009), but already for 10% in the UK a decade earlier (Maresh et al. 2002). In Finland, the vaginal approach seems to

be the determinant for performing BSO rarely (2%), and the fact that VH has been the most common method since 2002 may argue against concomitant BSO. It seems also the wide implementation of LH has played a part in making vaginal BSO uncommon.

Complications

Unsurprisingly, when major complication rates of the Patient Insurance Centre and FINHYST are compared, retrospective register rates are lower. For all hysterectomy types, in the prospective FINHYST, incidences appeared to be around four-fold. Analysis of complications of the Patient Insurance Centre by their appearance in FINHYST uncovered no selection bias; thus patients seemed not to be withdrawn by their gynaecological surgeons from the prospective study because of major complications. This verification promotes the reliability of FINHYST.

FINHYST serves as a reminder of those with a history of CS as being at risk for bladder injury, a well-known association (Rooney et al. 2005, David-Montefiore et al. 2007). Patient Insurance Centre data on bladder injuries is clearly underestimated. Apparently intraoperative detection has made filing these complications unnecessary, since only a small minority of the 42 injuries appearing in FINHYST were present: four bladder injuries, and two VVFs. Similarly, gastrointestinal injuries diagnosed early, causing no need for stoma surgery, went unreported. The retrospective data cannot therefore be used to evaluate developments in intraoperative detection rates of bladder or bowel injuries, or in actual rates for these complications. Comparisons with the prospective national evaluation, however, indicate a positive development towards more frequent early diagnosis: In 1996, 78% of bladder injuries, and 63% of gastrointestinal injuries were detected intraoperatively (Mäkinen J, unpublished data); compared to 88% and 83% in 2006. This is of particular importance with bowel injuries, which are the most severe complications. A new mindset was suggested in a recent study, which classified bladder injuries, distinguished from severe adverse effects, as minor complications (Donnez et al. 2009). Comparisons of FINHYST and the Patient Insurance Centre suggest that patients can to some extent accept the occurrence of such injuries, when they are recognised and repaired instantly.

Data on ureter injuries in the Patient Insurance Centre, however, are reliable and similar to data in the prospective FINHYST. The national learning curve in LH reached a plateau of around 0.3% at the millennium. The early phase of LH in Finland was unfortunate in producing many injuries; in 1993 the incidence was 1.9% (Härkki et al. 2001). Since then, incidence has decreased by 84%; on average, 11% per year. None of the ureter injuries in 2000-2006 resulted in nephrectomy, whereas during the previous decade three kidneys were lost due to this complication (Härkki et al. 2001). A similar reduction was observed in a French tertiary laparoscopy centre: A learning curve of 695 LHs in 1989-1995, compared to 952 LHs in 1996-1999, showed a decrease in ureter injuries from 0.6% to 0.2% (Wattiez et al. 2002). One meta-analysis showed the average ureter injury incidence as being 0.3% (Meikle et al. 1997) and a review for this thesis of the 26 758 LH operations in 16 studies from outside Finland (Table 2) showed injuries were 65 in total (0.24%); many of the studies were conducted in single centres.

Thus, in Finland ureter injuries fell to an average level, and in contrast to laparoscopy centres, this development occurred on a national scale. Such LH results have not been published from any other country.

In a decade, bowel injuries in VH and ureter injuries in LH have significantly decreased (Mäkinen et al. 2001). In 1996, the experience of the surgeon affected occurrence of organ injuries: Those with prior experience exceeding 30 operations had significantly fewer ureter and bladder injuries in LH, and bowel injuries in VH (Mäkinen et al. 2001). In 2006, no significant difference appeared for any organ injuries or major complications as a whole by this arbitrary level of 30 operations, initially chosen in keeping the 1996 results in mind. The reason that these results currently are out-dated must be related to education and current wider experience in minimally invasive hysterectomies, meaning higher competence in general, resulting in fewer injuries. Possibly, the level of experience for which any difference is evident is higher (Jones 2000). It also seems that annual number of surgeries plays a role (Rogo-Gupta et al. 2010). Minimally invasive methods have outnumbered AH in all hospital types. Complications of FINHYST were not higher in hospitals outside university clinics; in fact, the opposite was evident for major bleeding and infection complications in AH, and postoperative bleeding and overall complications in VH. Evidence of complications increasing in academic teaching hospitals is supported by results from Australia and the USA (Spisbury et al. 2008, Juillard et al. 2009). Since the early years after introduction of LH, the outcome in favour of larger hospitals (Härkki-Siren et al. 1999) has altered, and currently no differences were observable between hospital types in complications of LH. This means that all hysterectomy methods have become routine surgery for Finnish gynaecologists.

Removal of an enlarged uterus can be challenging. In FINHYST, uterine size of 500 g or more associated with bladder injuries and with complications overall. The correlation for increasing haemorrhage was strongest with uterine size, and not surprisingly uterine size of 500 g or more associated also with operative haemorrhage of 1000 ml or more. Similarly, uterine size of 500 g or more increased transfusion rates in AH (Hillis et al. 1996). Further studies on such large uteruses compared methods: Perioperative complications were higher in AH than in VH (Benassi et al. 2002, Taylor et al. 2003), and less bleeding occurred in LAVH than in VH (Chang et al. 2005). In FINHYST, large uteruses were still mostly removed abdominally (78%).

In 1996, in Finland one surgery-related death occurred for each type of hysterectomy (Mäkinen et al. 2001), whereas in the current study, no deaths occurred. Similarly the recent DHD study in 2004-2006 observed no hysterectomy-related deaths (Hansen et al. 2008a). The newest method, LH, has also been relatively safe: In Finland, in the 15-year period 1992-2006, a death occurred in only one of the 27 827 LHs, whereas in the recent only-3-year period of 2005-2007 7 deaths occurred in 20 026 laparoscopic cholecystectomies (LCC) (Antikainen et al. 2010, number of LCC operations HDR, unpublished data). The only LH-related death occurred in 1996; its cause was a massive PE (Härkki et al. 2001, Mäkinen et al. 2001). Direct comparisons of complication rates can be difficult due to differing study designs and definitions of complications. The DHD investigators have not reported exact complication rates, but overall, a reoperation in 2006, regardless of cause, occurred for 4%. If major complications of the eVALuate study (Garry et al.

2004) were calculated by definitions similar to those of FINHYST, they would result in 4.1% for AH, 4.5% to 4.6% for LH, and 3.0% for VH – remarkably similar to FINHYST figures.

Postoperative adhesions are a natural consequence of tissue trauma and healing. Because one-fifth of the FINHYST patients with adhesiolysis had in their past neither endometriosis nor any surgery, application of adhesiolysis separately in the statistical model was necessary. Analysis resulted in adhesiolysis emerging in the context of many complications, and being the most important risk factor for major and total complications as a whole. Adhesions arising from clinical pathology, such as endometriosis, cannot be avoided, but to prevent iatrogenic adhesions, FINHYST results should further promote choice for minimally invasive hysterectomy methods.

Compared to 1996, thrombosis prophylaxis (TP) in 2006 was more frequent for all hysterectomy types (Mäkinen et al 2001). In LH, the rise was from 22% to 59%; simultaneously, mean operation time had decreased by 16 minutes, while the VTE incidence decreased from 0.3% to 0.1%. Most VTEs are diagnosed after discharge (White et al. 2003, Sweetland et al. 2009). Some missing VTEs were suspected, as the only two pulmonary embolisms (PE) were reported by the gynaecologists in FINHYST in 2006. Thorough verifications were therefore performed and these two cases represented only a third of actual VTEs. Similarly in 1996, the actual true incidence may very well be much higher. Nevertheless, VTE in the context of benign disease in 2006 occurred rarely, and both LH cases had major predisposing factors (Study IV). As a quality assessment, it seems TP was generally realised well; no VTE occurred in patients without TP. The verified FINHYST results are reliable, whereas register-based incidences may be overestimated (Severinsen et al. 2010). FINHYST, however, cannot reply to enquiries as to how many VTEs or PE-induced deaths were prevented. Although the ACCP recommends no routine TP for operations entirely laparoscopic (Geerts et al. 2008), it should be kept in mind that LH has the longest duration. In 1996 the LH-related VTE incidence in Finland was 0.3%, including one PE-related death (Mäkinen et al. 2001). Moreover, a recent register study on LH observed a VTE incidence of 0.9% (Ritch et al. 2011).

In surgery for gynaecologic malignancies, no increased risk for bleeding complications was apparent with TP (Einstein et al. 2007). Regarding FINHYST on benign disease, TP doubled the odds for postoperative haemorrhage or haematoma, when all hysterectomies were analyzed together. Further, by type of hysterectomy, with TP, the risk for postoperative haemorrhage or haematoma increased in AH, but no difference was apparent with LH. In VH for uterine prolapse, TP associated strongly with postoperative haemorrhage. In addition, for AH only, the risk for postoperative transfusion was also increased, possibly reflecting the severity of the complication. It seems that these complications are related to extent of surgery: in AH, where heavy tissue manipulation and large incisions are combined, and in VH for prolapse, where concomitant vaginal repair is usual for the majority.

The study design was not randomised but was an observational cohort - with analyses made also separately for each type of hysterectomy. These are clearly different operations, despite their having the same goal. In our study, postoperative bleeding of TP users at the index

hospitalization, occurring in 2.7% to 3.6% was lower than the 7% in the DHD (Hansen et al. 2008b), but similar to the 3.7% from a recent meta-analysis of abdominal and pelvic surgery (Rasmussen et al. 2009).

In AH, the proportion of the obese, and in VH regarding prolapse, the proportion of the elderly is higher, and could thus suggest that natural coagulation may be reinforced in non-receivers of LMWH in both groups. TP analyses, however, were adjusted for age and BMI. As the timing of TP was not recorded, results on TP as not affecting operative bleeding complications cannot be interpreted. Typically, patients arrive in the hospital on the morning of the operation. Because of convenience, presumably the initiation of TP was mostly postoperative.

Obesity has been related to excessive operative bleeding (more than 500 ml) in LH (Heinberg et al. 2004), and in VH, but not in AH (Rasmussen et al. 2004). Similarly in FINHYST, the effect was observed in LH and VH, but not in AH, in which operative haemorrhage of 1000 ml or more was similarly frequent in the obese and in those of normal weight. Among postoperative complications, Rasmussen et al. (2004) were surprised to find a higher risk for wound haematoma in those of normal weight, suspecting that diagnostics for haematoma in the obese are more difficult. In FINHYST, the risk for postoperative haemorrhage or haematoma was lower in AH with increasing BMI, and no cases appeared in the extremely obese. The possibility of a true benefit from obesity exists, as not only haematomas were included in FINHYST, but also postoperative haemorrhage requiring clinical intervention. Vascularisation of adipose tissue in itself is relatively poor. Thrombosis associates to a lesser degree with laparoscopic surgery (Geerts et al. 2008) than with open surgery, where the larger tissue damage activates the coagulation system. Outsized obese patients are exposed to even greater tissue damage, accelerated by blunt trauma caused by wound retractors. This may call for further physiological coagulation efficacy, resulting in protection against postoperative bleeding.

Infections overall are the most frequent complications occurring with hysterectomy. In the current study, febrile events in LH occurred more frequently with those less experienced gynaecological surgeons, who also performed more slowly. When duration of operation was included in the model (Study V), the probability for infections significantly increased with duration of the LH operation. It seems that the laparoscopic approach, although allowing the abdominal cavity to be less exposed, did not protect from this phenomenon already earlier evident for AH and VH (Shapiro et al.1982, Olsen et al. 2009).

Late-onset pelvic infections were associated with LH and VH. In general, subgroups of infections were the only complications showing an independent association with certain hysterectomy methods in the adjusted model. In fact, the excess of pelvic infections in LH and VH is the reason why the total infection difference, compared to that in AH, was non-significant, even if AH was associated independently with wound infections, febrile events, and UTIs. Because UTIs are also commonly treated by general practitioners outside hospitals, presumably some data were lost. UTIs' association with AH may well be caused by the shorter hospital stay of those undergoing other hysterectomy types. A vaginal approach may well predispose to pelvic infection, possibly by colonization of the surgical site more with the vaginal

flora. For LH, gynaecologists in Finland have traditionally used a technique in which the vaginal vault is closed vaginally. With VH, indications other than prolapse, when compared to prolapse, raised the odds for pelvic infection to over three-fold. This may reflect the difficulty of vaginally performed haemostasis of the non-prolapsed vaginal vault. Moreover, those operated on for prolapse are older, and they in general bleed less.

The reason why complications of hysterectomy associate with younger age (McPherson et al. 2004, Spilsbury et al. 2008, Olsen et al. 2009) has lacked any explanation. In FINHYST, haemorrhage decreased with age. Analysing all hysterectomies together, operative haemorrhage of 1000 ml or more, early-onset postoperative haemorrhage or haematoma, late-onset pelvic infections (haematoma or abcess), infections in total, and complications in total were reduced for women aged 55 or more, in comparison with those aged less than 45; operative haemorrhage of 1000 ml or more was also reduced for those aged 45-55. Hormonal status affects both size and vascularization of the uterus, but composition of the vaginal flora should also be considered. It is evident that the vaginal flora is affected by estrogen, and athrophic vaginal mucosa in postmenopausal women lacks lactobacilli bacteria, which may protect the vagina against colonisation by potential pathogens (Raz and Stamm 1993). Nevertheless, we have no information as to the magnitude of estrogen therapy used by those postmenopausal in FINHYST. In Finland in 2005, 27% of women aged 50-59, and 20% aged 60-69 received reimbursement for the cost of hormonal therapy involving estrogen; in addition, the reimbursement rate for local estrogen therapy in any women aged over 40 was 10% (Salmi et al. 2006). This data from a year prior to FINHYST may suggest that the majority of postmenopausal patients have been without HT. It is thus possible that the main reason for the reduction both in haemorrhagic but also infection complications may be the reduced bleeding of the elderly. Collections of blood, and vascular pedicles burned into necrotic tissue are both ideal sites for infection.

By type of hysterectomy in cases lacking antibiotic prophylaxis (AP), infectious morbidity was highest with VH. In 1996, the infections occurring most commonly with VH (Mäkinen et al. 2001) were more than halved in 2006. In one decade, AP overall became more common, rising from 82.1% to 97.5%. An ever more important change was that in 2006, AP in general was mostly realised involving the wider-spectrum cefuroxime; the predominance of the narrow-spectrum nitroimidazole as the only prophylactic agent had ended. Due to its narrow spectrum, metronidazole may come in handy in treatment of bacterial vaginosis (BV), which evidently is associated with risk for posthysterectomy pelvic infection (Soper et al. 1990, Persson et al. 1996). BV is important due to its high prevalence, ranging from 15 to 30% (Persson et al. 1996, Holzman et al. 2001), and in the Finnish pap-smear screening population in 12% (Nieminen and Paavonen, 1997).

In FINHYST, because no additional risk-reducing effect was observable after combining metronidazole with cefuroxime, use of metronidazole seemed unnecessary, and a waste of money, in large-scale routine prophylaxis. The majority of postoperative pelvic infections involve anaerobic bacteria (Hager 2003), which probably also explains the eagerness to use anaerobic agents: In FINHYST in 2006, metronidazole alone or in combination was given to as

many as 54%. It seems that in other countries too, use of additional anti-aerobic prophylaxis has been, and may still be, common; for example, recommendations from Denmark and Norway suggest combining metronidazole with cefuroxime. For prophylaxis in colorectal surgery, additional anaerobic coverage is recommended (Nelson et al. 2009), but the bacterial flora of the colon and the vagina are not identical. Most microbes involved in bacterial vaginosis (BV), including *G. vaginalis*, are susceptible to cefuroxime, although it is never used in treatment for an uncomplicated BV. The WHO reports trichomoniasis as the most common sexually transmitted disease, particularly in Africa, and causing in the USA an estimated 2 to 3 million infections in women per year (John and Petri, 2006). In Finland, however, it is rare: The pap-smear screening prevalence was 0.2% (Heikkilä and Jokinen, 2000). Thus, for trichomoniasis, also a risk factor for posthysterectomy infection (Soper et al. 2003), there exists no need for prophylactic metronidazole in Finland. Important anaerobic colorectal pathogens such as *Bacteroides fragilis* are involved in gynaecological polymicrobial postoperative infections. It seems, however, that such anaerobes, resistant to cefuroxime, either play a minor role in the surgical site of hysterectomy, or that prophylaxis targeted against the other bacteria of the vagina is sufficient, because anaerobic pathogens need the presence of other bacteria to initiate infection (McDonald and O'Loughlin 1993, Jousimies-Somer 2003, Brooks et al. 2007).

Although FINHYST was a non-randomised study, its sample size was large, and the prospective approach makes complication rates more accurate. Due to its observational study design, confounding factors were controlled for by application of logistic regression analyses. Regarding simultaneous cefuroxime and metronidazole prophylaxis, only a single earlier study on hysterectomy AP was available; one with 68 VH operations randomised into three groups. Infection morbidity was significantly higher with metronidazole given alone, with no difference in cefuroxime prophylaxis combined with metronidazole or not; FINHYST supported these results (Kauer et al. 1990).

The flaws of FINHYST are several: In studying methods of hysterectomy, if the aim is direct comparison of complications, the cases operated on by each approach should be similar. Randomised studies in surgery may have ethical problems. To control for the many confounders such as unequal experience of the surgeons in multicentre studies can be difficult. Furthermore, randomised studies always have criteria excluding those out of the ordinary, which are included in real-life non-randomised cohorts. As FINHYST was not a randomised trial, and we could not affect the sample sizes of the different groups, statistical power could not be calculated specifically beforehand. The annual number of hysterectomies, however, was estimated to be over 6 000, so comparisons for many complications were expected to be sufficiently powerful. The patients operated on by different methods differed in many respects, but in particular by age and by indications for hysterectomy. Logistic regression was therefore applied, to adjust for confounders. This model, which to aim for comparable and coherent results was the same for all hysterectomy methods; therefore it was somewhat difficult to build. Not all control variables were applicable to each analysis, usually due to the lack of complications within a certain variable; such as adhesions and large uteruses both being few in VH. Therefore in Studies IV and V, uterus size was applied as linear. Although it was difficult to build a uniform model feasible for all, the strength of the national FINHYST is its large number of complications

collected because of its prospective approach. Risk factors for complications, in addition, were always specifically analysed within the different hysterectomy methods, AH, LH, VH, in order to provide more accuracy. Such large cohorts, particularly for LH, are rare.

As differences between hysterectomy methods turn out to be mostly non-existent, the conclusion is likely that the choice of type of hysterectomy was well realised. Yet, pelvic infections were more common in both methods involving vault closure vaginally, compared to abdominal closure. Laparoscopic closure could possibly reduce such morbidity; and the current enthusiastic world-wide research on robotic gynaecologic surgery may provide an answer to this question. The FINHYST in 2006 included a patient questionnaire. A future publication will show how the patients themselves experienced their convalescence and evaluated their particular type of hysterectomy.

The wide, and possibly even increasing implementation of minimally invasive hysterectomy methods in our country may have one unexpected negative effect: As AH has become rare, reserved for most challenging cases, the pool of residents in training will have less and less experience performing it. Yet, a postpartum hysterectomy may be essential for in bleeding catastrophes unresponsive to conservative treatment modalities. Obstetricians on call should thus stay familiar with the principles of AH.

CONCLUSIONS

1. Hysterectomy rates for benign disease have declined, while the minimally invasive methods have surpassed the previous dominance of AH; this outcome is similar in all public hospital types: university, central, and local hospitals.

2. During the early years after the introduction of LH in Finland, the incidence of ureter injuries was high, but after the millennium it had declined to an acceptable level of 0.3%. In 2006, overall complications occurred in AH to 19.2%, in LH to 15.4%, and in VH to 11.7%. Major complications occurred in AH to 4.0%, in LH to 4.3%, and in VH to 2.6%, with no significant differences between hysterectomy types. Most bladder and bowel injuries were detected and repaired intraoperatively (88% and 83%), which essentially reduced patients' need to seek compensation.

3. Complications overall associated with adhesiolysis (OR 2.48), uterine size of 500 g or more (OR 1.44), and concomitant surgery (OR 1.28), while age over 55 was risk-reductive (OR 0.61). Adhesiolysis was also a risk factor for major complications (OR 2.41). Risk factors for bladder injury were previous caesarean section (OR 4.01) and uterine size of 500 g or more (OR 2.88). Infections were associated with those overweight (OR 1.61), obese (OR 1.67), and extremely obese (OR 1.82). Specifically in AH, the risk for wound infections for the overweight or obese was five-fold, compared to normal-weight patients. The risk for febrile events, wound infections, and urinary tract infections was lower in LH than in AH. Compared to AH, the risk for pelvic infections was over five-fold for LH and VH.

4. With pharmaceutical thrombosis prophylaxis (TP) given to 64.8%, VTE with hysterectomy for benign disease was rare (0.1%). Postoperative haemorrhage or haematoma was associated with TP in VH for prolapse (OR 4.82) and in AH (OR 2.87), but not in other hysterectomy types. The risk for postoperative haemorrhage or haematoma was reduced with older age in VH, and with obesity in AH. Bleeding during surgery increased with BMI, and fell with increasing age.

5. Compared to a decade earlier, postoperative infections were reduced, while antibiotic prophylaxis had become more frequent (97.5%) and involved a wider spectrum. Cefuroxime was effective in prophylaxis against infections. Metronidazole appeared ineffective, with no additional risk-reducing effect when combined with cefuroxime.

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Appendix 1.

The numbers of FINHYST hysterectomies by individual hospitals. Type of hospital: a, university hospital; b, central hospital; c, local hospital; d, private hospital. Table continues to the next page.

Name of hospital in Finnish	Type of hospital	Total n	%	AH		LH		VH	
				n	%	n	%	n	%
HYKS Kätilöopiston sairaala	a	442	8.4	115	26.0	145	32.8	182	41.2
HYKS Naistenklinikka	a	389	7.4	72	18.5	240	61.7	77	19.8
TYKS Naistenklinikka	a	310	5.9	75	24.2	125	40.3	110	35.5
OYS Naistenklinikka	a	273	5.2	24	8.8	183	67.0	66	24.2
Etelä-Pohjanmaan keskussairaala	b	235	4.5	97	41.3	24	10.2	114	48.5
Pohjois-Karjalan keskussairaala	b	234	4.4	9	3.8	153	65.4	72	30.8
TAYS Naistenklinikka	a	200	3.8	27	13.5	78	39.0	95	47.5
Keski-Suomen keskussairaala	b	199	3.8	21	10.6	20	10.1	158	79.4
Satakunnan keskussairaala	b	187	3.5	88	47.1	19	10.2	80	42.8
Päijät-Hämeen keskussairaala	b	183	3.5	43	23.5	45	24.6	95	51.9
KYS Naistenklinikka	a	160	3.0	26	16.3	43	26.9	91	56.9
Valkeakosken aluesairaala	c	158	3.0	14	8.9	17	10.8	127	80.4
HYKS Jorvin sairaala	a	156	3.0	24	15.4	32	20.5	100	64.1
Etelä-Karjalan keskussairaala	b	143	2.7	56	39.2	35	24.5	52	36.4
Keski-Pohjanmaan keskussairaala	b	140	2.7	14	10.0	56	40.0	70	50.0
Hyvinkään sairaala	c	115	2.2	4	3.5	59	51.3	52	45.2
Kainuun keskussairaala	b	114	2.2	13	11.4	58	50.9	43	37.7
Kuusankosken sairaala	c	103	2.0	42	40.8	39	37.9	22	21.4
Kymenlaakson keskussairaala	b	102	1.9	27	26.5	47	46.1	28	27.5
Kanta-Hämeen keskussairaala	b	99	1.9	21	21.2	27	27.3	51	51.5
Savonlinnan keskussairaala	b	89	1.7	39	43.8	12	13.5	38	42.7
Porvoon sairaala	c	86	1.6	7	8.1	40	46.5	39	45.3
Lohjan sairaala	c	85	1.6	34	40.0	17	20.0	34	40.0
Rauman aluesairaala	c	81	1.5	15	18.5	14	17.3	52	64.2
Länsi-Pohjan keskussairaala	b	80	1.5	37	46.3	5	6.3	38	47.5
Lapin keskussairaala	b	78	1.5	42	53.8	6	7.7	30	38.5
Vammalan aluesairaala	c	72	1.4	29	40.3	2	2.8	41	56.9
Vaasan keskussairaala	b	72	1.4	13	18.1	16	22.2	43	59.7
Mikkelin keskussairaala	b	68	1.3	37	54.4	3	4.4	28	41.2
Salon aluesairaala	c	63	1.2	24	38.1	2	3.2	37	58.7
Mäntän aluesairaala	c	61	1.2	11	18.0	14	23.0	36	59.0
Forssan sairaala	c	60	1.1	22	36.7	9	15.0	29	48.3
Länsi-Uudenmaan sairaala	c	52	1.0	8	15.4	17	32.7	27	51.9
Loimaan aluesairaala	c	41	0.8	16	39.0	10	24.4	15	36.6
Oulaskankaan sairaala	c	41	0.8	11	26.8	3	7.3	27	65.9
Pietarsaaren aluesairaala	c	41	0.8	7	17.1	12	29.3	22	53.7
Raahen aluesairaala	c	36	0.7	6	16.7	22	61.1	8	22.2
Iisalmen sairaala	c	34	0.6	30	88.2	0	0.0	4	11.8
Ahvenanmaan keskussairaala	b	34	0.6	14	41.2	0	0.0	20	58.8
Varkauden sairaala	c	33	0.6	1	3.0	3	9.1	29	87.9

Nokian terveyskeskus	c	28	0.5	3	10.7	1	3.6	24	85.7
Turunmaan sairaala	c	23	0.4	9	39.1	0	0.0	14	60.9
Sairaala Laseri, Terveystalo, Helsinki	d	22	0.4	0	0.0	20	90.9	2	9.1
Vakka-Suomen sairaala	c	14	0.3	12	85.7	0	0.0	2	14.3
Koskiklinikka, Tampere	d	11	0.2	3	27.3	2	18.2	6	54.5
Pieksämäen sairaala	c	7	0.1	6	85.7	0	0.0	1	14.3
Sairaala Pulssi, Turku	d	6	0.1	1	16.7	3	50.0	2	33.3
Heinolan sairaala	c	5	0.1	4	80.0	0	0.0	1	20.0
Sairaala Lapponia, Kemijärvi	c	4	0.1	0	0.0	0	0.0	4	100.0
Sairaala Mehiläinen, Turku	d	4	0.1	2	50.0	1	25.0	1	25.0
Sairaala Lasaretti, Kuopio	d	2	0.0	0	0.0	0	0.0	2	100.0
Sairaala Mehiläinen, Helsinki	d	2	0.0	0	0.0	0	0.0	2	100.0
Operon, Terveystalo, Tampere	d	2	0.0	0	0.0	0	0.0	2	100.0
Total		5279	100.0	1255	23.8	1679	31.8	2345	44.4

Appendix 2.

FINHYST 2006 (Leikkaava lääkäri täyttää) Sivu 1
Rengasta oikea vaihtoehto. Lomake täytetään kaikista muista kohdunpoistoista paitsi syövistä, borderline munasarjakasvaimista ja synnytyksen jälkeisistä kohdunpoistoista

Potilaan nimi ja SOTU (mielellään tarra): _____
Sairaala _____
Toimenpidepäivä: _____ Lomakkeen täyttöpäivä: _____
Leikkaaja:**1**. erikoislääkäri / **2**.erikoistuva lääkäri
Leikkaajan kokemus ko. leikkauksessa: **1**.alle 10 kpl / **2**. 10-30 kpl / **3.** yli 30 kpl

Kohdunpoisto:
1. a. Abdominaalinen totaali / **b**. abdominaalinen amputaatio
2. a. LH (uterinat yläkautta) / **b.** LAVH (uterinat alakautta) / **c.** laparoskooppinen amputaatio
3. Vaginaalinen
4. Konversio (mistä mihin _____, syy_____)
5. Kohdun paloittelu sen ulos saamiseksi

TÄRKEIN preoperatiivinen syy miksi leikattiin (vain **YKSI** vaihtoehto): ICD-10 _____
1. Myoma(t)
2. Menorrhagia
3. Dysmenorrhea
4. Endometrioosi
5. Laskeumat
6. Adnextuumori
7. Muu, mikä_____
Muuttuiko tärkein diagnoosi leikkauksen jälkeen? **1**.ei / **2**. kyllä: uusi dg (ICD-10) _____

Potilaan pituus _____ cm, paino _____ kg
Pariteetti:_____ joista alatiesynnytyksiä _____ kpl ja sektioita _____ kpl
Aikaisemmat muut vatsanalueen leikkaukset: laparoskopioita _____ kpl, laparotomioita _____ kpl

Antibioottiprofylaksia:
1. ei
2. kyllä: **a.** kefuroksiimi / **b.** metronidatsoli / **c.** muu, mikä _____ + annos _____
Lääkkeellinen tromboosiprofylaksia:
1. ei
2. kyllä: **a.** miniheparini / **b.** muu, mikä _____ + annos _____+ kesto (vrk) _____

Leikkauksen kesto (min) (aika 1. viillosta sulkuun) _____
Arvioitu/mitattu vuoto (ml) _____
Uteruksen paino ilman adnexeja (g) _____
Leikkaajan arvio leikkauksen vaikeudesta:
1. erittäin helppo/ **2**. helppo/ **3.** tavallinen/ **4** vaikea/ **5.** erittäin vaikea, miksi _____

Hemostaasimenetelmä(t):
1. Ligatuurat
2. Bipolaaripoltto
3. Monopolaaripoltto
4. Ultraääniveitsi
5. Muu (Esim. Ligasure), mikä _____

Liitännäistoimenpiteitä:
1. Ei
2. Kyllä
A. a. toisen adneksin poisto / **b** .molempien adnexien poisto
B. Vaginaaliset plastiat: **a**. KA / **b.** KP
C. Inkontinenssin korjaus: **a**. TVT / **b**. TOT / **c.** muu _____
D. Enteroseelen korjaus
E. Leikkausta hankaloittavien kiinnikkeiden irrottelu
F. Muu, mikä _____

Leikkauksen **aikana** havaittu komplikaatio:
1. Ei
2. Kyllä
A. Yli 1000ml leikkausvuoto
B. Verisuonivaurio**: a.** epigastricasuonet / **b.** suuret suonet (aorta, v.cava, iliacat) / **c.** muu suoni, mikä _____
C. Rakkovaurio
D. Uretervaurio
E. Suolivaurio
F. Tekniset laiteongelmat, mikä _____
G. Muu, mikä _____

Miten komplikaatio hoidettiin _____

Leikkauksen **jälkeen** osastolla todettu komplikaatio:
1. Ei
2. Kyllä
A. Reoperaatio, syy_____
B. Postoperatiivinen vuoto/hematoma
C. Haavainfektio (vaatinut antibiootin, punktion tai dreneerauksen)
D. Virtsatieinfektio (Uricult > 10^5)
E. Epäselvä kuumeilu (aksillaarinen lämpö ≥ 38°C)
F. Syvä laskimotromboosi
G. Keuhkoembolia
H. Rakkovaurio
I. Uretervaurio
J. Suolenvetovaikeus
K. Suolivaurio
L. Hernia, mikä _____
M. Muu ongelma, mikä _____

Miten komplikaatio hoidettiin_____

Potilas sai verensiirron
1. Ei
2. Kyllä **a.** ennen leikkausta ____ punasoluyksikkö/ **b**. leikkauksen aikana ____ punasoluyksikköä/ **c**. leikkauksen jälkeen _____ punasoluyksikköä

Kotiutuspäivämäärä _____ Sairasloma (vrk) _____ (sisältää sairaalassa oloajan)
Potilas **1.** on työssä / **2**. ei ole työssä

FINHYST 2006 JÄLKIKOMPLIKAATIOLOMAKE (Lääkäri täyttää)

Täytetään vain mikäli potilas joutuu uudestaan sairaalaan komplikaation takia

Potilaan nimi ja SOTU (mielellään tarra):_____
Sairaala: _____
Kohdunpoistopäivä: _____
Lomakkeen täyttöpäivä: _____

Komplikaation toteamispäivä _____

Havaittu komplikaatio:

1. Reoperaatio, syy _____
2. Verensiirtoon johtanut anemia
3. Haavainfektio (vaatinut antibiootin, punktion tai dreneerauksen)
4. Virtsatieinfektio (Uricult > 10^5)
5. Epäselvä kuumeilu (Aksillaarinen lämpö ≥ 38 °C)
6. Lantionpohjan infektio (hematoma ja/tai abskessi)
7. Syvä laskimotromboosi
8. Keuhkoembolia
9. Rakkovaurio
10. Uretervaurio
11. Suolenvetovaikeus
12. Suolivaurio
13. Hernia, mikä _____
14. Muu ongelma, mikä _____

Miten komplikaatio hoidettiin
_____
_____
_____

Sairaalassa oloaika (vrk) _____
Uusi sairasloma (lisä vrk) _____
Potilas **1.** on työssä / **2**. ei ole työssä