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HYSTERECTOMY ON BENIGN INDICATIONS AND PELVIC FLOOR DYSFUNCTION – CLINICAL AND EPIDEMIOLOGICAL ASPECTS

Catharina Forsgren

Karolinska Institutet

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ABSTRACT

The objectives of this thesis were to investigate the annual rates for hysterectomy on benign indications, to evaluate the effects of hysterectomy on bowel function, to identify risk factors for vaginal vault prolapse, to examine the association between hysterectomy and pelvic organ fistula disease, and to determine risks of subsequent pelvic floor surgery after vaginal hysterectomy.

We performed a nationwide register based cohort study to investigate the annual rates, types and indications for hysterectomy. All women who went through hysterectomy for benign disease in Sweden from 1987 through 2003 (n=121,947) were included. We found that the overall rate of hysterectomy on benign indications has remained reasonably stable. Major trends involved a notable decrease in rates of abdominal hysterectomy, an increased use of vaginal hysterectomy, and an increased number of hysterectomies performed for pelvic organ prolapse.

In a prospective long-term follow-up study we evaluated the effects of hysterectomy on bowel function. One-hundred and twenty patients undergoing hysterectomy for benign conditions answered a questionnaire on bowel habits before, one and three years after surgery. Neither abdominal, nor vaginal hysterectomy was associated with symptoms of constipation, but having the operation was associated with a mild deterioration in anal continence status.

Among women having had a hysterectomy, we performed a nested case-control study to identify risk factors for vaginal vault prolapse surgery after hysterectomy. Case subjects were 117 women with vaginal vault prolapse after hysterectomy and control subjects were 326 women having had hysterectomy but no surgery for vaginal vault prolapse. Data on determinants was extracted from the Swedish Inpatient Register and self-reported questionnaires. We concluded that previous surgically managed pelvic floor disorder was the main risk factor for the development of vaginal vault prolapse subsequent to a hysterectomy.

In a nationwide cohort study based on Swedish health care registers, we studied the risk for pelvic organ fistula surgery associated to hysterectomy on benign indications. The cohort consisted of 182,641 women having hysterectomy and 525,826 women not undergoing the procedure. We found that pelvic organ fistula surgery is four times more common in women after hysterectomy. The highest fistula rates were observed the first year after surgery, after laparoscopic and total abdominal hysterectomy, and among older women having had hysterectomy.

To determine the risks for pelvic organ prolapse and stress urinary incontinence surgery after vaginal hysterectomy, we used the same population sample as above but the exclusion criteria's were modified and the exposure was defined differently. We concluded that vaginal hysterectomy is by itself associated with higher risks than total abdominal hysterectomy for subsequent pelvic organ prolapse and stress urinary incontinence surgery. If the vaginal hysterectomy was performed due to pelvic organ prolapse, these risks were further increased.

LIST OF PUBLICATIONS

This thesis is based on the following papers, referred to in the text by their roman numerals:

I. Hysterectomy on benign indications in Sweden 1987-2003: a nationwide trend analysis.

Lundholm C, Forsgren C, Johansson AL, Cnattingius S, Altman D.

Acta Obstetricia et Gynecologica Scandinavica 2009;88:52-8.

II. Effects of hysterectomy on bowel function- a three-year, prospective cohort study

Forsgren C, Zetterström J, López A, Nordenstam J, Anzén B, Altman D.

Diseases of the Colon and Rectum 2007;50:1139-45

III. Risk factors for vaginal vault prolapse surgery in postmenopausal hysterectomized women

Forsgren C, Zetterström J, López A, Altman D.

Menopause 2008;15:1115-9.

IV. Hysterectomy for benign indications and risk of pelvic organ fistula disease.

Forsgren C, Lundholm C, Johansson AL, Cnattingius S, Altman D.

Obstetrics and Gynecology 2009;114:594-9.

V. Vaginal hysterectomy and risk of pelvic organ prolapse and stress urinary incontinence

Forsgren C, Lundholm C, Johansson AL, Cnattingius S, Nyman- Iliadou A, Zetterström J, Altman D.

Submitted

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1 LIST OF ABBREVIATIONS

AH	Abdominal hysterectomy
BMI	Body mass index
BSO	Bilateral salpingo-oophorectomy
CCIS	Cleveland Clinic Incontinence Score
CI	Confidence interval
HR	Hazard ratio
HRT	Hormone replacement therapy
ICD	International Classification of Diseases
ICS	International Continence Society
LAVH	Laparoscopy-assisted vaginal hysterectomy
LH	Laparoscopic hysterectomy
MUI	Mixed urinary incontinence
NOMESCO	Nordic Medico-Statistical Committee
NNH	Numbers needed to harm
NRN	National register number
OR	Odds ratio
POP	Pelvic organ prolapse
POP-Q	Pelvic organ prolapse quantification system
SD	Standard deviation
SLE	Systemic Lupus Erytematosus
SUI	Stress urinary incontinence
RCT	Randomized clinical trial
TLH	Total laparoscopic hysterectomy
VH	Vaginal hysterectomy
TVT	Tension free Vaginal Tape
TVT-O	Tension free Vaginal Tape Obturator
UI	Urinary incontinence
UUI	Urgency urinary incontinence
%	Percent

2 INTRODUCTION

For many women deciding on having their uterus removed is an important and emotionally difficult decision. Nevertheless, hysterectomy is the second most common surgical procedure in women worldwide and almost every third women in the US have undergone a hysterectomy at the age of 60 years.(1) The vast majority of hysterectomies are performed on benign indications,(2) and the surgical procedure is generally associated with few complications.(3) However, many important long-term outcome measures remain undecided and effects on the pelvic floor remain incompletely understood.

It has been postulated that hysterectomy disrupts local nerve supply and distorts pelvic anatomy. It is therefore reasonable to assume that pelvic organ function might be adversely affected by the operation.(4) According to several studies, hysterectomy is a risk factor for pelvic organ prolapse (POP),(5-7) and urinary incontinence (UI),(8-11) and has been associated with bowel dysfunction, pelvic organ fistula disease and sexual dysfunction. Pelvic organ dysfunction generates substantial morbidity among women, results in important costs for healthcare systems worldwide, (12-14) and affects most domains of individual quality of life and daily function.(15, 16) In case of severe dysfunction, surgery often remains the mainstay of treatment,(17) and in the US for example, more than 300,000 procedures for POP are performed annually.(18) The population-based prevalence of UI ranges from 25% up to 49% depending of definition and population.(16, 19, 20) Bowel dysfunction and constipation is also a common problem affecting between 2% and 27% of the female population in industrialized countries.(21)

Despite the fact that both hysterectomy and pelvic organ disorders are so common in the general population, relatively little attention has been paid to the association. Urogynecological disorders have historically had a low status within the gynecological discipline. Furthermore, diseases which affect the lower urinary tract are by many considered a part of the natural aging process. Current knowledge on the relation between hysterectomy and subsequent pelvic organ disease has also been hampered by the lack of high quality epidemiological research, the lack of valid outcome measures for many of the disorders, by the focus on perioperative surgical morbidity, and for not considering the effects of various types of hysterectomy.(22) In recent years, however, an increasing number of studies have been devoted to the effects of hysterectomy on the pelvic floor. This trend has coincided with an increased awareness in both the general and medical community about urogynecological disorders, as well as, the emergence of effective surgical treatments.(16)

Nevertheless, many important outcome measures of hysterectomy remain unexplored and the overall aim of this thesis is to evaluate different aspects of the effect of hysterectomy on the pelvic floor and pelvic organs. Considering the immense number of hysterectomies performed every year, the potential risks for subsequent pelvic floor disease might have important implications for women's health worldwide.

3 BACKGROUND

3.1 ANATOMICAL CONSIDERATIONS

3.1.1 Development of the urogenital system

The development of the genital system is closely integrated with that of the urinary system, both originating from the intermediate mesoderm of the dorsal body embryonic wall. In females, the absence of the sex-determining region on the Y chromosome (SRY), results in formation of ovaries and female genital ducts. In addition, genes on the X chromosome and some of the autosomes have been shown to play key roles in female genital differentiation.(23) Between the fourth and sixth gestational week, migration of the primordial germ cells to the posterior body wall results in induction of the genital ridges. The genital ridges are then enlarged and fused into the genital cord. During the seventh week, the Mullerian ducts fuse into the midline to form the uterovaginal canal.

The urinary system also develops from the intermediate mesoderm. The bladder is formed from the superior region of the primitive urogenital sinus, created by dividing of the cloaca by the urorectal septum. The intermediate constricted region of the primitive urogenital sinus gives rise to the membranous urethra. The definitive urogenital sinus forms the vestibule of the vagina in females. Absence of testosterone influence will lead to a regression of the primitive Wolffian ducts, responsible for the developmental blue print of the ureters and the bladder trigone. The embryonic development of all organs is completed by the tenth gestational week, and the remaining antenatal period is dedicated to growth and maturation of the fetus.

3.1.2 The uterus

The uterus is a thick-walled, smooth muscle organ positioned between the bladder and the sigmoid colon and rectum deep in the pelvic cavity. The upper part of the uterus is suspended by the broad and the round ligaments, while its lower portion is imbedded in the fibrous tissue of the pelvis. The uterus is divided into two segments defined by the isthmus. The portion above the isthmus is termed the body (corpus) and that below, the cervix. The cervix is supported to the lateral pelvic side-wall by the cardinal ligaments and to the sacrum by the uterosacral ligaments. The part of the uterus body which lies above the points of entrance of the uterine tubes is known as the fundus. Arterial vascularisation of the uterus is provided by branches from the uterine artery, from the hypogastric arteries; and the ovarian artery, from the abdominal aorta. The innervations of the uterus are entirely autonomic, arising from the inferior hypogastric plexus (sympathetic) and the pelvic splanchnic nerves (parasympathetic from S2-4). The afferent fibers travel with the sympathetic efferent's to T10-12 and L1 spinal cord segments.(24)

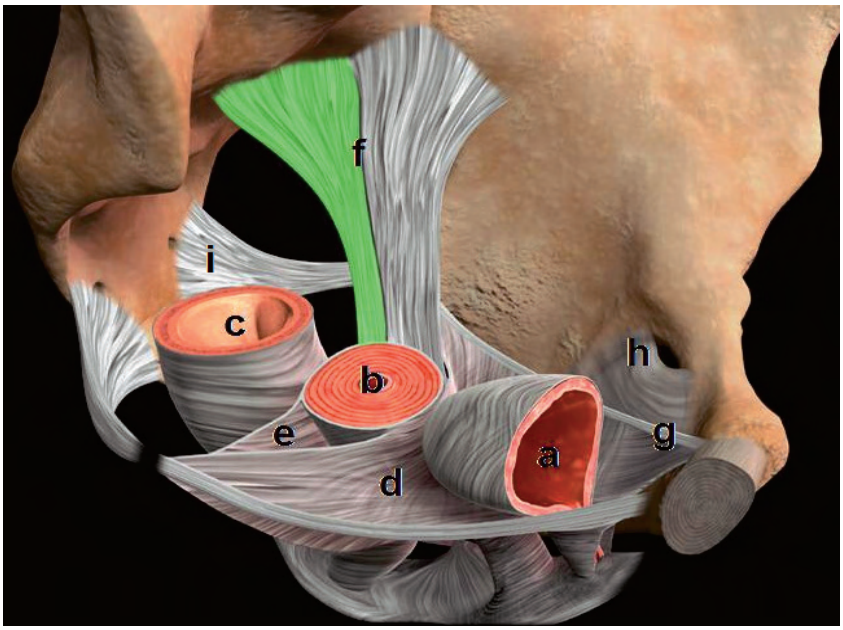
3.1.3 The female pelvic floor

The intricate architecture of the female pelvic floor is built by striated muscle, smooth muscle, connective tissue, blood vessels, and nerves. The primary aim of the soft tissue pelvic floor, surrounded by the bony pelvis, is to contain and support the pelvic organs within the abdominal cavity. The pelvic floor is a complicated system and the section bellow provides a brief summary of clinically relevant anatomical structures.

Fascias of the pelvic floor

To anchor the soft tissue pelvic floor, fascias and ligaments are strongly attached to the sidewalls of the pelvic bones. The arcus tendineus fascia pelvis (Figure 1) of the endopelvic fascia runs the entire length of the vagina and suspends the lateral aspects of the anterior vaginal walls. The endopelvic fascia is a dense fibrous connective tissue layer, positioned between the peritoneum and the levator muscles. The rectovaginal fascia is the part of the endopelvic fascia that continues down the posterior wall. It provides support to the distal rectum and prevents the rectum from bulging forward into the posterior vagina. The rectovaginal fascia runs at right angles to the pelvic floor muscles and is supported laterally from the pelvic floor muscles. The upper segment of the fascia is anchored proximally to the uterosacral ligaments. The mid-vagina rests on the rectovaginal fascia posteriorly and is separated from the bladder and urethra anteriorly by a part of the endopelvic fascia called the pubocervical fascia. The pubocervical fascia provides support for the bladder and urethra and is attached to the cervix at the top of the vagina.(25)

Figure 1. Fascias and ligaments of the female pelvic floor.

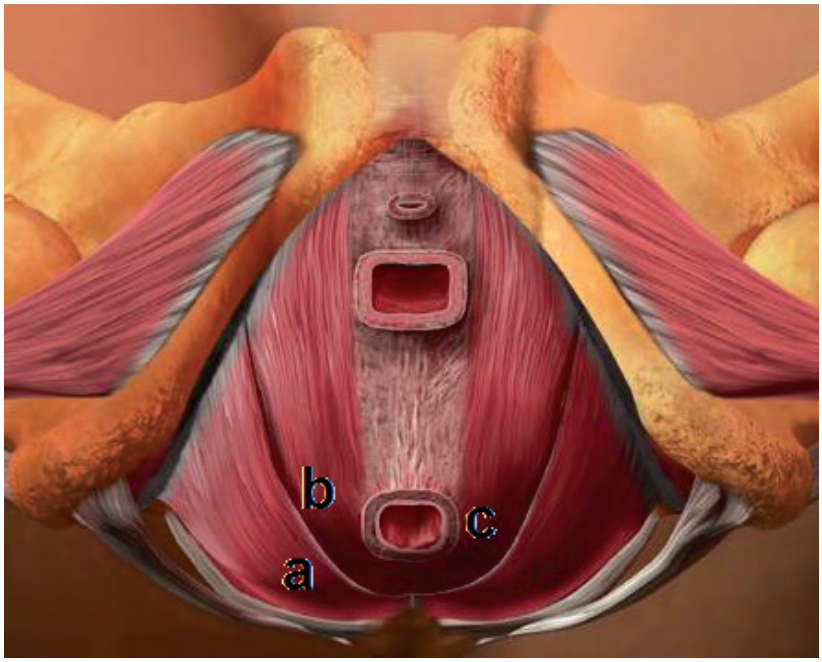


Reprinted with permission from Ethicon US. Letters denote: a. bladder, b. cervix, c. rectum, d. pubocervical fascia, e. rectovaginal fascia, f. uterosacral ligaments, g. arcus tendineus fascia pelvis, h. obturator foramen, i. sacrospinous ligament.

The pelvic diaphragm

Functionally, the levator ani muscle (Figure 2) and the endopelvic fascia serve an interactive role in maintaining continence and pelvic support.(26) The levator plane supports the visceral structures of the pelvis in between the sacrum and the inferior margins of the symphysis. The levator ani muscle consists of three parts: the pubococcygeus, the puborectalis, and the iliococcygeus muscles. The pubococcygeus and the puborectalis muscles form a U-shape as they originate from the pubic bone on either side of the midline and pass behind the rectum to form a sling.(25)

Figure 2. The levator ani muscles



Reprinted with permission from Ethicon US. Letters denote: a. ileococcygeus, b. pubococcocygeus, c. puborectalis

Perineum and cervix

The perineum, and perineal body, stabilizes the lower pelvic floor and is attached to the pelvic side-wall by the transverse perineal muscles. The perineum is defined by the distal borders of the pelvic bony structures consisting of the ischiopubic ramus, ischial tuberositas, pubic bone and the coccyx. The cervix consists of dense connective tissue and serves as a cornerstone of the upper female pelvic floor. The cervix is supported to the lateral pelvic side-wall by the strong cardinal ligaments and to the sacrum by the uterosacral ligaments.(27)

3.2 HYSTERECTOMY

3.2.1 History

Hysterectomy dates back to ancient times. Vaginal hysterectomy (VH) was performed by Soranus of Ephesus, 120 years A.D., and reports of hysterectomy being used in the Middle Ages exist. At this time, hysterectomy nearly always involved extirpation of a prolapsed uterus by strangulation, and the patient rarely survived. The first reported elective hysterectomy, using surgical instruments was performed through a vaginal approach by Conrad Langenbeck in 1813.(28) The first abdominal hysterectomy (AH) was performed by Charles Clay of Manchester in 1843 but the patient died in the immediate post-operative period. It was not until 1853 that Ellis Burnham from Lowell, Massachusetts achieved the first successful AH.(28)

Early hysterectomies were performed without anesthesia with a mortality of about 70%, mainly due to sepsis from leaving a long ligature in cervix (to encourage the drainage of pus). Introduction of cauterizing of the cervical stump brought the mortality rate down to about 8%. Hysterectomy became increasingly safer with the introduction of anesthesia, antibiotics, blood transfusions, and antiseptic surgical procedures. During the 1930s, Richardson introduced the total AH to avoid serosanguineous discharge from the cervical remnant, and the risk of cervical carcinoma developing in the stump. Abdominal and vaginal approaches remained the only two options until the latter part of the 20th century. In 1989 the first laparoscopic-assisted VH (LAVH) was performed by Harry Reich,(29) and in 1993 he reported the first total laparoscopic hysterectomy (TLH).

3.2.2 Rates of hysterectomy

Hysterectomy is now the second most frequently performed surgical procedure in women (after cesarean section) throughout the world. The rate of hysterectomy differs between countries, but also within countries, depending on differences in morbidity, health economical aspects, traditions and attitudes. (30, 31) In Table 1 the numbers and rates of hysterectomy (including radical hysterectomy) in the Nordic countries in 2006 are being presented.

Table 1. Hysterectomy (including radical hysterectomy) by age in the Nordic countries

Age (years)	Denmark	Faroe Islands	Finland	Iceland	Norway	Sweden
Number of patients in 2006						
<25	10	-	5	1	9	19
25-44	1,953	2	1,670	163	1,334	2,093
45-64	3,078	17	4,280	230	2,604	4,479
>65	1,043	5	1,563	47	886	2,191
Total	6,084	30	7,518	441	4,832	8,771
Rates per 100 000 women in 2006						
25-44	259	137	250	381	206	175
45-64	424	316	574	671	454	290
>65	221	131	310	244	225	246
Total	222	126	290	294	207	192

Figures are derived from a report by the Nordic Medico-Statistical Committee (NOMESCO).(32) NOMESCO was set up in 1966, following a recommendation by the Nordic Council and is responsible for the coordination of health statistics in the Nordic countries. Hysterectomy statistics in the Nordic countries are characterised by relatively high rates of surgery in Finland and Island (Table 1) and lower rates in Sweden and the Faroe Islands. This is concurrent with previous reports, in Finland the rate of hysterectomy in 1995 was estimated to be 414 per 100,000 women which was twice as high as in Sweden and Denmark.(33)

However, the rates of hysterectomy in the Nordic countries are considerably lower than in many other countries. In the US approximately 600,000 operations are made annually,(1) and almost one third of women have had a hysterectomy at the age of 60 years, and in Great Britain the corresponding figure is every fifth woman.(34) The approximate hysterectomy rate reported in the US has been 538 per 100,000, in Switzerland the rate has been 1,661 per 100,000 and in the Netherlands 381 per 100,000.(33, 35, 36) But, the rate of hysterectomy in the US has decreased slightly to 510 per 100,000 women in 2005.(37) From 1997 through 2005 hysterectomy rates decreased an average of about 1.9% per year and most of the decrease was observed in-between 2003 and 2006.(38) The explanation for this trend is not known, but one reason is thought to be an increased use of alternative treatments, including endometrial ablation or resection,(39) intrauterine-levonorgestrel releasing devices (40) and embolization of the uterine arteries.(41)

3.2.3 Indications for hysterectomy

Approximately ninety percent of hysterectomies are performed on benign indications to improve quality of life,(42) and the most common indication for surgery is uterine fibroids.(2, 38, 43) Other indications for hysterectomy on benign indications are dysfunctional bleedings, uterine prolapse, benign tumors, endometriosis, and adenomyosis.

3.3 TYPES OF HYSTERECTOMY

3.3.1 Total hysterectomy

When performing a total hysterectomy the entire uterus including the cervix is removed leaving the ovaries and the fallopian tubes (Figure 3A). It used to be clinical practice in Sweden to perform hysterectomy with removal of both the adnexas (bilateral salpingo-oophorectomy (BSO)) (Figure 3B), mainly to prevent ovarian cancer. But a change of trend has been seen: in 2003 only 1.5% of hysterectomies performed in Sweden included BSO (www.sfog.se/ARG+intressegrupper/arg-forord/Info61.pdf). Oophorectomy is more commonly performed in concurrence with abdominal or laparoscopic hysterectomy than with VH.(44)

3.3.2 Subtotal hysterectomy

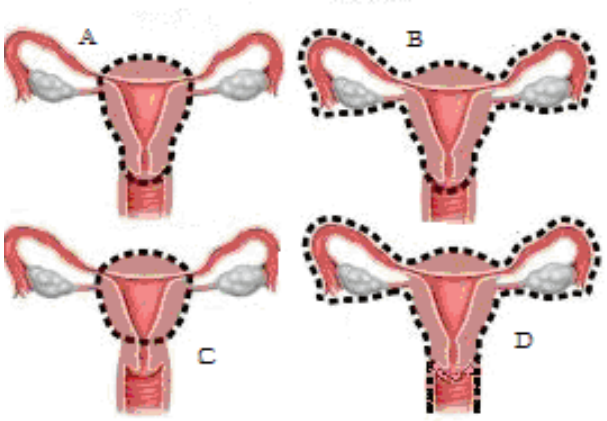
In subtotal AH, only the uterus is removed and the cervix is preserved (Figure 3C). The main disadvantage with this procedure is that it leaves the woman at risk for cervical cancer and for dysfunctional bleedings.(45)

3.3.3 Radical hysterectomy

Radical hysterectomy is performed in women with cervical cancer or endometrial cancer that has spread to the cervix (Figure 3D). At the time of radical hysterectomy, the uterus, cervix, proximal part of the vagina, ovaries, fallopian tubes, lymph nodes, lymph channels, and tissue in the pelvic cavity that surrounds the cervix are removed.

For the purpose of this thesis the term "hysterectomy" from now on refers to hysterectomy on benign indications only.

Figure 3. Types of hysterectomy



A. Total hysterectomy, B. Total hysterectomy with bilateral salpingo-oophorectomy, C. Subtotal hysterectomy, D. Radical hysterectomy

3.4 APPROACHES TO HYSTERECTOMY

3.4.1 Abdominal hysterectomy

AH has traditionally been used as the surgical approach for gynecological malignancies or when other pelvic pathology is present such as endometriosis, abdominal adhesions, and when the uterus is enlarged. It also remains the 'fallback option' if the uterus cannot be removed by another approach.(3, 46)

3.4.2 Vaginal hysterectomy

VH was originally used only for uterine prolapse, or when vaginal prolapse surgery was indicated, but has become more widely used for dysfunctional bleedings when the uterus is of a fairly normal size. Compared to AH, VH is less invasive and has the advantages of quicker return to normal activities, less postoperative pain and fewer perioperative infections. Thus, the conclusion of systematic reviews is that VH should be performed in preference to AH.(46)

3.4.3 Laparoscopic hysterectomy

Hysterectomy performed by laparoscopy has three subcategories: 1) LAVH is where a part of the hysterectomy is performed by laparoscopic surgery, but the uterine vessels are ligated vaginally, 2) laparoscopic hysterectomy (LH) is where the uterine vessels are ligated laparoscopically but a part of the operation is still performed vaginally, 3) total laparoscopic hysterectomy (TLH) is where the entire operation is performed laparoscopically and there is no vaginal surgery except for the removal of the uterus, if a morcellator is not used.(3) Compared with AH, LH is associated with a higher rate of major complications, takes longer to perform but is associated with less postoperative pain and shorter hospital stay.(46) In patients where VH is not possible it has been recommended that LH should be performed in preference to AH.(3)

3.5 EFFECTS OF HYSTERECTOMY

3.5.1 Short-term complications

Hysterectomy is regarded as a safe procedure with a low perioperative morbidity rate and relatively few short-term complications.(47) The mortality rate is estimated to 0.4% and the rate of severe complications has been reported to 3%.(48) In Table 2 perioperative complications in relation to mode of hysterectomy is described, the data is adopted from a systematic review of 27 randomized clinical trials (RCT) with 3,643 participants (Table 2).(49)

Table 2. Perioperative complications of hysterectomy.

Complications	Mode of hysterectomy		
	Abdominal hysterectomy	Vaginal hysterectomy	Laparoscopic hysterectomy
Wound infection	7.4	0	1.9
Fever or unspecified infection	13.1	7.7	10.0
Thrombo-embolism	0	0	0.6
Urinary tract injury	0.9	1.6	2.3
Bowel injury	0.7	0	0.2
Vascular injury	0.8	0.9	1.8
Blood transfusion	3.3	3.9	4.2
Pelvic hematoma	6.0	4.0	3.9
Vaginal cuff infection	2.1	1.9	4.2
Urinary tract infection	4.9	1.3	4.8
Laparatomy	-	2.7	4.1

Figures are percentages

3.5.2 Quality of life

The short-term effect of hysterectomy on quality of life is satisfactory according to most studies.(50) Two years after having had a hysterectomy, 96% of women reported that having had a hysterectomy completely or mostly resolved their problems in a study by Kjerulff et al.(51) In the Maine Women's Health Study, participating women reported a significant overall improvement in pelvic discomfort, urinary symptoms, and psychological and sexual symptoms at one year after hysterectomy.(52) In the Maryland Women's Health Study, patients were followed for up to 2 years after

hysterectomy for non-malignant conditions. Symptoms related to the underlying indication for surgery, as well as, associated symptoms of depression, anxiety, and overall quality of life, improved after hysterectomy.(53)

3.5.3 Long-term effects

The biological long-term effects of hysterectomy are not as well investigated as perioperative morbidity and the short-term consequences. In a Cochrane review from 2009,(3) the authors concluded that data were still lacking for many important long-term outcome measures and that further research in the field was needed. Among other long-term outcomes that should be considered in the surgical decision making are effects of hysterectomy on the pelvic floor including: sexual function, POP, UI, bowel dysfunction, and pelvic organ fistula formation.

3.6 HYSTERECTOMY AND PELVIC FLOOR DYSFUNCTION

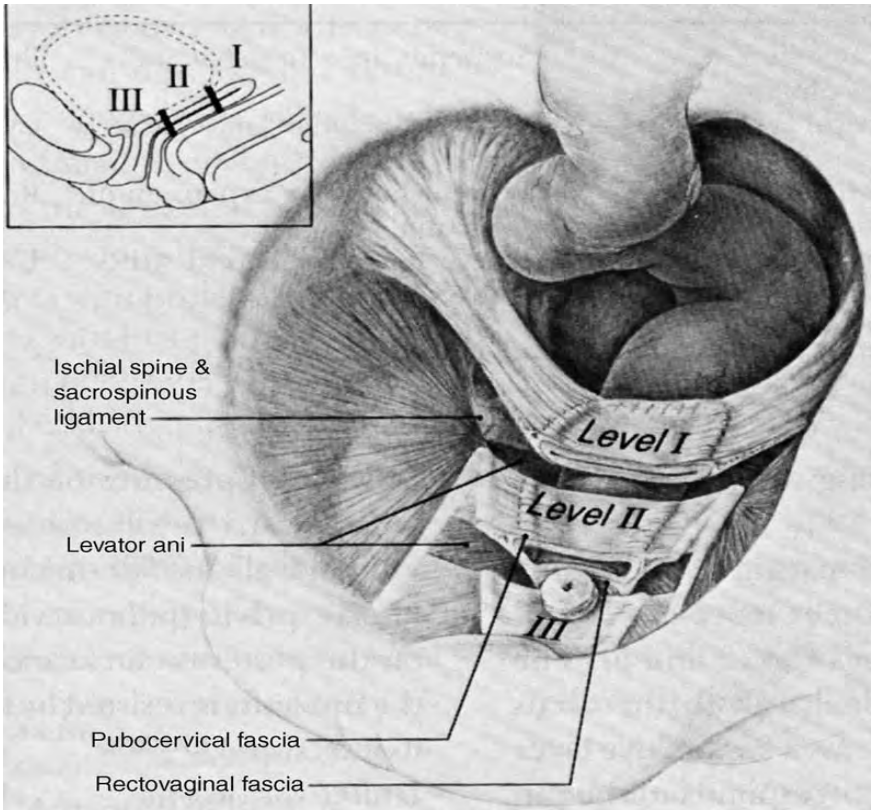
3.6.1 Pathophysiological mechanisms

There are several possible mechanisms for the development of pelvic floor dysfunction subsequent to hysterectomy. Direct iatrogenic injury to the soft tissue supportive structures and disruption of the supporting fascias and ligaments are actions which may distort pelvic organ anatomy subsequent to a hysterectomy. Changes of anatomical relationships between the bowel, bladder, and vagina after surgery may have a direct impact on the function of these organs. Alterations of pelvic organ function could also be attributed to changes in functional dynamic anatomy and innervations of pelvic organs.(4, 54) Furthermore, a decreased collateral blood supply to the pelvic organs and their surrounding tissues may have a long-term impact on pelvic organ function.

Disruption of the supporting fascia and ligaments

DeLancey described three levels of normal vaginal support (Figure 4) (55) and depending on the degree of disruption to the supporting fascia and ligaments, various types of prolapse may occur after hysterectomy. The first level of support (Level I) is represented by vertical fibers of the paracolpium, which are a continuation of the cardinal ligaments. Insufficient suspension of the vaginal apex by these ligaments can lead to vaginal vault prolapse after surgery. Disruption to level II vaginal support (pubocervical or rectovaginal fascia) may result in development of anterior vaginal wall prolapse (cystocele) or posterior vaginal wall prolapse (recto- entero- sigmoideo- or peritoneocele). Cadaver studies have shown that it is not possible to evert the vaginal apex as long as these fascias are intact.(55) In level III, the attachments of the distal vagina to the medial margins of the levator ani muscles are very dense, to ensure that the lower portion of the vaginal wall remains attached in this region.

Figure 4. Levels of vaginal support as described by DeLancey.



At level I, the paracolpium suspends the vagina from lateral pelvic walls. Fibers of level I extend both vertically and also posteriorly toward the sacrum. At level II, the vagina is attached to the arcus tendineus fascia of the pelvis and superior fascia of levator ani muscles. Reprinted with permission from the author. DeLancey J. Anatomical aspects of vaginal eversion after hysterectomy. Am J Obstet Gynecol 1992; 166: 1717–1728.

Risk of nerve damage during hysterectomy

The bilateral inferior hypogastric plexa provide sympathetic and parasympathetic innervation to the lower pelvic viscera and are located in close proximity to the proximal vagina and distal rectum. During the course of surgery, the pelvic plexus may be at risk for injury in several areas: at the division of the cardinal ligaments, at the blunt dissection of the bladder from the uterus, at the dissection of the paravaginal tissue,(4) and at the removal of the cervix.(56) The pelvic floor muscles, as well as, urethral and anal sphincters are also innervated by distal branches of the pudendal nerves, supplying motor and sensory innervations.

Urinary incontinence

Damage to the distal branches of the pudendal nerves and the inferior hypogastric plexa might impede the intricate urethral sphincter closing mechanism and cause chronic or progressive denervation injury. This may eventually lead to the development of

incontinence.(8, 54) Post hysterectomy alterations in urethral innervations and anatomical conditions also give rise to changes of urethral pressure dynamics and bladder neck support, resulting in a deterioration of urethral function.(55) However, stress urinary incontinence (SUI) and urge urinary incontinence (UUI) may have different pathophysiology as well as different predisposing risk factors.(57)

Bowel dysfunction

The pelvic plexus is of paramount importance in the coordinated contractions of the smooth muscle of the bowel (58) and impairment of the innervations can possible result in bowel dysfunction and constipation. Sharp or blunt severing of pelvic organ supportive tissues, at the time of hysterectomy, may interfere with the anorectal innervation, mainly the pudendal nerve, and provide the pathophysiologic basis for anal incontinence. The etiology of bowel dysfunction after hysterectomy may also involve changes in rectal support and dynamics.(22)

Iatrogenic injuries during surgery

Iatrogenic injury to the urinary tract and bowels occasionally occur during hysterectomy.(59, 60) The incidence of urinary tract injury, detected by cystoscopy, was reportedly as high as 4.3% in a recent study.(61) The formation of fistulas between pelvic organs subsequent to hysterectomy is thought, among other factors, to be a complication of iatrogenic injury to the organs involved. Possible mechanisms behind fistula formation in the aftermath of hysterectomy includes injury during the dissection of the bladder, sutures incorporated into the bladder, and direct injury to the lower urinary tract or to the bowels,(62, 63) most commonly the rectum.(59) Without the dense smooth muscle uterus in place to act as a protective buffer, postoperative infections of the vagina or paravaginal tissues may act as a source for fistula formation soon after surgery, a process which may be precipitated by injury to the surrounding pelvic organs.

3.6.2 Sexual function

Consistent evidence suggests that the majority of women have unchanged or improved sexual function 1–2 years after hysterectomy.(52, 53) It has been suggested that subtotal AH provides a better postoperative sexual function,(64) but this notion was refuted by a systematic review of Lethaby et al.,(65) which concluded that there was no evidence to support the concept that leaving the cervix was associated with improved sexual function. However, many of the long-term effects of hysterectomy on sexual function are still unknown.(50)

3.6.3 Pelvic organ prolapse

POP is a major cause of morbidity affecting up to 50% of parous women over 50 years of age.(66) In the US, approximately 300,000 inpatient surgical procedures for POP are performed each year,(18) and in Sweden the corresponding figure is 7,000 procedures per year (www.socialstyrelsen.se/statistik). POP also causes important costs for the healthcare systems worldwide.(67) Women with POP may present with a variety of complaints, such as bladder and bowel emptying difficulties, urinary and fecal incontinence, or vaginal mechanical symptoms such as bulging, pelvic heaviness or the feeling of pelvic pressure. The symptom most strongly correlated to the presence

of advanced prolapse is considered to be the sensation of a vaginal bulge and globus feeling.(68)

Classification of pelvic organ prolapse
In 1996 the International Continence Society (ICS) presented a system to quantify and characterise POP according to vaginal topography, the POP-Q.(69) Although other systems are still in use, most often the Baden-Walker halfway system, the POP-Q remains the only validated tool for prolapse grading and quantification. According to the POP-Q, predefined measures of vaginal topography (anatomic points in the vagina and perineum) are used to assign an ordinal stage of prolapse in relation to the hymen. Absence of prolapse is defined as stage 0 and stage IV represents complete vault eversion.

Risk factors for pelvic organ prolapse
The etiology of POP is almost certainly multifactorial,(70) and several predisposing factors are suggested in the literature. Jelovsek et al. propose that established risk factors for POP are: vaginal delivery, advancing age and obesity.(6) Other possible predisposing factors include obstetrical factors, parity,(5, 71, 72, 73) increased fetal weight,(66, 74) and instrumental delivery.(71) Also other environmental risk factors have been identified such as occupations which entails heavy lifting,(75) chronic constipation,(76) connective-tissue disorders,(77) and genetic factors.(78) Most clinicians agree that hysterectomy is a risk factor for POP but only in recent years have epidemiological evidence to support this notion been presented.(5-7) Nonetheless, many aspects of the association are poorly understood and the effects of time have not been adequately accounted for due to the lack of long-term data.

Treatment of pelvic organ prolapse
Surgery remains the mainstay of treatment for POP although conservative management such as pessaries are still in widespread use.(79) Surgical treatment for POP can be categorized as reconstructive or obliterative surgical techniques. Reconstructive surgery for POP aims to anatomically correct the prolapsed vagina while maintaining its function and providing relief of prolapse symptoms. Meanwhile, obliterative surgery is mainly performed on elderly, no longer sexually active women, where normal function of the vagina becomes secondary to the reduction of severe prolapse symptoms. There is a wide variety of surgical treatments but no consensus on which is the gold standard surgical procedure. Traditionally, anterior and posterior repair and VH are among the most frequently performed operations in prolapse surgery.(80) The introduction of site specific repair,(81) and biological and synthetic implants are widening the surgical options and changing surgical routines.(80)

3.6.4 Urinary incontinence

UI may negatively affect quality of life with wide-ranging human and social implications causing distress, embarrassment and loss of self assurance.(82) Symptoms of UI are common especially among elderly, afflicting 17-46% of woman over 60 years old,(8) with a population-based overall prevalence ranging from 25 to 49% depending of definition.(16, 19, 20)

Urinary incontinence subtypes

SUI is the complaint of involuntary leakage of urine at sudden increased abdominal pressure such as heavy lifting, sneezing or coughing.(83) The prevalence of SUI peaks in the fifth decade of life and gradually decreases with older age.(84) UUI is the complaint of involuntary leakage accompanied by or immediately preceded by urinary urgency.(83) Mixed UI (MUI) contains components of both SUI and UUI. The prevalence of UUI and MUI is thought to increase with age.(84) Other definitions of incontinence frequently used is over active bladder (OAB) defined as the presence of urgency and frequency (either daytime or night-time), with or without UI,(83) and lower urinary tract symptoms (LUTS) describing a wide variety of urinary symptoms including those of UI.

Risk factors for urinary incontinence

Common risk factors associated with UI include childbirth, increasing age, overweight and obesity, and other comorbidities.(84) The association between hysterectomy and the development of UI has been a subject of much debate with a lack of convincing data establishing causality. Although several observational studies imply that hysterectomy is associated with a deterioration of bladder function,(8, 10, 11) other studies have come to opposite results.(52, 85) There are a few randomized clinical trials studying the short-term associations of hysterectomy and UI (Table 3) but none have investigated the long-term effects. Furthermore, evidence from randomised clinical trials and prospective clinical cohort studies have been limited by the lack of non-hysterectomized control groups.(86, 87) Thus, the effects of hysterectomy compared to not having had a hysterectomy at all remains disputed. There are also discrepancies between studies using self-reported questionnaires to describe lower urinary tract function and studies using objective measures such as urodynamics.(54)

Table 3. Randomized clinical trials comparing urinary incontinence symptoms after total abdominal hysterectomy versus subtotal abdominal hysterectomy.

First author, country and year of publication	Number of participants	Duration of follow-up	Urinary incontinence symptoms
Thakar, UK, 2002 (88)	279	1 year	Less symptoms in both groups
Gimbel, Denmark, 2003 (89)	319	1 year	Less symptoms after total abdominal hysterectomy
Learman, USA, 2003 (90)	135	2 years	Less symptoms in both groups

Treatment of stress urinary incontinence

Alternatives available for treatment of SUI includes surgery, physiotherapy (including pelvic floor muscle training, electric stimulation, acupuncture, and vaginal devices), and pharmacologic treatment. Pelvic floor muscle training is generally considered the

first-line conservative management of SUI and is consistently better than no treatment or placebo treatment.(91) Second-line treatment includes surgery, of which the midurethral polypropylene vaginal tape procedures (TVT, TVT-O) are widely considered gold standard (92) given a lower morbidity although comparable clinical results when compared with colposuspension (57, 91, 93) Pharmacologic treatment options primarily targets UUI and OAB, whereas efforts to introduce drugs for the treatment of SUI have been largely unsuccessful (Duloxetin). The most frequently used treatment for OAB is anticholinergic substances such as tolterodin, darifenacin and solifenacin.(94) Traditionally, estrogens have been used to ameliorate incontinence symptoms but have not reduced incontinence episodes in any of several large randomized trials.(95, 96)

3.6.5 Bowel dysfunction

Bowel dysfunction is common in the female general population,(21) and particularly common among women with gynecological symptoms.(97, 98) Bowel dysfunction includes a wide range of symptoms and diagnoses such as constipation, irritable bowel syndrome, functional rectal emptying difficulties and anal incontinence. The co-morbidity between bowel dysfunction and other pelvic organ disorders is considerable.(99)

Constipation

The term constipation is used to describe a reduction in frequency of bowel movements, the need to strain, or the passage of a hard bowel motion. A recent consensus has been reached as to the definitions of constipation, termed the Rome definition, which also includes the time aspect, the sensation of incomplete evacuation, straining at defecation, hard pellets or stools, and the exclusion of irritable bowel syndrome.(100) First-line treatment of constipation is increased fluid and fiber intake, and physical activity. A patient who does not respond to these measures, which is often the case, is recommended an osmotic laxative such as lactulose. Colonic stimulants, such as bisacodyl should be reserved for patients with severe constipation, and in some particular cases surgery is performed.(21)

Anal incontinence

Anal incontinence is a socially embarrassing and physically disabling condition, and is defined as the uncontrollable and unwanted loss of feces or gas. Anal incontinence may result from damage to the anal sphincter complex, idiopathic (senile) degeneration of the sphincter, neurological disease, or nonsphincter causes (e.g., diarrhoea, dementia). Clinical treatment is conservative in the first instance, including absorbent pads or anal plugs, dietary advice, antidiarrheal medication, pelvic floor muscle training and biofeedback. In patients where anal sphincter defects are thought to contribute to the symptoms, secondary sphincter repair may be performed.(101)

The role of hysterectomy

Many women date the onset of bowel symptoms to hysterectomy, although there is no conclusive evidence to indicate causation. Several studies also attribute alterations of bowel function to a previous hysterectomy,(102, 103) usually resulting in constipation and rectal emptying difficulties.(104) But there is no agreement among researchers and

several studies and reviews have found no association between hysterectomy and bowel dysfunction.(22, 105) Some of the studies, showing an association between hysterectomy and bowel dysfunction, have been criticized for their retrospective nature and for not stratifying on bowel dysfunction according to type of hysterectomy.(22) Research has also been hampered by the lack of clear definitions for different types of bowel dysfunction.

3.6.6 Pelvic organ fistula

A fistula is defined as an abnormal epithelium lined duct which connects two organs. Pelvic organ fistula disease is a devastating condition which is difficult to treat and often demands repeat surgical interventions.(62, 106) Fistulas resulting from obstetric trauma remain a major problem in developing countries, whereas fistula disease as a complication of childbirth is rare in industrialized countries due to advances in modern obstetrical care.(107) Instead, pelvic surgery, and hysterectomy in particular, are widely considered a major cause of genital fistula disease.(106) According to some authors, 90% of the fistulas associated to pelvic surgery are caused by AH.(108) Other important causes of fistulas include pelvic radiation, malignancy, infection, trauma or foreign bodies.(62) The incidence of fistulas after hysterectomy on benign indication is unknown, but has been estimated to be less than 1%.(109) The true incidence of pelvic organ fistula in the general population is also uncertain but has been estimated to range between 0.3 and 2%.(62)

Types of fistulas

The main types of fistulas are; urogenital fistula, intestinogenital fistula, urointestinal fistula, anorectal fistula and non-specified pelvic organ fistula (Table 4). The exact etiology of fistulas in relation to hysterectomy is incompletely investigated.

Table 4. Types of fistulas and the pelvic organs involved

Type and subtypes of fistula	Organs involved
Urogenital fistula	
Vesicovaginal fistula	Bladder and vagina
Ureterovaginal fistula	Ureter and vagina
Intestinogenital fistula	
Rectovaginal fistula	Rectum and vagina
Colovaginal fistula	Colon and vagina
Urointestinal fistula	
Colovesical fistula	Colon and bladder
Rectovesical fistula	Rectum and bladder
Ileovesical fistula	Small bowel and bladder
Appendicovesical fistula	Appendix and bladder
Anorectal fistula	Anus and rectum
Non-specified pelvic organ fistula	Unknown pelvic organs

Treatment of pelvic organ fistulas

Fistulas to the female urogenital tract are notoriously difficult to treat,(110) and often require repeat surgery, as well as, major surgery. The type of surgery varies much depending on type of fistula, for example vesicovaginal fistulas can be repaired by the transvaginal route with a high success rate and minimal morbidity.(62) While in other fistula types, the vaginal access is insufficient, and abdominal repair is necessary.(111)

4 AIMS

The overarching aim of this thesis is to study the effects of hysterectomy on benign indications on pelvic organs and pelvic floor function using clinical and epidemiological methodology.

The specific aims were to:

1. investigate the annual rates, types and indications for hysterectomy on benign indications in Sweden 1987- 2003 (Paper 1).

2. prospectively evaluate long-term effects of abdominal and vaginal hysterectomy on bowel function (Paper II).

3. identify risk factors for surgically managed vaginal vault prolapse after hysterectomy for benign indications (Paper III).

4. study the association between hysterectomy for benign indications and pelvic organ fistula disease and to estimate the effect of various hysterectomy techniques on the association (Paper IV).

5. assess if risks of subsequent pelvic organ prolapse and stress urinary incontinence after vaginal hysterectomy are attributable to the procedure itself or to the preoperative surgical indication (Paper V).

5 PATIENTS

Ethical approval from the Research Ethics Committee at Karolinska Institutet was obtained prior to initiation of all studies (ethical permit numbers 04-691/5 paper I, IV and V, 00-224 paper II and 2005/1296-31 paper III).

5.1 PAPER I

Based on the Swedish Inpatient Register we included all women who had undergone a hysterectomy in Sweden from January 1, 1987 through December 31, 2003. During the study period a total of 155,505 hysterectomies were performed. We excluded 33,558 patients due to malignant indications, leaving 121,947 hysterectomized women for analyses.

5.2 PAPER II

Patients scheduled for elective hysterectomy on benign indications were recruited at the Department of Obstetrics and Gynecology, Danderyd Hospital. A total of 121 consecutive patients were invited to participate and 120 agreed after written and oral informed consent. Seventy-six patients underwent AH and 44 VH. In the abdominal cohort, 17 patients underwent BSO and six patients unilateral salpingo-oophorectomy. None of the women in the VH group had bilateral or unilateral salpingo-oophorectomy. The predominant indication for hysterectomy was dysfunctional bleedings. Mean age at the time of surgery was 49.5 (SD±8.7) years.

5.3 PAPER III

Using hospital inpatient records, we identified all patients having had post hysterectomy vaginal vault prolapse surgery at the Department of Obstetrics and Gynecology, at Danderyd Hospital or Karolinska Hospital, between 1996 and 2005. For each patient with vaginal vault prolapse surgery, we randomly selected three control participants from the Swedish Inpatient Register. The controls had also had hysterectomy, but had no record of vaginal vault prolapse surgery, and they were individually matched by year of birth to the case subjects. Ninety out of 117 women in the case group and 233 out of 326 women in the control group agreed to participate. The mean age at hysterectomy was 54.6 (SD±13.0) years in the case group and 59.4 (SD±12.6) years in the control group.

5.4 PAPER IV

We defined our exposed cohort by identifying all records in the Swedish Inpatient Register indicating a performed hysterectomy from January 1, 1973, until December 31, 2003 (exposed cohort). For every woman having had a hysterectomy, we randomly selected three women not having had the procedure from the Register of the Total Population. Women with an intact uterus were defined as our unexposed cohort and individually matched to hysterectomized women by year of birth, calendar date for the hysterectomy (start of follow-up), and county of residence at the year of hysterectomy. Exclusion criteria implemented for both the exposed and unexposed group included: 1) if fistula surgery preceded or concurred with study entry; 2) if the hysterectomy was

performed on malignant indications; 3) if the patient had any record in the Cancer Register at the entry to the cohort; 4) if the patient had any record of Crohns disease, ulcerous colitis, or diverticular disease, before, or at entry to the cohort, or; 5) if the patient was younger than 18 years of age at study entry. The final study population available for analysis included 182,641 women having had a hysterectomy and 525,826 women not having had a hysterectomy. Mean age at study entry was 49.5 (SD±10.9) years in the exposed cohort and 49.1 (SD±10.7) years in the unexposed cohort.

5.5 PAPER V

The study population was derived from the same population sample as the study group in Paper IV but the exclusion criteria's were modified. In the exposed cohort, we included only women having: VH with concurrent POP repair, VH without prolapse repair, and women having total AH for other indications than POP. Exclusion criteria implemented for both groups were: 1) if POP or SUI surgery had preceded study entry, 2) if the hysterectomy was performed on malignant indications, 3) if the subject had any record in the Cancer Register at entry, or 4) if the subject was younger than 18 years of age. The final study cohort consisted of 697,801 women: 118,601 women having had a hysterectomy and 579,200 individually matched women not having had a hysterectomy.

6 METHODS

6.1 STUDY DESIGN

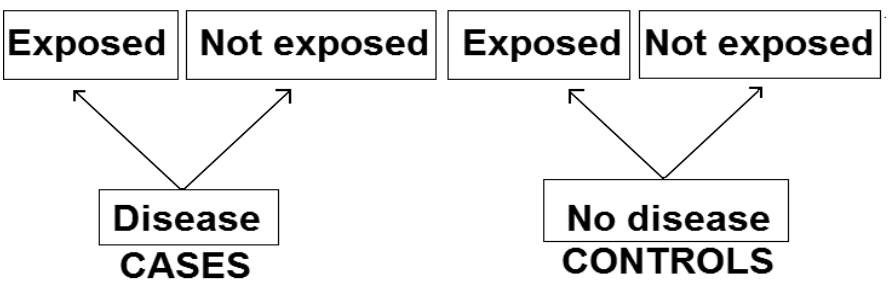
Introduction

Epidemiology, "the study of what is upon the people", is derived from the Greek terms *epi* = upon, *demos* = people, *logos* = study. In the 19th century Dr John Snow and his identification of the Broad street water pump as the cause for the Soho cholera epidemic, is considered the first example of what was to become classic epidemiology.(112) The purpose of epidemiology is to better understand disease causation and to prevent disease in groups of individuals.(113) Epidemiology assumes that disease is not distributed randomly in a group of individuals, and that identifiable subgroups are at increased risk of particular diseases. For example, Doll and Hill's studies in the 1950s showed that smokers who smoked ten to twenty cigarettes a day, had a lung cancer mortality rate that was about ten times higher than that for non-smokers, which contributed to the determination that smoking causes lung cancer.(114) Different study designs may be chosen because of suitability for investigating the question of interest, timing constraints, resource limitations, or other considerations. I here provide a short summary of study designs used in the present thesis.

The case-control study

Case-control studies are observational studies where the researcher begins with a group of individuals who have a disease (cases) and then selects a group of individuals who do not have the disease (controls) (Figure 5). The groups are then compared in terms of past exposures. If a certain exposure is associated with, or has caused the disease, a higher proportion of past exposure among the cases, than among the controls, would be expected. Advantages of the case-control study are that it can be completed in less time, with lower expense than a cohort study and the methodology is particularly useful in the investigation of rare diseases. In study III we performed a nested case-control study, the term nested, signifying that the cases and the controls were taken from a common cohort of people, in this case women having had a hysterectomy. The "disease" was defined as vaginal vault prolapse and several exposures were investigated, for example parity and mode of hysterectomy.

Figure 5. Schematic description of a case-control study.



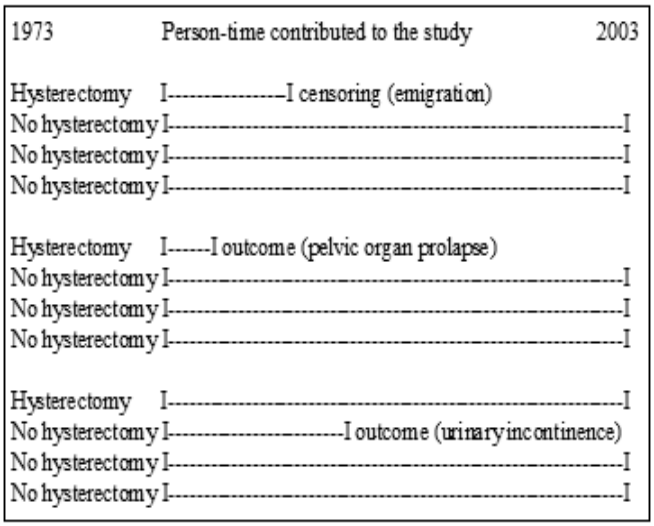
The cohort study

The cohort study is a type of observational study where subjects are selected based on their exposure status. The study subjects should be at risk of the outcome under investigation at the beginning of the study; this usually means that they should be disease free when the cohort study starts. The cohort is followed over time to assess their later outcome status.

Paper IV and V are cohort studies using prospectively collected data. The exposure was defined as hysterectomy and the exposed cohort consisted of all women having had a hysterectomy in Sweden from January 1, 1973, until December 31, 2003. The unexposed cohort consisted of a matched group of women not having had a hysterectomy. The outcome, signifying the event to happen, was defined as pelvic organ fistula, POP or SUI surgery (in paper IV and V respectively).

In a cohort study the time aspect is important to consider, thus we evaluated the data with survival analysis. Instead of considering only the number of events we studied the incidence rate which represents the number of events per person-years. Person-years are the actual time at risk, in years, that every woman contributed to the study (Figure 6). Person-time was calculated from the entry to the cohort (date of hysterectomy or the corresponding date for the non-hysterectomized women) until the first occurrence of the outcome /event, censoring, or end of follow-up (December 31, 2003). Women who are censored contributed person-time until the day of censoring, whereas women who are excluded did not contribute to any person-time. Censoring in paper IV included diagnosis of Crohns disease, ulcerous colitis, diverticular disease, any type of cancer disease, death or emigration, and in paper V included any type of cancer disease, death or emigration.

Figure 6. Schematic description of the person-time contributed to the study on an individual basis.



6.2 DATA SOURCES

Questionnaires

We used questionnaires to collect data about the patients in paper II and III. The questionnaire in paper II consisted of two parts, one part covering general health, gynecological history, current medications and lifestyle. The other part covered current bowel function. The questionnaire in paper III contained only questions regarding general health, gynecological and obstetrical history, current medications and lifestyle (both questionnaires supplied in Appendix).

The questionnaire on bowel function,(115) is recommended by the Swedish Society of Colorectal Surgeons and has proven to be valid, reliable, sensitive to change over time and easily comprehended in previous studies. It has been used by our research team in several published studies.(116, 117) Response alternatives are measured on an ordinal scale based on frequency of symptoms. The response alternatives are categorized as: no symptoms, symptoms less than or once per week, more than once per week, or daily. Questions about anal incontinence symptoms were combined to form an index according to the Cleveland Clinic Incontinence Score (CCIS),(118) and were used to assess anal incontinence in paper II (Table 5 and 6). Normal anal continence is considered all CCIS from 0 to 7 (Table 6).

Table 5. Anal incontinence points forming the Cleveland Clinic Incontinence Score.

Frequency	Symptoms of anal incontinence and points given			
	Gas leakage	Liquid stool leakage	Solid stool leakage	Use of protective pads
Occasionally	1	4	7	1
> 1/ Week	2	5	8	2
Daily	3	6	9	3

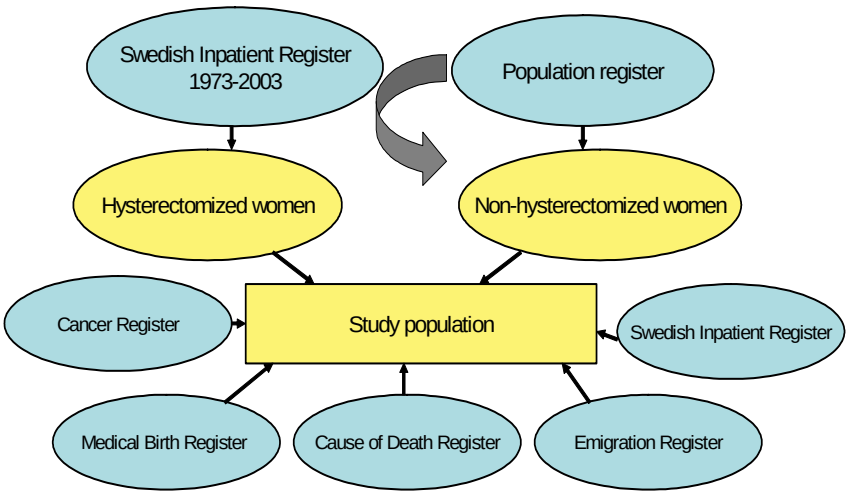
Table 6. Anal incontinence index Cleveland Clinic Incontinence Score

Score	Anal incontinence
0--	Perfect continence
1--7	Good continence
8--14	Moderate incontinence
15--20	Severe incontinence
21--	Complete incontinence

Nationwide Swedish registers

In paper I, III, IV and V we used data from the Swedish Inpatient Register. This was possible due to the individually unique national registration number (NRN), assigned to all Swedish residents at immigration or birth. The NRN allows unambiguous record linkage across all national registers. Using the NRNs, our cohorts in paper IV and V were linked to other nationwide Swedish registers (Figure 7), including the Cancer Register, the Emigration Register, and the Cause of Death Register. Information on parity was derived from the Medical Birth Register, which contains data on childbirths in Sweden since 1973 and onwards.

Figure 7. Schematic view of record linkage across the Swedish national registers



The Swedish Inpatient Register

The Swedish Inpatient Register contains data on individual hospital discharge diagnoses according to the International Classification of Diseases (ICD). ICD-7 was used until 1968, ICD-8 from 1968 through 1986, ICD-9 from 1987 through 1996, and ICD-10 thereafter (Table 7). In 1973, the register covered more than 60% of the population, in 1983 the coverage was 85%, and from 1987 it has complete national coverage (http://www.socialstyrelsen.se).

The individual inpatient discharge records also contain the dates of hospital admission and discharge, and up to 12 operation codes according to the Swedish Classification of Operations and Major Procedures (Table 8). Ninety-eight percent of records achieved correct coding for surgical procedures with a less than 1% yearly loss to registration when cross-checked with hospital charts.(119) Classification of diagnosis and surgical procedures used in paper I,III,IV and V, are listed in Table 7 and 8.

Table 7. Diagnosis for surgery according to the ICD 8-10 used in paper I, III, IV and V.

	International Classification of Diseases codes		
Diseases and indications for surgery	ICD -8	ICD -9	ICD -10
Urogenital fistula	599B	619	N360, N820, N821
Intestinogenital fistula	629, 80, 565B	619B	N822, N823, N824
Urointestinal fistula	596B, 596C	619A	N321, N322
Anorectal fistula	565,10	565B	K603, K604, K605
Unspecified pelvic organ fistula	619C, 619W, 619X	619C, 619W, 619X	N825, N828, N829
Dysfunctional bleedings	6262, 6264, 6266, 6270, 6259, 6269	6264, 6270, 6268, 6269	N92.0, N92.1 N92.4, N92.5, N92.6
Uterine prolapse	6239	6181, 6182, 6183, 6184	N81.2, N81.3, N81.4
Uterine fibroids	218	218	D25.9
Ovarian cysts and benign tumours	220, 228, 2113, 2560, 6152	220, 6202	D27.9, N83.2
Endometriosis	6253	6171-6176, 6178, 6179	N80.1-9
Adenomyosis	6253	6170	N80.0

Table 8. Classification of surgical procedures according to the Swedish Classification of Operations and Major Procedures used in Paper I, III, IV and V

	Operation codes for surgical procedures	
Surgical procedure	Operation code 1973–1996	Operation code 1997–2003
Abdominal total hysterectomy	7210	LCD00
Abdominal subtotal hysterectomy	7211	LCC10
Vaginal hysterectomy	7261, 7262	LCD10
Vaginal hysterectomy with concurrent pelvic organ prolapse surgery	7467	LEF13
Laparoscopy-assisted vaginal hysterectomy	-	LCD11
Laparoscopic total hysterectomy	-	LCD01–04
Anterior colporraphy	7460	LEF00
Posterior colporraphy	7461	LEF03
Vaginal enterocele obliteration	7466	LEF40
Manchester procedure	7462	LEF10
Colpocleisis	7464	LEF23
Partial colpocleisis	7463	LEF20
Abdominal sacrocolpopexy	-	LEF50
Vaginal sacrospinous fixation	-	LEF53
Kennedy or Kelly sutures	7470	LEG00
Abdominal and laparoscopic Burch colposuspensions	6355	KDG20-21
Stamey procedures,	6356	KDG10
Marshal-Marchetti-Krantz procedures	6358	KDG20-21
Ingelman-Sundberg plasty, IVS	7472	LEG20
Suburethral slings and tension free vaginal tapes	7471	LEG10, LEG 96

6.3 PAPER I

We performed a descriptive observational cohort study. It was a nationwide study based on the Swedish Inpatient Register to investigate the annual rates, types and indications for hysterectomy on benign indications in Sweden 1987-2003. The source of data, classification of surgical procedures, and diagnosis for the operation was derived from the Swedish Inpatient Register based on the Swedish Classification of Operations and Major Procedures and the International Classification of Disease (ICD) versions 9 and 10.

6.4 PAPER II

This was a prospective clinical cohort study investigating bowel symptoms in women subsequent to hysterectomy. A written questionnaire (Appendix) was completed before surgery, including questions to determine symptoms of constipation, bowel emptying difficulties, manually assisted defecation, and anal incontinence on ordinal scales.(115)

Patients were subsequently evaluated at 1 and 3 years postoperatively by using an identical questionnaire. General health and obstetric history, including information about obstetric sphincter lacerations was registered in a separate protocol.

6.5 PAPER III

We performed an observational nested case-control study to identify risk factors for surgically managed post hysterectomy vaginal vault prolapse. For patients and controls alike, data on determinants was extracted from the Swedish Inpatient Register and self-reported questionnaires. All cases and control subjects were contacted by ordinary mail, and requested to complete and return a standardised questionnaire regarding general health, gynecological and obstetrical history, current medications and lifestyle. From the Swedish Inpatient Register we gathered information about the date and mode of hysterectomy, as well as, information on POP and SUI surgery prior, or subsequent, to the hysterectomy.

6.6 PAPER IV

We performed a nationwide register-based observational cohort study, using Swedish health care registers, to study the association between hysterectomy and pelvic organ fistula disease. The exposed cohort (women with hysterectomy) and the unexposed cohort (women with no hysterectomy) were identified in the Swedish Inpatient Register 1973–2003. The outcome was defined as surgery for pelvic organ fistula disease. Using NRNs, our cohorts were linked to other nationwide Swedish registers, including the Cancer Register, the Emigration Register, and the Cause of Death Register. The women were followed up from the time of entry into the cohort, until the first occurrence of pelvic organ fistula surgery, censoring (Crohns disease, ulcerous colitis, diverticular disease, any type of cancer disease, death, emigration) or end of follow-up (December 31, 2003), whichever came first.

6.7 PAPER V

In this nationwide observational cohort study based on Swedish health care registers, we aimed to determine if the risk for POP and SUI after VH is mainly attributable to the surgical procedure or to the preoperative surgical indication. The exposed cohort (women with hysterectomy) and the unexposed cohort (women with no hysterectomy) were identified in the Swedish Inpatient Register 1973–2003. The outcome was defined as surgery for POP or SUI. Using national registration numbers, our cohorts were linked to the Cancer Register, the Emigration Register, the Cause of Death Register and the Medical Birth Register. Person-time at risk was calculated from the date of entering the study until end of follow-up, which was defined as: first occurrence of either POP or SUI surgery, any type of cancer disease, death, emigration, or end of study period, whichever came first. The primary outcome measures were dichotomised as present or not present. Surgically managed POP after hysterectomy was also categorized by the anatomical compartment involved: anterior prolapse repair, posterior prolapse repairs, and total prolapse surgery, each analyzed separately.

7 STATISTICAL ANALYSES

7.1 PAPER I

Hysterectomy rates were calculated as number of events per 100,000 person-years, where the number of person-years was estimated as the sum of the mean number of women above 18 years of age, residing in Sweden each year, according to Statistics Sweden (http://www.scb.se). The Inpatient Register covers all hysterectomies performed in Sweden from 1987 and onwards, thus, there is no random error due to sampling procedures. Consequently, statistical inference such as confidence intervals (CIs) and calculation of p-values for hypothesis tests is redundant, when exploring the situation in the country regarding hysterectomy rates. All age-adjusted rates were calculated using the standard population method with the mean population 2003 as standard population in one year age intervals. All calculations were performed using SAS 9.1 software (Cary, NC, USA).

7.2 PAPER II

Non-parametric data were analyzed by using the Wilcoxons matched pairs test for continuous data. Risk factor analysis was performed using multivariate logistic regression. Results from logistic regression are presented as odds ratio (OR) with 95% CIs. A p-value < 0.05 was considered significant for all analyses. Statistical analysis was performed using Statistica software (Statistica®, Statsoft Inc., Tulsa, OK, U.S.A.).

7.3 PAPER III

Analyses were restricted to subjects responding to the questionnaires. Non-parametric continuous data were analyzed using the Mann-Whitney U-test for independent samples. Risk factor analyses were performed using univariate logistic regression. Co-variates found to be statistically associated with the outcome in univariate analyses, were entered into a multivariate logistic regression model to compute adjusted ORs. Results from logistic regression are presented as ORs with 95% CIs. A p-value < 0.05 was considered significant for all analyses. Statistical analyses were performed using Statistica software (Statistica®, Statsoft Inc., Tulsa, OK, U.S.A.).

7.4 PAPER IV

Crude (unadjusted) incidence rates for fistula disease were calculated as the number of fistula operations per 100,000 person-years, with 95% CIs based on the Poisson distribution. The association between pelvic organ fistula disease and hysterectomy was estimated using a Cox proportional-hazards model, stratified on the matching variables (age, county, and calendar time) for all analyses. The hazard ratio (HR) was used as a measure of risk and is presented with 95% CIs. The time scale used in all analyses was time since study entry in years. Likelihood ratio tests were used to formally assess effect of exposure. Because the HRs were significantly non-proportional over follow-up time, we included interactions with time in the model by splitting each record on time and using interaction terms with time bands (cut-offs at 1, 2, 3, 5, and 10 years). Statistical analyses were performed using Stata Intercooled (Release 10. StataCorp LP, College Station, TX).

7.5 PAPER V

Crude incidence rates were calculated as the number of POP or SUI operations per 100,000 person-years, with 95% CIs based on the Poisson distribution. Comparisons on the impact of modes of hysterectomy, and indications for surgery, on the subsequent risk for pelvic floor surgery were performed using Cox regression models, stratifying on the matching strata and using time-since-entry as the underlying timescale. The estimated HRs from these models were used as measures of association and are presented with 95% CIs. Likelihood ratio tests were used to formally assess the effect of exposure. The HRs were tried out for proportionality over time with proportional hazard test.

Information on number of childbirths and mode of delivery was only available from 1973 and onwards, i.e., after the introduction of the population-based Swedish Medical Birth Register. We therefore restricted the analyses on the effects of childbirth to a subsample of women born 1952 or later and thus covered most of these women's reproductive period. In this subsample, the effects of hysterectomy were adjusted for number of vaginal deliveries as a continuous variable. Statistical analyses were performed using Stata Intercooled (Release 10. StataCorp LP, College Station, TX).

8 RESULTS

8.1 PAPER I

8.1.1 Rates of hysterectomy

Overall rates of hysterectomy on benign indications and mean age at surgery in Sweden 1987-2003 are presented in Figure 8. During the study period the most common indications for hysterectomy on benign indications were: uterine fibroids (leiomyoma) (51%); dysfunctional bleedings (13%); uterine prolapse (8%); endometriosis (7%); and other benign tumours (8%). Most indications for hysterectomy were relatively stable in proportions over the study period except for POP which increased by four-fold. From 1987 to 1999 the annual overall hysterectomy rates increased from 178/100,000 person-years to 232/100,000 person-years (Figure 8). Thereafter, the overall hysterectomy rate declined and phased out around 210/100,000 person-years in 2003, a decrease of 11%. Rates of hysterectomy by indications over time are presented in Table 9.

Figure 8. Overall rates of hysterectomy on benign indications and mean age at surgery in Sweden 1987-2003

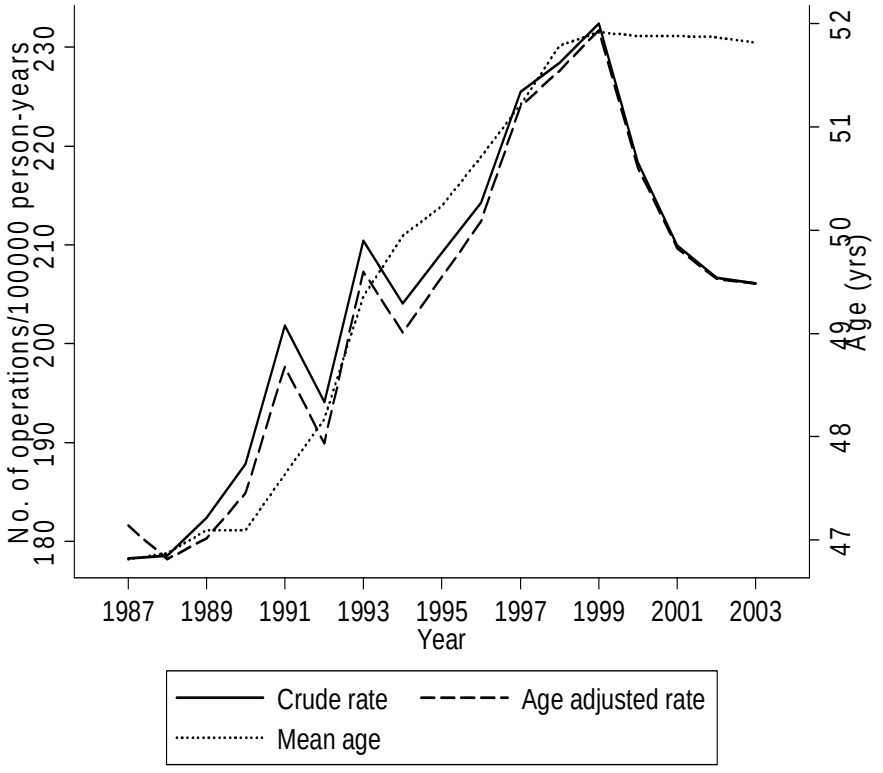


Table 9. Rates, proportions and mean age at hysterectomy by indication and time period.

	1987-1990			1991-1994			1995-1997			1998-2000			2001-2003		
	Rate	Percent	Age	Rate	Percent	Age	Rate	Percent	Age	Rate	Percent	Age	Rate	Percent	Age
Dysfunctional bleedings	25	14	43.3	26	13	44.4	24	11	45.4	25	11	46.2	27	13	45.3
Uterine prolapse	7	4	64.3	12	6	65.8	17	8	66.2	24	11	66.1	30	14	64.1
Endometriosis	14	8	44.1	14	7	44.7	14	7	46.2	15	6	47.0	11	5	46.1
Uterine fibroids	102	56	46.0	112	55	47.3	115	53	48.6	106	47	49.4	88	42	48.8
Other benign tumors	11	6	60.1	14	7	60.3	18	8	61.3	21	9	61.2	22	9	61.0
Other diagnosis*	21	12	48.0	25	12	50.2	29	13	53.4	35	15	53.2	32	15	53.2
Total	182	100	47.3	203	100	49.1	216	100	51.1	226	100	52.2	207	100	52.2

Rates of hysterectomy calculated per 100,000 person-years.

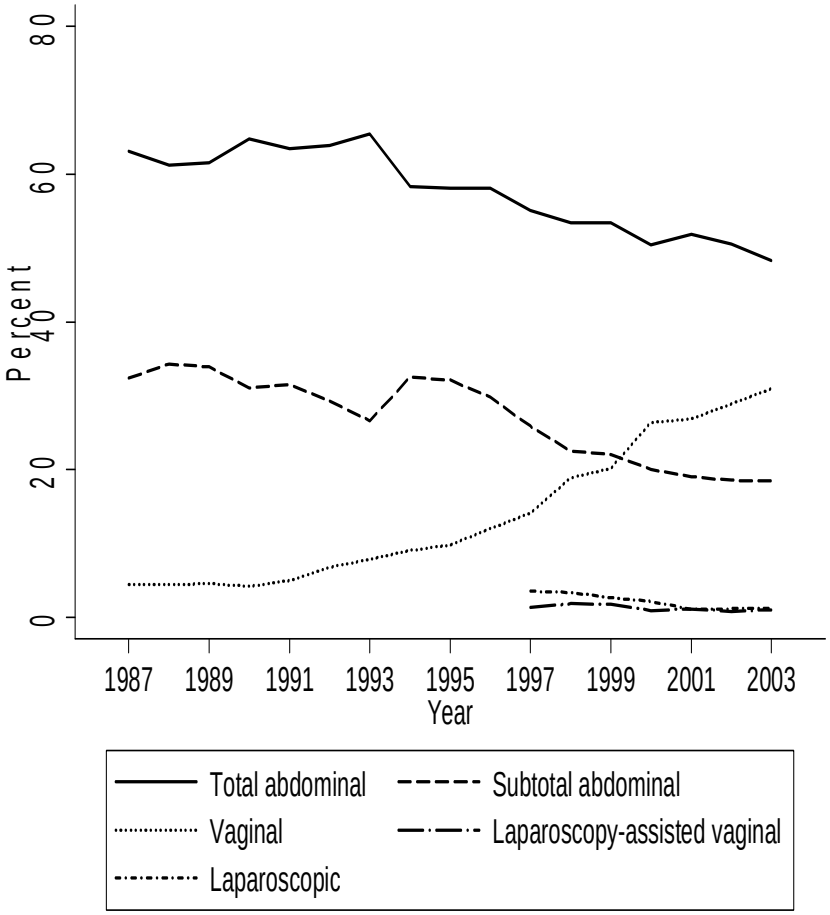
*Other diagnosis include: adenomyosis, dysmenorrhea, ovarian cysts, cervix dysplasia, metropathia haemorrhagica cystica, and endometrial hyperplasia.

No information on indication for hysterectomy = 0.02%

8.1.2 Surgical techniques

The percentage of hysterectomies, performed by the various surgical techniques over time is presented in Figure 9. Both total and subtotal AH decreased in use during the observational period. Total AH was the most commonly used surgical route and technique throughout the study period and VH increased steadily.

Figure 9. Use of various hysterectomy techniques in Sweden 1987-2003.



8.1.3 Age at hysterectomy

Rates, proportions and mean age at hysterectomy, by hysterectomy technique, and time period are described in Table 10. Total AH contributed to 63% of all hysterectomies in 1987-1990, while in 2001-2003 the corresponding figure was 50%. A similar decrease in use was observed for subtotal AH which decreased from 33% in 1987-1990, to 19% in 2001-2003 (Table 10). From 1987 to 1997 the mean age at surgery increased

gradually, after which a plateau was reached (Figure 8). By large, the overall increase in age at surgery may be credited to increased ages at total and subtotal AH (Table 10). The increased age at hysterectomy could also be attributed to a proportionally increased use of VH, a surgical technique often chosen for patients with co-morbidity or elderly women (Table 10).

8.1.4 Vaginal hysterectomy

Table 11 shows the rates of VH by indication. Comprising only 4% of the total number of hysterectomies performed in 1987-1990, VH increased to 29% in 2001-2003. Rates of VH by prolapse indication increased by a five-fold, whereas rates of VH by other benign indications increased by a near 20-fold. The observed drop in mean age at VH from 1995 to 2003 coincided with an apparent widening of indications. The increased rates of VH were gradual and continued also after introduction of the LH techniques in 1997 (Figure 9). Following a brief surge at the time of the introduction of LH and LAVH in 1997, the rates of hysterectomies performed using these techniques peaked in 1998 (3 % and 2 % of all hysterectomies respectively) after which the use of both techniques declined. By 2003, LH and LAVH constituted approximately 1% of performed hysterectomies (Figure 9).

Table 10. Rates, proportions and mean age at hysterectomy by hysterectomy technique and time period.

Mode of hysterectomy	1987-1990			1991-1994			1995-1997			1998-2000			2001-2003		
	Rate	%	Age	Rate	%	Age	Rate	%	Age	Rate	%	Age	Rate	%	Age
Total abdominal	114	63	47.6	127	63	49.1	123	57	51.3	119	52	52.3	104	50	52.1
Subtotal abdominal	60	33	44.6	61	30	46.0	63	29	47.3	49	22	48.3	39	19	47.4
Vaginal	8	4	62.1	15	7	62.0	26	12	59.9	49	22	56.6	60	29	55.8
LAVH	-	-	-	-	-	-	1	0	47.5	3	2	49.8	2	1	51.0
Laparoscopic	-	-	-	-	-	-	3	1	46.9	6	3	47.7	2	1	47.3
All	182	100	47.3	203	100	49.1	216	100	51.1	226	100	52.2	208	100	52.2

LAVH denotes laparoscopy-assisted vaginal hysterectomy. Rates of hysterectomy calculated per 100,000 person-years. Mean age in years.

Table 11. Rates and numbers of vaginal hysterectomy by indication.

	1987-1990		1991-1994		1995-1997		1998-2000		2001-2003	
Indication for vaginal hysterectomy;	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Prolapse indication	852	6	1,505	11	1,637	16	2,448	23	3,098	29
Other indications*	234	2	519	4	1,110	10	2,776	26	3,325	31
Overall	1,086	8	2,024	15	2,747	26	5,224	49	6,423	60

* Other indications include: uterine fibroids, endometriosis, other benign tumors, adenomyosis, dysmenorrhea, ovarian cysts, cervix dysplasia, metropathia haemorrhagica cystica and endometrial hyperplasia. Rates of hysterectomy calculated per 100,000 person-years

8.2 PAPER II

8.2.1 Patient characteristics

Patients were followed up with an identical questionnaire at the mean of 12.7 (range, 10.9-13.8) months and 2.9 (range, 2.5-3.2) years after hysterectomy. Response rates were 115/120 (96%) and 107/120 (89%) respectively. One patient had undergone BSO after the one-year follow-up and was excluded from the analysis. Patient characteristics at three years follow-up, and abdominal surgical procedures prior to hysterectomy are presented in Table 12 and 13.

Table 12. Patient characteristics at three-year follow-up after hysterectomy

	All patients	Abdominal hysterectomy	Vaginal hysterectomy	Abdominal hysterectomy + BSO
	n= 107	n= 52	n=39	n=16
Mean age at surgery	49.5	46.9	49.2	58.8
Mean parity	1.9	1.7	2.1	1.9
Mean BMI	24.3	25.6	23.1	23.0
HRT	28 (26)	10 (19)	11 (28)	7 (44)*
Obstetric anal sphincter injury	7 (7)	3 (6)	3 (8)	1 (6)
Vaginal laceration	16 (15)	8 (15)	6 (15)	2 (13)
Child> 4,000g	21 (20)	10 (19)	7 (18)	4 (25)
Instrumental delivery	13 (12)	7 (13)	4 (10)	2 (13)
Deceased	2 (2)	2 (4)	0	0

BSO= Bilateral salpingo-oophorectomy BMI= Body Mass Index (=weight^2/length) HRT=Hormone replacement therapy. Figures are numbers of patients (%). *P < 0.05

Table 13. Abdominal surgical procedures performed prior to hysterectomy.

	Vaginal hysterectomy	Abdominal hysterectomy
	n=39	n=68
Appendectomy	9 (23)	7 (10)
Cholecystectomy	5 (13)	4 (6)
Ovarian resection	2 (5)	6 (9)
Salpingo-oopherectomy	0	4 (6)
Sterilization	1 (3)	2 (3)
Enucleation of uterine fibroids	2 (5)	2 (3)
Urinary incontinence surgery	1 (3)	2 (3)
Inguinal hernia	0	2 (3)
Ileus	0	1 (2)
Ileocecal resection	1 (3)	0
Extra uterine pregnancy	0	1 (2)
Ovarian tubar plasty	0	1 (2)

Figures are numbers of patients (%).

8.2.2 Anal incontinence

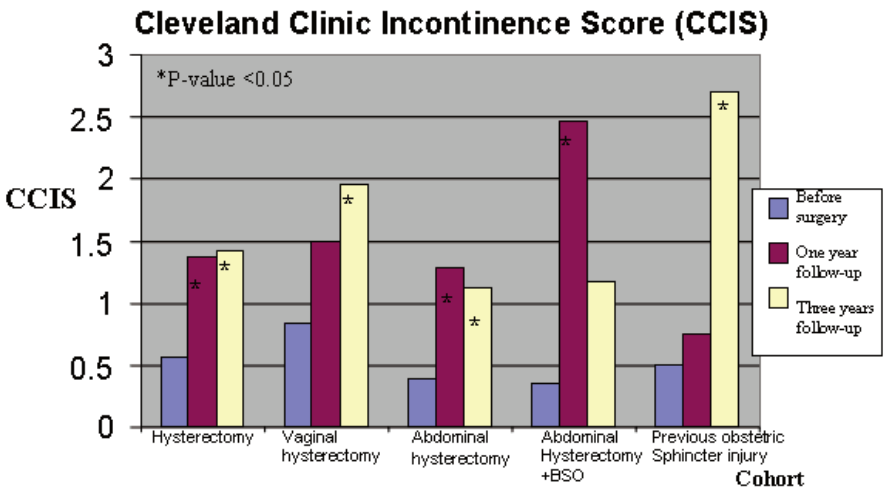
Abdominal hysterectomy

There was a significant increase in overall CCIS after AH at the one-year follow-up which persisted at the three-year follow-up, indicating a change in anal continence status after hysterectomy (Figure 10). Three patients with perfect anal continence preoperatively reported moderate incontinence (CCIS 11- 14) at the one-year follow-up. At three years follow-up one out of these three patients had perfect anal continence (CCIS 0), one remained moderately incontinent (CCIS 9) and one became severely incontinent (CCIS 16). There was a significant increase in CCIS one year after AH with concomitant BSO, although not persisting at the three-year follow-up (Figure 10). Two patients in this cohort, with perfect anal continence preoperatively reported moderate incontinence (CCIS 11) at the one-year follow-up. At the three-year follow-up one out of two had perfect continence (CCIS 0), and one became severely incontinent (CCIS 16). No cases of complete incontinence were reported.

Vaginal hysterectomy

There was an insignificant increase in CCIS after VH at the one-year follow-up, while the increase was significant at three-year follow-up (Figure 10). Two patients with perfect anal continence preoperatively reported moderate incontinence (CCIS 11 and 14) at the one-year follow-up. At the three-year follow-up one of them stated perfect continence (CCIS 0) and one remained moderately incontinent (CCIS 12). One patient with perfect continence preoperatively reported moderate incontinence (CCIS 11) at three-year follow-up. No cases of complete incontinence were reported.

Figure 10. Anal incontinence score according to CCIS before, one and three years after hysterectomy.



BSO= Bilateral salpingo-oophorectomy. CCIS 0= Perfect continence, 1-7= Good continence, 8-14= Moderate incontinence, 15-20= Severe incontinence, and >21= Complete incontinence.

8.2.3 Bowel symptoms

Abdominal hysterectomy

There were no significant overall changes in symptoms of constipation after AH (Table 14). Preoperatively, 24/76 (32%) reported rectal emptying difficulties, 31/76 (41%) reported incomplete bowel evacuation and 11/76 (14%) reported manually assisted defecation. After one-year 27/74 (35%) reported rectal emptying difficulties, 34/74 (45%) incomplete bowel evacuation and 8/74 (11%) manually assisted defecation. After three years, 24/68 (35%) reported bowel emptying difficulties, 27/68 (40%) incomplete bowel evacuation and 8/68 (12%) manually assisted defecation. Preoperative defecation frequency increased significantly at the one-year follow-up, persisting at the three-year follow-up.

Vaginal hysterectomy

There were no significant overall changes in symptoms of constipation after VH (Table 14). Preoperatively 14/44 (32%) reported rectal emptying difficulties, 15/44 (34%) incomplete bowel evacuation and 12/44 (28%) manually assisted defecation. After one year, 16/40 (40%) reported rectal emptying difficulties, 20/40 (50%) incomplete bowel evacuation and 7/40 (17%) manually assisted defecation. After three years, 16/39 (41%) reported bowel emptying difficulties, 12/39 (31%) incomplete bowel evacuation and 13/39 (33%) manually assisted defecation. There were no significant changes in defection frequency after one year or three years, compared to before surgery.

Table 14. Symptoms of constipation in patients after hysterectomy

	Abdominal hysterectomy			Vaginal hysterectomy		
	Before surgery (n=76)	One year after surgery (n=74)	Three years after surgery (n=68)	Before surgery (n=44)	One year after surgery (n=40)	Three years after surgery (n=39)
Bowel- emptying difficulties	24 (32)	27 (35)	24 (35)	14 (32)	16 (40)	16 (41)
<=1 per week	14 (18)	16 (21)	12 (18)	6 (14)	10 (25)	6 (15)
>1 per week	8 (11)	10 (13)	11 (16)	2 (5)	3 (8)	6 (15)
daily	2 (3)	1 (1)	1 (1)	6 (14)	3 (8)	4 (10)
Incomplete bowel evacuation	31 (41)	34 (45)	27 (40)	15 (34)	20 (50)	12 (31)
<=1 per week	25 (33)	24 (32)	12 (18)	10 (23)	15 (37)	6 (15)
>1 per week	5 (7)	9 (12)	14 (21)	3 (7)	2 (5)	6 (15)
daily	1 (1)	1 (1)	1 (1)	2 (5)	3 (8)	0
Digitation	11 (14)	8 (11)	8 (12)	12 (28)	7 (17)	13 (33)
<=1 per week	7 (9)	6 (8)	3 (4)	9 (20)	5 (13)	5 (13)
>1 per week	3 (4)	2 (3)	4 (6)	1 (2)	1 (3)	3 (10)
daily	1 (1)	0	1 (1)	2 (5)	1 (3)	1 (5)
Defecation frequency/ week	7.5	9.8*	8.5*	6.9	8.0	7.3

Figures are number of patient (%). *= P <0.05

8.2.4 Predictors of bowel dysfunction

Number of vaginal deliveries, overall parity, delivery of a child >4,000 g, vaginal laceration at delivery, HRT following hysterectomy, high BMI at surgery, high BMI at follow-up and concomitant BSO at the time of hysterectomy did not show any significant association with adverse alterations in bowel function or anal continence at three years follow-up (Table 15). Risk factor analyses indicated that previous obstetric sphincter injury was associated with an increased risk of anal incontinence subsequent to hysterectomy (OR 2.1, 95% CI 1.1-2.9). Increasing age at surgery was also associated with a higher risk of anal incontinence, although with borderline significance (OR 1.08, 95% CI 1.02-1.14) (Table 15).

Table 15. Factors associated with fecal incontinence three years after hysterectomy.

Multivariate logistic regression analysis		
Associated factor	Adjusted OR (95% CI)	P -value
Age at parity	1.08 (1.02-1.14)	0.008
Parity	0.9 (0.3-2.8)	0.9
Obstetric sphincter injury	2.1 (1.1-2.9)	0.02
Instrumental delivery	1.2 (0.2-6.3)	0.8
Delivery of child > 4,000 g	0.6 (0.1-3.1)	0.3
Vaginal laceration	0.9 (0.2-4.6)	0.9
Abdominal hysterectomy	0.6 (0.2-2.1)	0.4
Vaginal hysterectomy	2.1 (1.0-2.6)	0.1
HRT after surgery	1.3 (0.3-5.2)	0.8
BMI at surgery	1.0 (0.9-1.2)	0.8
BMI three years follow-up	0.9 (0.8-1.05)	0.4

OR= Odds Ratio CI= Confidence Interval HRT=Hormone replacement therapy

BMI= Body Mass Index (=weight^2/length)

8.3 PAPER III

8.3.1 Study group characteristics

Mean age at response of the questionnaire was 72.8 (±9.7 SD) and 71.3 (±8.7 SD) years for patients and controls respectively. Vaginal vault prolapse surgery was performed using: abdominal sacral colpopexy in 78 patients (88%), laparoscopic sacral colpopexy in 3 patients (3%), transvaginal sacrospinous fixation in 2 patients (2%) and other vault suspension procedures in 7 patients (7%). The overall response rate was 90/ 117 (74%) in patient subjects and 233/ 326 (71%) in control subjects. Reasons for not participating in the study are presented in Table 16.

Table 16. Reasons for not participating in the study

Reason	Case group	Control group
Unknown	18 (67)	77 (83)
Deceased	5 (19)	5 (5)
Protected identity	1 (4)	6 (6)
Severe disease	2 (7)	4 (4)
Non-Swedish speaking	1 (4)	1 (1)

Figures are number of patients (%)

On average, patients underwent vaginal vault prolapse surgery 13.7 (±11.1 SD) years after hysterectomy and at a mean age of 66.7 years (±9.8 SD). Detailed descriptive data and statistical comparisons are presented in Table 17.

Women who underwent vaginal vault prolapse surgery were significantly younger than controls at the time of hysterectomy; they more often had had pelvic floor surgery prior to hysterectomy, were more commonly treated with HRT and more frequently reported a family history of prolapse. Furthermore, patients significantly more often had vaginal deliveries, had fewer cesarean sections, were older when giving birth to their first child, reported a higher rate of severe vaginal laceration at delivery and more often had a delivery of a child with a birth weight of 4,000 g or higher.

Table 17. Demographic characteristics and comparison between cases and controls

	Case group n= 90	Control group n= 233	P-value
Age at hysterectomy† (years)	54.6 ± 13.0	59.4 ± 12.6	<0.01
Hysterectomy			
Abdominal*	63 (70)	177 (75.9)	0.3
Vaginal*	9 (10)	15 (6.4)	0.3
Laparoscopic*	2 (2.2)	3 (1.3)	0.5
Parity†	2.3 ± 1.1	2.1 ± 1.2	0.1
Vaginal delivery*	86 (95.6)	197 (84.5)	<0.01
Cesarean delivery*	1 (1.1)	19 (8.2)	0.02
Nulliparous*	4 (4.4)	23 (9.9)	0.1
Age at birth of first child † (years)	25.7 ± 4.5	24.3 ± 5.0	0.03
Severe vaginal laceration**	34 (37.7)	51 (21.8)	<0.01
Instrumental delivery*	8 (8.9)	9 (3.9)	0.1
Delivery of child > 4,000 g *	24 (26.7)	55 (23.6)	<0.05
Smoking*	6 (6.7)	27 (11.6)	0.3
Physical activity*	48 (53.3)	130 (55.8)	0.4
Body mass index (kg/m^2) †	25.0 ± 3.7	25.7 ± 4.3	0.4
Menopausal age† (years)	48.6 ± 4.6	49.6 ± 4.6	0.2
Hormone therapy*	39 (43.3)	78 (33.5)	<0.05
Tablets*	13 (14.4)	28 (12.0)	0.6
Creams*	25 (27.8)	45 (19.3)	0.1
Patches or gels*	3 (3.3)	7 (3.0)	0.5
Family history of prolapse*	29 (32.2)	50 (21.5)	<0.05
Asthma*	10 (11.1)	23 (9.9)	0.9
Rheumatism, SLE, Sclerodermia*	9 (10)	20 (8.6)	0.7
Diabetes*	4 (4.4)	26 (11.2)	0.05
Hypothyroidism *	15 (16.7)	25 (10.7)	0.2
Cortisone treatment*	5 (5.6)	15 (6.4)	0.7
Prolapse or incontinence surgery prior to vaginal vault surgery*	48 (53.3)	25 (10.7)	<0.001
Prolapse or incontinence surgery prior to or concurrently to hysterectomy*	37 (41.1)	43 (18.5)	<0.001

Comparison using Mann-Whitney U-test †= ± standard deviation. *= Number of patients (%).

**including obstetric sphincter injury

8.3.2 Pelvic organ prolapse and incontinence surgery

The women in the case group had gone through significantly more POP and SUI surgery prior to, or concurrently with hysterectomy, than control subjects. The different types of pelvic organ surgery are presented in Table 18.

Table 18. Pelvic organ prolapse and stress urinary incontinence surgery prior to the date for vaginal vault prolapse surgery.

	Case group n= 90	Control group n= 233	P-values
Anterior prolapse repair	15 (16.7)	10 (4.2)	P<0.001
Posterior prolapse repair	13 (14.4)	6 (2.6)	P<0.001
Manchester procedure	13 (14.4)	7 (3.0)	P<0.001
Colpocleisis or partial colpocleisis	1 (1.1)	-	P=0.11
Enterocele obliteration	5 (5.6)	2 (0.8)	P<0.01
Any pelvic organ prolapse surgery	35 (38.9)	21 (9.0)	P<0.001
Any stress incontinence surgery	15 (16.7)	10 (4.2)	P<0.001
Prolapse or incontinence surgery	48 (53.3)	25 (10.7)	P<0.001

Group comparison using Mann-Whitney U-test. Figures are number of patients (%).

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8.3.3 Covariate analysis

Table 19 shows the results of the unadjusted univariate logistic regression analysis. A number of potential risk factors were significantly associated with vaginal vault prolapse at univariate analysis. However, following adjustment in a multivariate logistic regression analysis, only POP or SUI surgery prior to hysterectomy (OR 2.8, 95% CI 1.0-7.7) remained significantly associated with surgically managed vaginal vault prolapsed. Furthermore, age at hysterectomy and POP or SUI surgery prior to vaginal vault surgery turned out to be associated with vaginal vault surgery although with borderline significance (Table 20).

Variables selected for final multivariate analysis were based on significant associations at univariate analyses. Cesarean section was not included in the final multivariate analysis due to insufficient number of observations in our case group.

Table 19. Variables tried for association and odds ratios for post hysterectomy vaginal vault prolapse in univariate analyses.

Associated factor	Unadjusted OR	95% CI	P-value
Age at hysterectomy (years)	1.03	1.01-1.05	<0.01
Abdominal hysterectomy	0.7	0.4-1.3	0.3
Vaginal hysterectomy	1.6	0.7-3.9	0.3
Laparoscopic hysterectomy	1.7	0.1-3.5	0.5
Parity	0.9	0.7-1.1	0.2
Vaginal delivery	3.9	1.4-11.4	0.01
Cesarean delivery	0.1	0.02-0.9	0.04
Nulliparous	0.4	0.1-1.3	0.1
Multiple vaginal deliveries*	1.3	0.8-2.2	0.3
Age at birth of first child	1.0	0.9-1.0	0.1
Severe vaginal laceration**	2.2	1.3-3.7	<0.01
Instrumental delivery	2.4	0.9-6.5	0.1
Delivery of child > 4,000 g	1.9	1.0-3.5	0.04
Smoking	0.7	0.3-1.6	0.3
Physical activity	0.8	0.5-1.4	0.4
Body mass index (kg/m^2)	1.0	0.9-1.1	0.7
Menopausal age	1.0	1.0-1.1	0.1
Hormone therapy	1.9	1.1-3.3	0.02
Family history of prolapse	2.3	1.3-4.0	<0.005
Somatic disease***	0.9	0.6-1.5	0.7
Prolapse at hysterectomy	1.2	0.5-2.5	0.7
Prolapse or incontinence surgery prior to or concurrently to hysterectomy	3.1	1.8-5.3	<0.001
Prolapse or incontinence surgery prior to vaginal vault surgery	9.1	5.1-16.3	<0.001

*Vaginal delivery of more than two children. **Includes obstetric sphincter injury

***Rheumatism, SLE, sclerodermia, hypothyroidism treated with levotyroxin, diabetes mellitus

Table 20. Adjusted odds ratios for risk factors associated with vaginal vault prolapse surgery in a multivariate analysis.

Associated factor	Adjusted OR	95% CI	P-value
Age at hysterectomy (years)	1.04	1.004-1.08	0.003
Vaginal delivery	3.8	0.4-33.3	0.2
Family history of prolapse	1.6	0.6-4.0	0.3
Severe vaginal laceration*	1.2	0.5-3.1	0.7
Delivery of child > 4,000g	1.6	0.6-4.2	0.3
Hormone therapy	0.8	0.3-1.8	0.5
Prolapse or incontinence surgery prior to vaginal vault surgery	9.1	3.6-23.4	<0.001
Prolapse or incontinence surgery prior to or concurrently to hysterectomy	2.8	1.0-7.7	0.04

Variables selected for final multivariate analysis based on significant associations at univariate analyses.

Cesarean section was excluded due to insufficient numbers *Includes obstetric sphincter injury

8.4 PAPER IV

8.4.1 Study group characteristics

The final study population available for analysis included 182,641 women having a hysterectomy (exposed cohort) and 525,826 women not undergoing hysterectomy (unexposed cohort), encompassing more than 8 million person-years at risk. During the follow-up period, 469 cases of fistula surgery were identified in the exposed cohort and 384 in the unexposed cohort (Table 21). The overall number needed to harm (NNH) was 5,700 i.e. that if 5,700 individuals are exposed to hysterectomy on benign indications, one will develop surgically managed pelvic organ fistula disease that would not have done so otherwise.

Table 21. Characteristics of the study cohort.

	Hysterectomy	No hysterectomy
No. of subjects	182,641	525,826
No. of fistulas	469	384
Person-time in years	1,970,076	6,114,023
Fistula rates per 100 000 person-years (95% CI)	23.8 (21.8-26.1)	6.3 (5.7-6.9)
Age at study entry (years mean (SD))	49.5 (10.9)	49.1 (10.7)
Follow-up time (years mean (SD))	10.8 (8.1)	11.6 (7.8)

Rates of fistula surgery calculated per 100,000 person-years.

8.4.2 Rates of fistula disease

The rates of various fistula diagnoses with regard to hysterectomy status and mode of hysterectomy are presented in Table 22. The most common type of fistula observed in the exposed cohort was urogenital fistula followed by intestinogenital fistula. In the unexposed cohort, intestinogenital and anorectal fistula were the most common types, whereas urogenital fistulas were infrequent (Table 22). LH was associated with the highest rate of overall fistula surgery, more than three times higher than the corresponding rate for total AH. The lowest rate of fistula surgery was seen in the subtotal AH group. Fistula surgery after LH, VH and AH was dominated by urogenital fistulas whereas intestinogenital fistulas were the most common type in the subtotal AH group (Table 22).

Table 22. Pelvic organ fistula types in women with and without hysterectomy.

	Total		Urogenital fistula		Intestinogenital fistula		Urointestinal fistula		Anorectal fistula		Unspecified fistula	
	n	Rate (95% CI)	n	Rate (95% CI)	n	Rate (95% CI)	n	Rate (95% CI)	n	Rate (95%CI)	n	Rate (95% CI)
All hysterectomy	469	23.8 (21.7-26.1)	198	10.0 (8.7-11.6)	188	9.5 (8.3-11.0)	24	1.2 (0.8-1.8)	31	1.6 (1.1-2.2)	28	1.4 (1.0-2.1)
Mode of hysterectomy:												
Total abdominal n= 117,242	371	27.5 (24.8-30.4)	174	12.9 (11.1-15.0)	136	10.1 (8.5-11.9)	22	1.6 (1.1-2.5)	18	1.3 (0.8-2.1)	21	1.6 (1.0-2.4)
Subtotal abdominal n= 44,754	69	13.7 (10.8-17.3)	8	1.6 (0.8-3.2)	43	8.5 (6.3-11.5)	2	0.4 (0.1-1.6)	10	1.9 (1.1-3.7)	6	1.2 (0.5-2.7)
Vaginal n= 18,828	22	20.2 (13.3-30.7)	10	9.2 (4.9-17.1)	9	8.3 (4.3-15.9)	0	-	2	1.8 (0.5-7.3)	2	0.9 (0.1-6.5)
Laparoscopic[1] n= 1,783	7	95.9 (45.7-201.1)	6	82.2 (36.9-182.9)	0	-	0	-	1	13.7 (1.9-97.2)	0	-
No hysterectomy	384	6.3 (5.7-6.9)	22	0.4 (0.2-0.6)	216	3.5 (3.1-4.0)	43	0.7 (0.5-1.0)	94	1.5 (1.3-1.9)	9	0.2 (0.1-0.3)

Rates of fistula surgery calculated per 100,000 person-years. [1] Includes laparoscopy assisted vaginal hysterectomy and total laparoscopic hysterectomy.

8.4.3 Risks of fistula disease

HRs of pelvic organ fistula disease depending on mode of hysterectomy and time since surgery are presented in Table 23. During the first two years after surgery, total AH was associated with the highest risk of fistula disease, thereafter the risk did not essentially differ between the various types of hysterectomy (Table 23).

Table 23. Numbers and hazard ratios for pelvic organ fistula disease depending on mode of hysterectomy and time since surgery.

Mode of hysterectomy	Time since surgery (years)						Total	
	0-1		1-2		>2			
	n	HR (95%CI)	n	HR (95% CI)	n	HR (95% CI)	n	HR (95%CI)
Total abdominal n= 117,242	214	1.0 (Ref)	20	1.0 (Ref)	137	1.0 (Ref)	371	1.0 (Ref)
Subtotal abdominal n= 44,754	14	0.2 (0.1-0.3)	6	0.9 (0.3-2.2)	49	1.0 (0.7-1.3)	69	0.5 (0.4-0.6)
Vaginal n= 18,828	13	0.3 (0.2-0.6)	1	0.2 (0.03-1.8)	8	1.0 (0.5-2.1)	22	0.4 (0.3-0.7)
Laparoscopic n= 1,783	6	-	0	-	1	-	7	1.8 (0.9-3.9)

Laparoscopic hysterectomy includes laparoscopy assisted vaginal hysterectomy and total laparoscopic hysterectomy.

8.4.4 Age at hysterectomy

In Table 24, HRs for pelvic organ fistula disease are presented stratified by age at hysterectomy (or at study entry for controls) and time since surgery. Regardless of age at hysterectomy, the overall risk for fistula disease was more than twenty times higher in women with hysterectomy, than in women with an intact uterus, during the first year after surgery. When stratifying for age at hysterectomy, we found that the relative risk of fistula disease, one to two years after hysterectomy, was higher among women who were at least 50 years at hysterectomy, compared with younger women (HR 7.7, 95% CI 3.0-20.3 and HR 1.8, 95% CI 0.9-3.5, respectively).

8.4.5 Time from hysterectomy

The relative risk estimates for fistula disease over time from hysterectomy, or study entry for the unexposed cohort, are presented in Table 25. The highest risk for fistula surgery after hysterectomy was observed during the first and second year after surgery (HR 21.2, 95% CI 14.9-30.2 and HR 3.0, 95% CI 1.8-5.1, respectively). Thereafter, the risk for fistula surgery remained higher among exposed compared to unexposed women, although the risk increase was moderate and remained stable for the duration of the observational period.

Table 24. Numbers and hazard ratios of pelvic organ fistula disease in relation to hysterectomy status, age at hysterectomy and time since surgery

Age at hysterectomy/ study entry (years)	Time since surgery (years) 0-1 Number of fistulas	0-1 HR (95% CI)	1-2 Number of fistulas	1-2 HR (95% CI)	>2 Number of fistulas	>2 HR (95% CI)
18 - 49						
No hysterectomy	22	1.0 (Ref)	22	1.0 (Ref)	248	1.0 (Ref)
Hysterectomy	150	20.4 (13.0-31.9)	13	1.8 (0.9-3.5)	146	1.8 (1.5-2.2)
50 years or older						
No hysterectomy	14	1.0 (Ref)	7	1.0 (Ref)	69	1.0 (Ref)
Hysterectomy	91	22.5 (12.6-40.2)	13	7.7 (3.0-20.3)	47	2.2 (1.5-3.2)

Cox proportional-hazards model, stratifying on the matching variables age, county and calendar time

Table 25. Hazard ratios for pelvic organ fistula disease subsequent to hysterectomy over time.

Time since surgery/ study entry (years)	Hazard ratios: hysterectomy verses no hysterectomy (95% CI) 0-1	1-2	2-3	3-5	5-10	>10	Overall
No hysterectomy	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Hysterectomy	21.2 (14.9-30.2)	3.0 (1.8-5.1)	2.0 (1.1-3.7)	1.7 (1.1-2.7)	1.6 (1.2-2.2)	2.2 (1.7-2.9)	3.8 (3.3-4.3)

Cox proportional-hazards model, stratifying on the matching variables age, county and calendar time.

8.5 PAPER V

8.5.1 Study group characteristics

The final study cohort consisted of 697,801 women: 118,601 women having a hysterectomy and 579,200 individually matched women not having a hysterectomy. During almost 8 million person-years at risk we observed a total of 1,189 cases of POP surgery and 1,086 cases of SUI surgery. Cohort characteristics are presented in Table 26.

Table 26. Characteristics of study cohort

	No hysterectomy n=579,200	Vaginal hysterectomy for pelvic organ prolapse n=10,190	Vaginal hysterectomy for other indications* n=7,145	Total abdominal hysterectomy for other indications* n=101,266
Pelvic organ prolapse**	821	44	13	311
Stress urinary incontinence**	742	43	8	293
Mean age at study entry, years (SD)	50.3 (11.1)	64.6 (11.6)	46.6 (8.0)	48.2 (9.7)
Mean follow-up time, years (SD)	11.5 (7.8)	6.4 (5.9)	5.1 (5.3)	12.4 (8.1)
Median parity, number of children (min-max)†	2 (0-15)	2 (0-9)	2 (0-9)	2 (0-9)

*Other indications includes: dysfunctional bleedings, uterine fibroids, benign tumours, endometriosis, adenomyosis, dysmenorrhea, ovarian cysts, uterine cervical dysplasia, metropathia haemorrhagica cystica and endometrial hyperplasia. ** Number of surgical procedures

† Women born 1952 or later (n= 112,621)

8.5.2 Mode of hysterectomy

Table 27 shows the incidence rates and HRs for POP and SUI surgery with regard to mode of hysterectomy. The highest risk for POP and SUI surgery was observed in patients having VH for POP and the incidence rate was 5-6 times higher than in women not having a hysterectomy (Table 27). Women operated on with VH for other reasons than prolapse had also a higher risk for subsequent POP surgery (HR 3.6, 95% CI 2.0-6.5) and SUI surgery (HR 2.6 95% CI 1.2-5.3) compared to women not having a hysterectomy. Subsequent to total AH the risk for POP and SUI were also higher than in the women not undergoing hysterectomy, but considerably lower than after VH (Table 27).

Table 27. Incidence rates and hazard ratios for pelvic organ prolapse and stress urinary incontinence surgery depending on mode of hysterectomy

	Pelvic organ prolapse surgery			Stress urinary incontinence surgery		
	Number of events	Incidence rate (95% CI)	Hazards ratio (95% CI)	Number of events	Incidence rate (95% CI)	Hazard ratio (95% CI)
No hysterectomy	821	124 (116-133)	1.0	742	112 (104-120)	1.0
Vaginal hysterectomy for pelvic organ prolapse	44	679 (505-912)	4.9 (3.4-6.9)	43	663 (492-894)	6.3 (4.4-9.1)
Vaginal hysterectomy for other indications*	13	356 (206-612)	3.6 (2.0-6.5)	8	219 (109-437)	2.6 (1.2-5.3)
Total abdominal hysterectomy for other indications*	311	248 (222-277)	2.0 (1.8-2.4)	293	233 (208-262)	2.1 (1.8-2.4)

Incidence rates per 100 000 person-years (95%CI) Cox proportional-hazards model, stratifying on the matching variables age, county, and calendar time *Other indications includes: dysfunctional bleedings, uterine fibroids, benign tumors, endometriosis, adenomyosis, dysmenorrhea, ovarian cysts, uterine cervical dysplasia, metropathia haemorrhagica cystica and endometrial hyperplasia.

Table 28. Hazard ratios and parity-adjusted hazard ratios for pelvic organ prolapse and stress urinary incontinence (women born in 1952 or later).

		Pelvic organ prolapse surgery			Stress urinary incontinence surgery		
	Total number of women	Number of events	HR (95% CI)	Parity-adjusted HR (95% CI)	Number of events	HR (95% CI)	Parity-adjusted HR (95% CI)
No hysterectomy	92,367	28	1.0	1.0	29	1.0	1.0
All hysterectomy	20,254	14	2.2 (1.2-4.3)	2.3 (1.2-4.5)	14	2.3 (1.2-4.5)	2.4 (1.3-4.7)
Vaginal hysterectomy for pelvic organ prolapse	675	0	-	-	0	-	-
Vaginal hysterectomy for other indications*	3,733	4	5.2 (1.7-16.6)	5.4 (1.7-17.4)	4	5.7 (1.8-18.2)	6.2 (1.9-20.3)
Total abdominal hysterectomy for other indications*	15,846	10	1.8 (0.9-3.8)	1.6 (1.3-2.0)	10	1.9 (0.9-4.0)	2.0 (0.9-4.2)

Cox proportional-hazards model, stratifying on the matching variables age, county, and calendar time. * Other indications includes: dysfunctional bleedings, uterine fibroids, benign tumors, endometriosis, adenomyosis, dysmenorrhea, ovarian cysts, uterine cervical dysplasia, metropathia haemorrhagica cystica and endometrial hyperplasia

8.5.3 Parity-adjusted hazard ratios

Parity-adjusted HRs for POP and SUI are presented in Table 28. The analysis was performed in a subgroup of 112,621 women born in 1952 or later, where information on parity was available. Compared to women not undergoing hysterectomy, the risks of POP and SUI surgery was five to six times higher after VH for other indications than prolapse. The risk for POP surgery after AH increased by 60% but there was no significant risk increase for SUI surgery after AH (Table 28). There were insufficient numbers of observations to provide a reliable estimate for the risk associated for VH with concurrent POP.

8.5.4 Indication for hysterectomy

Incidence rates for POP and SUI surgery in relation to the medical indications for hysterectomy are presented in Table 29. Also when mode of hysterectomy was disregarded, the overall rate of subsequent POP and SUI surgery was more than twice as high in women having hysterectomy for prolapse disease than for other indications (Table 29). There were no major differences in rates of surgically managed POP and SUI subsequent to hysterectomy for dysfunctional bleedings, uterine fibroids or other miscellaneous diagnoses.

Table 30 presents incidence rates for POP and SUI, in relation to medical indications for women having hysterectomy for reasons other than prolapse. The highest rates of POP and SUI were observed in women subsequent to VH regardless of medical indication. The overall highest rate of POP and SUI surgery was seen subsequent to VH performed due to dysfunction bleedings.

Table 29. Number of events and incidence rates for pelvic organ prolapse and stress urinary incontinence surgery depending on medical indication for hysterectomy.

	Indication for hysterectomy							
	Dysfunctional bleedings n=14,579		Prolapse disease n=9,172		Uterine fibroids n=61,217		Various indications* n=33,422	
	n	Rate (95% CI)	n	Rate (95% CI)	n	Rate (95% CI)	n	Rate (95% CI)
Pelvic organ prolapse surgery	55	306 (235-398)	39	685 (500-937)	102	299 (246-363)	172	221 (190-256)
Stress urinary incontinence surgery	55	306 (235-398)	37	650 (471-896)	92	270 (219-331)	160	205 (176-240)

Incidence rates per 100 000 person-years (95%CI) * Various indications including; benign tumors, endometriosis, adenomyosis, dysmenorrhea, ovarian cysts, uterine cervical dysplasia, metropathia haemorrhagica cystica and endometrial hyperplasia

Table 30. Number of observations and incidence rates for pelvic organ prolapse and stress urinary incontinence surgery depending on medical indication for hysterectomy and on hysterectomy technique.

	Indication for abdominal hysterectomy						Indication for vaginal hysterectomy					
	Dysfunctional bleedings		Uterine fibroids		Various indications*		Dysfunctional bleedings		Uterine fibroids		Various indications*	
	n	Rate (95% CI)	n	Rate (95% CI)	n	Rate (95% CI)	n	Rate (95% CI)	n	Rate (95% CI)	n	Rate (95% CI)
Pelvic organ prolapse surgery	75	308.1 (246-386)	252	233.4 (206-264)	116	273.4 (228-328)	29	347.6 (242-500)	88	261.8 (213-323)	28	258.8 (179-375)
Stress urinary incontinence surgery	75	308.1 (246-386)	224	207.5 (182-237)	115	271.1 (226-325)	26	311.7 (212-458)	72	214.2 (170-270)	31	286.6 (202-408)

Incidence rates per 100 000 person-years (95%CI). Hysterectomy for pelvic organ prolapse is excluded.* Various indications including; benign tumours, endometriosis, adenomyosis, dysmenorrhea, ovarian cysts, uterine cervical dysplasia, metropathia haemorrhagica cystica and endometrial hyperplasia

8.5.5 Pelvic organ prolapse surgery

The various types of POP surgery in relation to the mode of hysterectomy are presented in Table 31. In comparison to women not having hysterectomy, risk for anterior prolapse repair was highest after VH on prolapse indications (HR 3.5, 95% CI 2.9-4.3), followed by VH on other indications (HR 2.0, 95% CI 1.3-3.1) and AH (HR 0.9, 95% CI 0.8-1.0). For posterior vaginal wall prolapse repair, the pattern was similar but the risk estimates were greater. For total POP repair, VH with concurrent prolapse was also associated with the largest risk (HR 2.3, 95% CI 1.9-2.7). Total AH decreased the risk for total POP repair in comparison to both VH and no hysterectomy.

Table 31. Type of post hysterectomy pelvic organ prolapse surgery

	Anterior prolapse repair		Posterior prolapse repair*		Total pelvic organ prolapse repair **	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
No hysterectomy	1.0	Reference	1.0	Reference	1.0	Reference
Vaginal hysterectomy for pelvic organ prolapse	3.5	2.9-4.3	10.8	9.5-12.3	2.3	1.9-2.7
Vaginal hysterectomy for other indications†	2.0	1.3-3.1	4.6	3.6-5.8	0.7	0.4-1.2
Total abdominal hysterectomy for other indications†	0.9	0.8-1.0	3.4	3.2-3.6	0.4	0.3-0.4

Cox proportional-hazards model, stratifying on the matching variables age, county, and calendar time

* Includes enterocele obliteration

** Includes Manchester procedure, colpocleisis, partial colpocleisis, abdominal sacrocolpopexy, vaginal sacrospinous fixation.

† Other indications includes: dysfunctional bleedings, uterine fibroids, benign tumors, endometriosis, adenomyosis, dysmenorrhea, ovarian cysts, uterine cervical dysplasia, metropathia haemorrhagica cystica and endometrial hyperplasia

9 DISCUSSION

9.1 TRENDS OF HYSTERECTOMY

Hysterectomy surveillance allows audit of patterns of surgical utilization, identification of surgery related problems, and monitoring of intervention outcomes. For these reasons we used centralized prospective data based on nationally uniform classifications of both surgery and the underlying medical condition. These merits allows for a detailed trend analysis in a nationwide study. We found that the overall rate of hysterectomy on benign indications in Sweden has declined somewhat in recent years, but nonetheless has remained reasonably stable over the last decades. The introduction of minimally invasive treatment options has had a marginal effect on the rates of hysterectomy, but may have contributed to the slightly decreased overall rates observed after 1999. Shifts in trends were noticed primarily for various routes and modes of hysterectomy: with a considerable decrease in rates of AH techniques, increased use of VH, and a generally increased mean age at the time of surgery.

The issue of what should be considered 'appropriate' rates of hysterectomy for benign conditions remains undecided and cannot be answered so easily. The differences in practice and attitudes are mirrored by the large variations in overall hysterectomy rates between countries with similar demographics. In our study the overall hysterectomy rate was 210 per 100,000 person-years in 2003 to compare with in the US where the rate was 510 per 100,000 person-years in 2005.(37) The underlying causes for the large variations in overall hysterectomy rates between countries might reflect differences in morbidity, but probably mainly reflects differences in practice and attitudes among physicians and healthcare systems.(30) A study performed in the early 1990s in North Carolina, USA, found that gynecologists were more prone to perform hysterectomy at higher rates if they were further away in time from their training, practiced in areas with fewer gynecologists, or had more patients experiencing abnormal bleeding or cancer.(120) A recent survey completed by fellows of the American College of Obstetricians and Gynecologists, showed that younger age of the doctor and being in an academic practice was significantly associated with a decreased inclination to recommend hysterectomy to patients.(121)

The low perioperative morbidity and cost-effectiveness associated with VH makes it an attractive and definitive treatment option compared to both AH, as well as, less invasive treatment options such as transcervical resection of uterine fibroids or endometrial ablation.(3) Contrary to the general trend of increasing age at the time of surgery, mean age at VH decreased. This may reflect a broadening of indications towards younger women of reproductive or perimenopausal age.

POP was the only surgical indication for hysterectomy with a noticeable change in trends. Having a hysterectomy for prolapse was four times as common in 2003 compared to 1987. This probably reflects a change in attitudes towards the treatment of POP, but could also be attributed to advances of modern anesthesiology which allows surgeons to operate women in higher ages. This notion is supported by an overall increasing mean age at hysterectomy over the study period. In women having a hysterectomy for POP, the vast majority were performed using the vaginal route. However, the change in trend for hysterectomy on

prolapse indications coincided with generally increased rates of VH and an apparent widening of the indications for the procedure beyond uterine prolapse.(3, 122)

Use of a nationwide and continuously updated register of high quality adds to the strengths of this study. All Swedish citizens have similar access to a single publicly funded healthcare system. This suggests that selection bias would have a limited role in the observed national trends, in particular compared to countries with healthcare provided mainly by private health insurances. Nonetheless, differences in socioeconomic status may affect care seeking behaviour, although it is unclear how. According to one study, women from higher socioeconomic strata were more prone to undergo hysterectomy,(123) but according to another study rates of hysterectomy were higher in women with lower level of education and lower yearly income.(124) Care seeking behaviour may also be affected by women's propensity for elective surgery, which was illustrated in a cohort study where women having hysterectomy also underwent hallux valgus surgery and varicose-vein stripping, more frequently than did individuals not undergoing hysterectomy.(11)

9.2 BOWEL FUNCTION AFTER HYSTERECTOMY

We found no evidence to support the notion that hysterectomy results in constipation or rectal emptying difficulties within three years of surgery. Hysterectomy, independent of route, may however be associated with a mild deterioration in continence status following surgery.

Numerous investigators suggest that hysterectomy is associated with the development of bowel dysfunction such as, manually assisted defecation, rectal emptying difficulties, decreased bowel emptying frequency and constipation.(102-104) Studies supporting this notion are mainly retrospective whereas the present study, and other previously reported prospective studies and reviews (22, 105, 125, 126) do not show any association between hysterectomy and symptoms of constipation or rectal emptying difficulties. The reason for this discrepancy is likely to be found in differences in study methodology, where retrospective studies often are limited by recall bias and inability to account for the temporal chain of events.

Anal incontinence symptoms following both AH and VH increased significantly at three years follow-up. The reported symptoms were mild in both cohorts, with a mean continence score moving from "perfect" to "good" after three years. Frank fecal incontinence was uncommon in both groups. The clinical significance of the overall deterioration in continence status following hysterectomy may therefore be questioned. Implications on quality of life caused by an increased frequency of incontinence symptoms may, however, be considerable in individual patients and warrants further studies in groups at particular risk. We recognize that increasing age of the patients in the present study may amplify the effects of hysterectomy on the sphincter continence mechanisms, but given that the observational time period was restricted to three years, this poses a minor limitation. Age at surgery, and a history of obstetric anal sphincter injury, was associated with anal incontinence at multivariate regression analysis. This suggests that the observed changes in continence status following hysterectomy were multifactorial and that our findings are not entirely explained by senile degenerative changes by themselves. Obstetrical anal sphincter laceration is an established risk factor for anal incontinence in women and our finding of an increased risk in patients with a history of anal sphincter injury was not surprising.

In this prospective study, patients served as their own controls. We recognize that a parallel non-hysterectomized cohort would have added strength to the analysis. Furthermore, a questionnaire study is limited to subjective symptom assessment and is subjective to interpretation. We did not include objective measurements of dysfunction in this study and it remains uncertain to what extent diagnostic tools, such as anorectal manometry or defecography accurately correlates to symptom severity.(127-129)

9.3 RISK FOR POST HYSTERECTOMY VAGINAL VAULT PROLAPSE

A history of POP or SUI surgery was the strongest risk factor for surgically managed vaginal vault prolapse in a multivariate setting. This is in accordance with other studies and reviews (130-132) and supports the notion that an intrinsic weakness of the pelvic floor, at the time of hysterectomy, is the key determinant for POP to occur subsequent to the procedure.(77) One should also consider the possibility that pelvic floor surgery in itself may result in changes of vaginal pressure dynamics and as such, predispose for vaginal vault prolapse requiring surgical intervention.(133) The mode of hysterectomy did not turn out to be of any predictive value for the development of vaginal vault prolapse. This finding is in agreement with a recent study,(131) but considering that approximately 70% of our study subjects underwent AH, it is likely that the comparison is underpowered due to the few subjects having had other types of hysterectomy. Obstetrical factors did not turn out to be of predictive value for vaginal vault prolapse. Therefore, our study suggest that obstetrical events may not be as important in the development of vaginal vault prolapse in specific, as they are in the development of anterior or posterior vaginal wall prolapse for which there is abundant evidence of association.(6)

Our cases included only women who had undergone surgical repair for vaginal vault prolapse, which may be considered a more advanced stage of disease, and as such our data may not be generalized to a population with milder presentations of pelvic floor insufficiency. Using questionnaires as source of data might introduce recall bias, but in order to reduce that methodological problem we chose to use the Inpatient register with regard to the dates and occurrences of surgical procedures. The power calculation was not fulfilled but the study sample size was still sufficient to detect a significant association with our main a priori risk factor. We therefore do not believe that this is a major limitation of our study, while at the same time recognizing, that some of the less common exposures may require larger study populations to obtain unambiguous statistical power for detection of associations.

In conclusion, it might be useful to evaluate apical vaginal support in women that undergo hysterectomy after pelvic floor surgery, to determine the need for preventive measures or concurrent interventions at the time of the procedure. However, the usefulness and benefits of such a proactive approach needs to be further investigated in prospective comparative clinical studies.

9.4 HYSTERECTOMY AND PELVIC ORGAN FISTULA DISEASE

Based on nationwide register data, we found that the rate of fistula surgery was four times higher among women having had a hysterectomy, than among women with an intact uterus. The highest overall fistula rates were observed after LH and total AH and among older

women. During the first year after surgery the overall risk for fistula disease was more than twenty times higher in women after a hysterectomy, than for women with an intact uterus. Without the dense uterus in place to act as a protective buffer, postoperative infections of the vagina or paravaginal tissues, may act as a source for fistula formation soon after surgery, a process which may be precipitated by injury to the surrounding pelvic organs. This would explain the striking risk increase for fistula surgery observed within the first year of hysterectomy.

Our main findings provide robust epidemiological support to previous studies where pelvic surgery and hysterectomy in particular, have been identified as risk factors for fistula disease in developed countries.(106, 108, 134) The overall most common types of fistula were urogenital fistula and intestinogenital fistula. Urogenital fistula is thought to originate from dissection of the bladder, from sutures incorporated into the bladder, or direct injury to the lower urinary tract.(62, 63) This could also contribute to the striking risk increase for fistula surgery observed within the first year of hysterectomy. In concurrence with other researchers,(62, 108, 109) we found that the rate of fistula disease was higher in women subsequent to total AH than after VH. Hysterectomy by way of laparotomy, may introduce a higher risk for pelvic organ fistula disease because of its greater invasiveness and higher incidence of infections, compared with the vaginal approach.(49)

The risk of pelvic fistula disease was higher in women having had their hysterectomy at 50 years or older. This observation can presumably be attributed to peri- and postmenopausal estrogen deficiency resulting in degenerative changes of the vaginal tissues, which in turn may affect tissue susceptibility to infectious and/or inflammatory processes. Older women may also have a higher incidence of comorbidity associated with poor tissue healing and susceptibility to infections.

LH has been associated with a low perioperative morbidity and shorter recovery than AH,(46) and is therefore advocated as the technique of choice if VH is not possible.(49) However, recent epidemiological studies suggest that laparoscopic techniques are associated with increased risks for both SUI and POP surgery, compared to abdominal and vaginal methods.(7, 11) In accordance with these findings, we found the highest rates of pelvic organ fistula surgery in the laparoscopic hysterectomy group. The majority of fistulas in the laparoscopic hysterectomy group were urogenital fistulas, confirming results from previous studies, with higher rates of bladder and ureteral lesions after laparoscopic hysterectomy.(60)

Our study is limited by the lack of information on some potential effect modifiers such as diabetes and obesity, which is treated primarily in community care. Also, the influence of lifestyle-factors such as smoking and HRT could not be taken into account. Smoking has recently been recognized to enhance the development of vesicovaginal fistulas, probably because of delayed or altered wound healing.(134)

Due to the highly invasive nature of pelvic organ fistula surgery, misclassification due to undetected cases performed as outpatient procedures, should be of limited consequence. The high quality registers and homogenous classification systems for exposure and outcomes, reduces the risk of misclassification of both exposure (hysterectomy) and the outcome (fistula surgery), whereas exclusion of all fistula cases occurring before study entry effectively increases the internal validity. The nationwide, large scale study design, using prospectively

collected data over three decades, further strengthens our conclusions. Although rarely encountered in a general population, pelvic organ fistula disease may have devastating effects on all aspects of quality of life and should be taken into account in the surgical decision making.

9.5 VAGINAL HYSTERECTOMY

Studies performed in the general population have confirmed a notion held by many clinicians, i.e. that hysterectomy increases the risk for pelvic floor disorders.(7, 11) In our large cohort study we were able to show that VH performed in women with manifest pelvic floor disease, carried the highest risks for subsequent POP and SUI surgery. This finding is hardly surprising if one considers posthysterectomy prolapse, or incontinence, as a deterioration or relapse of an already manifest disease. Recurrence of POP is common and according to a regional study in the US, as much as one third of women having POP surgery require secondary procedures for the same condition.(130)

More importantly though, we were also able to demonstrate that VH for reasons other than prolapse, increases the risk for both POP and SUI surgery. After adjusting the analysis for number of childbirths, in a subset of the cohort, risks were nearly a three-fold higher after a VH when compared to total AH. These results suggest that the increased risk for pelvic floor sequela after VH is not entirely attributable to the underlying medical conditions for surgery or to childbirth related selection of women to the procedure. Since both VH and AH involves complete removal of the uterus and cervix, one may reason that performing a hysterectomy by a vaginal approach involves more intraoperative tension to the apical vaginal support, and that inadequate access to the surgical area may impede reconstruction of the upper vaginal segment.

When considering only the indication for hysterectomy, rather than the surgical technique, women operated on because of prolapse disease had higher rates of ensuing pelvic floor surgery. This corroborates studies suggesting that previous POP is a strong risk factor for pelvic floor disease later in life.(15, 131) Regardless of approach and indication, hysterectomy carries a greater risk for posterior vaginal wall prolapse. This phenomenon could involve failure to effectively re-establish adequate ligamentous support of the posterior upper vagina and apex at the time of hysterectomy.(135)

Due to the observational nature of the present study, patients selected for a VH may differ from those selected for an abdominal approach with regard to pelvic floor relaxation, parity and indication for the procedure. To address this issue we categorized the hysterectomies by indication and we excluded all subjects with a record of surgically corrected prolapse or incontinence prior to the hysterectomy. Parity may have a confounding effect on the association because parous women are more often selected for VH than for AH and childbirth is a risk factor for POP and UI. We therefore adjusted the regression analysis for number of childbirths in a subset of women with known obstetrical history. Nonetheless, we cannot fully adjust for selection bias caused by gynecologic surgeons selecting patients for VH based on vaginal laxity, surgical accessibility and mobility of the uterus, factors which would contribute to postoperative POP being more common after VH. The time of follow-up was shorter after VH compared to after AH which is explained by a gradual change of practise in Sweden with a proportionally increased use of VH in the last decade. The women who went

through VH for other indications were younger at surgery and had a shorter follow-up time than the other women. As a result they contributed to less time at risk compared to women in the other groups, and it is possible that the risk for POP and SUI subsequent to VH for other indications than POP therefore may have been underestimated.

To the best of our knowledge this is the first attempt to try and separate the risk for surgically managed pelvic floor disorders attributable to the VH procedure itself, from other predisposing factors associated with the operation. Our findings rely on prospectively collected data over three decades and encompass almost eight million person-years at risk. Standardized tools for classification of both surgical procedures and diagnoses reduce the risk of misclassification, whereas random sampling of unexposed controls from the same population from where the cases arose limits the risk for selection bias.

In conclusion, the results of the present study suggests that having a VH is associated with a greater risk for ensuing POP and SUI surgery than total AH, when compared to not having a hysterectomy at all. The risk is further increased if VH is performed due to POP. Given current trends in gynecological surgery, where VH is increasingly performed in women of reproductive age, a long-term increased risk for posthysterectomy POP and SUI attributed to VH may influence women's choice of treatment.

9.6 CLINICAL IMPLICATIONS

As a result of this thesis, a number of questions with implications for future research and clinical practise have been raised. The appropriate rates of hysterectomy for benign conditions in Sweden remain undecided. It is, however, important to continue to survey the trends of surgery and the reasons for them, since widening of the surgical indications and the promotion of a definitive surgical solution to women of reproductive age, may have long-term consequences for patients at risk. The minor decline in rates of hysterectomy observed at the break of the new millennium may be related to new conservative and minimally invasive treatment options, such as intrauterine-levonorgestrel releasing devices, endometrial ablation or resection, and embolisation of the uterine arteries. The question whether or not these new treatment options will effectively change the rates and indications of hysterectomy remains unanswered, but may be of importance for women's health in years to come.

In order for women to make an informed decision on whether or not to have a hysterectomy, information on immediate outcomes of surgery, as well as, risk of developing disorders later in life should be considered. Identifying women for which hysterectomy is associated with increased risks for postoperative pelvic organ dysfunction is therefore important. Epidemiological studies may pave the way for an individualized treatment founded on a woman's predisposing factors such as heritability, age, medical history, and other environmental exposures. Based on individual predisposition, counseling on advantages and disadvantages regarding various modes of hysterectomy, can be weighed against alternative treatments. To conclude, the findings of the present thesis may be at help in guiding and managing patients with benign gynecological disease facing hysterectomy.

10 CONCLUSIONS

The specific aims are repeated with the conclusion for the convenience of the reader:

1. *Aim:* To investigate the annual rates, types and indications for hysterectomy on benign indications in Sweden 1987- 2003 (Paper 1).

   Conclusion: The overall rate of hysterectomy on benign indications has remained reasonably stable in Sweden over the last decade. Major trends involved decreased use of abdominal hysterectomy, increased use of vaginal hysterectomy, and an increased number of hysterectomies performed for pelvic organ prolapse.

2. *Aim:* To prospectively evaluate long-term effects of abdominal and vaginal hysterectomy on bowel function (Paper II).

   Conclusion: Neither abdominal nor vaginal hysterectomy was associated with constipation or rectal emptying difficulties three years after surgery. Abdominal and vaginal hysterectomy was, however, associated with a mild deterioration of anal continence.

3. *Aim:* To identify risk factors for surgically managed vaginal vault prolapse after hysterectomy (Paper III).

   Conclusion: Women with a history of surgically managed pelvic floor disorders are at increased risk of developing vaginal vault prolapse subsequent to a hysterectomy.

4. *Aim:* To study the association between hysterectomy and pelvic organ fistula disease, and to estimate the effect of various hysterectomy techniques on the association (Paper IV).

   Conclusion: Pelvic organ fistula surgery is four times more common in women after hysterectomy compared to women not having the procedure. The highest fistula rates were observed during the first year after surgery, after laparoscopic and total abdominal hysterectomy, and among older women.

5. *Aim:* To determine if risks of subsequent pelvic organ prolapse and stress urinary incontinence after vaginal hysterectomy are attributable to the procedure or the preoperative surgical indication (Paper V).

   Conclusion: Vaginal hysterectomy is associated with greater risks than total abdominal hysterectomy for postoperative pelvic organ prolapse and stress urinary incontinence surgery. If the vaginal hysterectomy is performed due to pelvic organ prolapse these risks increase further.

11 POPULÄRVETENSKAPLIG SAMMANFATTNING

Att bestämma sig för att ta bort livmodern (hysterektomi) är för flertalet kvinnor ett stort och kanske emotionellt laddat beslut. Trots detta uppskattas att en tredjedel av den kvinnliga befolkningen i USA kommer att genomgå denna operation före 60 års ålder. I Sverige utförs ca 9000 operationer varje år, cirka 90 % av dessa operationer utförs av andra orsaker än cancer med syftet att förbättra kvinnans livskvalitet. Hysterektomi ger mycket goda kortsiktiga resultat men vi vet mindre om långtidseffekterna. Ett flertal studier har visat att hysterektomi påverkar bäckenbottenfunktionen negativt och ökar risken för till exempel framfall och urinläckage. Orsakerna till detta är inte helt kända. Vid beslutet att genomgå en operation för att förbättra livskvalitet är läkarens roll som rådgivare mycket viktig. Beslutet bör utgå från väl underbyggd kunskap om såväl kortsiktiga som långsiktiga effekter av operationen. Huvudsyftet med denna avhandling är att utvidga just denna kunskap genom att i fem olika studier undersöka hur hysterektomi påverkar olika aspekter av bäckenbottenfunktionen.

Den första studien i denna avhandling baserar sig på det svenska slutenvårdsregistret och är en analys av trenderna för hysterektomi i Sverige under 16 års tid (1987-2003). Det svenska slutenvårdsregistret innehåller information om diagnoser och operationer gällande i Sverige sjukhusvårdade individer sedan 1964 och framåt. Denna registerbaserade studie inkluderade sammanlagt 121 947 kvinnor som genomgått hysterektomi av andra orsaker än cancer. Studien visade att antalet hysterektomier som görs i Sverige är ungefär konstant över tid men att antalet har fluktuerat något och nu minskat under de senaste åren. I början av tidsintervallet ökade det relativa antalet hysterektomier; från 178 per 100 000 personer och år till 232 per 100 000 personer och år. Därefter sjönk incidensen ca 11 % och vid studiens avslutande var incidencen 210 per 100 000 personer och år. Vi kunde också konstatera att det blir allt vanligare att operationen görs via slidan (vaginal hysterektomi) och att medelåldern vid operationen ökade från 47 år till 52 år. De vanligaste orsakerna till hysterektomi var muskelknutor (myom) och oregelbundna blödningar, men allt fler operationen gjordes också på grund av framfall. Den sjunkande frekvensen av hysterektomi, i slutet av perioden, förklaras sannolikt av att ett flertal alternativa metoder för att behandla myom och blödningar har blivit tillgängliga.

Den andra studien är en undersökning av hur magtarmfunktionen påverkas av hysterektomi. 120 kvinnor som alla genomgått hysterektomi vid Danderyds Sjukhus svarade på en enkät angående magtarmsymtom före, ett år, och tre år efter operationen. Med magtarmfunktion avses i första hand förstoppning och tarmtömningssvårigheter, men också ofrivilligt läckage av gas och avföring. Undersökningen visade att det inte i ökad utsträckning förekom symptom på förstoppning eller tarmtömningssvårigheter efter hysterektomi, jämfört med före. Däremot uppgav fler kvinnor förvärrade symptom på ofrivilligt läckage av gas och avföring efter hysterektomin. Dessa symptom var dock mycket milda och det är svårt att avgöra vilken klinisk betydelse de har.

Den tredje studien är en undersökning av riskfaktorer för framfall efter hysterektomi. I denna studie valde vi att undersöka en typ av framfall, som kallas vaginaltoppsprolaps, och som bara förekommer efter hysterektomi. Det innebär att slidans övre del sjunker ner efter att

livmodertapp och livmoder tagits bort och orsakar besvär genom att den buktar ut ur slidan och ger skavkänsla. I studien deltog två grupper av kvinnor: den första (fallgruppen) bestod av 90 kvinnor som genomgått hysterektomi och därefter opererats för vaginaltoppsprolaps och den andra (kontrollgruppen) bestod av 233 kvinnor som bara genomgått hysterektomi. Undersökningen visade att den viktigaste bidragande riskfaktorn för framfall av denna typ, utgjordes av tidigare operationer för bäckenbottensjukdom före den aktuella hysterektomin. Detta kan bero på att en svaghet i bäckenbotten finns redan före hysterektomin och sedan förvärras av operationen.

Den fjärde studien undersöker förekomsten av fistelsjukdom efter hysterektomi. Med fistelsjukdom avses i den här studien onormala gångar mellan slidan och inre organ som urinblåsa, urinledare och tarm. Fistlar uppkommer internationellt sett oftast efter förlossning, men tack vare den välfungerande förlossningsvården i Sverige är denna komplikation mycket ovanlig. I industrialiserade länder har istället buk- och bäckenoperationer tillskrivits en stor del av risken för fistelsjukdom. Vår studie baserar sig på det svenska slutenvårdsregistret under 30 års tid (1973-2003) och undersöker 182 641 kvinnor som genomgått hysterektomi och 525 826 kvinnor som inte genomgått hysterektomi. Studien visar att det är fyra gånger vanligare med fistelsjukdom hos kvinnor som genomgått hysterektomi, att tillståndet förekommer oftare hos äldre kvinnor, och är vanligast det första året efter operationen. Fortsättningsvis såg vi fler fistlar efter total hysterektomi utförd via buken (abdominell hysterektomi) och efter hysterektomi utförd med titthålskirurgi (laparoskopisk hysterektomi) än efter andra hysterektomi-metoder.

Den femte studien i avhandlingen är en undersökning av risken för framfall och urinläckage efter hysterektomi utförd via slidan (vaginal hysterektomi). Vaginal hysterektomi förordas som förstahandsval på grund av bland annat kortare vårdtider, men i några studier har man sett att metoden ökar risken för efterföljande framfall. Problemet har varit att urskilja effekter av själva operationen och följder av svagheter i bäckenbotten som funnits redan före operationen. Vi har därför i denna studie försökt att isolera effekten av själva operationsmetoden. Även denna studie är baserad på det svenska slutenvårdsregistret under åren 1973 och 2003 men vi undersökte ett något färre antal kvinnor än i den fjärde studien, detta på grund av striktare urvalskriterier. Studien baserar sig på 118 601 kvinnor som genomgått hysterektomi och 579 200 kvinnor som inte genomgått hysterektomi. Undersökningen visade att kvinnor som genomgått vaginal hysterektomi löper ökad risk för efterföljande framfall och urinläckage, både jämfört med kvinnor som inte hysterektomerats och jämfört med dem som genomgått abdominell hysterektomi. Vi såg också att kvinnor som genomgått vaginal hysterektomi på grund av framfall löpte högst risk för efterföljande bäckenbottensjukdom. Denna effekt kvarstod även då vi justerat de statistiska analyserna för bland annat antal födda barn.

Avslutningsvis har studierna i denna avhandling visat att hysterektomi kan ha negativa långsiktiga effekter på många aspekter av bäckenbottenfunktionen såsom magtarmsymptom, fistelsjukdom, framfall och urinläckage. När en kvinna i samråd med sin läkare fattar beslut om att genomgå en hysterektomi bör både läkare och patient vara väl informerade om effekterna av operationen, men också om vilka nya symtom som kan utvecklas över tid. Läkaren bör sträva efter att identifiera riskfaktorer hos kvinnor som av olika skäl löper ökad risk för bäckenbottensjukdom efter hysterektomi och därefter, i möjligaste mån, individualisera vården.

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14 APPENDIX

14.1 QUESTIONNAIRE PAPER II

Date for filling out the questionnaire: ……..
Name: ……..
Address: ……..
Social security number: …….. Occupation: ……..
Height: …….. Weight: ……..

Do you currently undergo treatment for any of the following conditions?
☐ Asthma ☐ Reumatism ☐ Bechterews disease ☐ Sclerodermia ☐ Osteoporosis
☐ Lupus erytematosus ☐ Sjögrens syndrome ☐ Other connective tissue disease
☐ Diabetes ☐ Over function of the thyroid gland ☐ Under function of the thyroid gland
Have you suffered from internal disease demanding hospital care? If so please specify: ……
Do you have any connective tissue disease such as rheumatism, Sjögrens syndrome or Bechterews disease in your family? ☐ Yes ☐ No
If Yes on the previous question:
What disease? ……..
Which family member? ☐ Mother ☐ Father ☐ Sibling ☐ Grandparents on my mothers' side ☐ Grandparents on my fathers' side

Do you currently use any of the medications below?
☐ Inhalatory cortisone ☐ Per oral cortisone ☐ Thyroid hormone ☐ Diabetes medication
Are you currently on any medication?
……
Do you use any of the below listed hormone treatments:
☐ Birth control pills ☐ Mini-pills ☐ Per oral estrogen ☐ Local estrogen vagitories
☐ Per oral combined hormone treatment ☐ Hormonal intrauterine device

Have you undergone previous abdominal surgery? ☐ Yes ☐ No
If Yes on the previous question, what kind of surgery and when?
☐ Open wound abdominal bowel surgery year……..hospital……..
☐ Rectal surgery year……..hospital……..
☐ Abdominal hernia surgery year……..hospital……..
☐ Appendix removal year……..hospital……..
☐ Gall bladder removal year……..hospital……..
☐ Other surgery :…… year……..hospital……..

Have you undergone previous gynecological surgery? ☐ Yes ☐ No
If Yes on the previous question, what kind of surgery and when?
☐ Vaginal wall prolapse surgery year……..hospital……..
☐ Hysterectomy due to uterine prolapse year……..hospital……..
☐ Vaginal hysterectomy year……..hospital……..
☐ Abdominal hysterectomy year……..hospital……..
☐ Unilateral salpingooopherectomy year……..hospital……..
☐ Bilateral salpingooopherectomy year……..hospital……..
☐ Uni- or bilateral salpingectomy year……..hospital……..
☐ Urinary incontinence surgery year……..hospital……..
☐ Other gynecological surgery: …… year……..hospital……..

How many times have you been pregnant? ……..
How many times have you delivered a child? …….. What years? ……..
How many times have you been delivered by Cesarean section? …….. What years? ……..
How many times have you delivered a child weighing more than 4,000 grams? ……..
How many times have you been delivered using vacuum extraction or forceps? ……..
Did you suffer a severe tear or sphincter damage at any of your deliveries? ☐ Yes ☐ No

If Yes on the previous question, what year? …….

Do you smoke? ☐ Yes ☐ No
If Yes on the previous question, for how long have you been smoking? …….

Bowel symptoms

Number of bowel motions/ week_____

Number of laxatives/ week_____

Do you experience any of the following symptoms?

	No	**< Once a week**	**≥ Once a week**	**Daily**
Blood in stools?	☐	☐	☐	☐
Mucous in stools?	☐	☐	☐	☐
Pain at bowel emptying?	☐	☐	☐	☐
Urgency for bowel emptying?	☐	☐	☐	☐
Bowel emptying difficulties?	☐	☐	☐	☐
Do you have to apply pressure to the back wall of the vagina to be able to empty your bowel?	☐	☐	☐	☐
Do you have to empty your bowel with your finger?	☐	☐	☐	☐
Do you support your pelvic floor during bowel motion?	☐	☐	☐	☐
Are you unable to distinguish between flatus and fecal contents in your rectum?	☐	☐	☐	☐
Do you have involuntary leakage of flatus?	☐	☐	☐	☐
Do you have involuntary leakage of soft stools?	☐	☐	☐	☐
Do you have involuntary leakage of firm stools?	☐	☐	☐	☐
Do you experience leakage of fluid around the anal opening?	☐	☐	☐	☐
Do you have to wear a pad due to leakage of stools?	☐	☐	☐	☐

14.2 QUESTIONNAIRE PAPER III

Initials: ……..
Occupation: ……..
Date for filling out the questionnaire: ……..
Height: …….. Weight: ……..

How many children do you have? ..... What years are they born? ……..
How many times have you vaginally delivered a child? ……. What years?
How many times have you been delivered using vacuum extraction or forceps? ……. What years? .....
How many times have you been delivered by Cesarean section? ……. What years? ……..
How many times have you delivered a child weighing more than 4,000 grams? ……. Vaginally? .....
How many times have you delivered a child cesarean section? .....
Did you suffer a severe tear of the vagina at any of your deliveries? ☐ Yes ☐ No
Did you suffer a obstetric sphincter damage at any of your deliveries? ☐ Yes ☐ No
If Yes on the previous question, what year? …….

Do you smoke? ☐ Yes ☐ No
If Yes on the previous question,;
How much have you been smoking? . ☐ 0-5 cig/d. ☐ 5-10 cig/d. ☐ 10-20 cig/d. ☐ >20 cig/d.
For how long have you been smoking? ☐ Smoker since > 5 year. ☐ Smoker since > 10 years.
☐ Smoker since > 20 years. ☐ Smoker since > 30 years.

Did you go through menopause?
☐ Yes I stopped menstruating at the age of…….
☐ No

I do physical exercise that makes me sweat
☐ Never ☐ Once a month. ☐ Less than once a month ☐ Once a week
☐ 2-3 times a week ☐ Every day

Do you currently undergo treatment for any of the following conditions?
☐ Asthma ☐ Reumatism ☐ Diabetes ☐ Sclerodermia
☐ Lupus Erytematosus ☐ Dysfunction of the thyroid gland

Have you suffered from any other disease? If so please specify:
……

Do you have any connective tissue disease such as rheumatism, Sjögrens syndrome or Bechterews disease in your family? ☐ Yes ☐ No

Does any of your family suffer from uterine prolapse or pelvic organ prolapse?
☐ Yes my: ☐ Mother ☐ Sister ☐ Aunt ☐ Other relative
☐ No

Do you currently use any of the medications below:
☐ Inhalatory cortison ☐ Per oral cortison ☐ Insulin ☐ Other diabetes medication

Do you currently use thyroid hormone (Levaxin)? ☐ Yes ☐ No
If Yes on the previous question; for how long? ☐ Since 5 years. ☐ Since 10 years.
☐ Since 15- 20 years ☐ Since > 20 years

Do you use any of the below listed hormone treatments:
☐ Per oral estrogen ☐ Local estrogen vagitories ☐ Estrogen patches