The importance of life-style factors for the outcome of gynaecological surgery

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"Stark för kirurgi - stark för livet"

The importance of life-style factors for the outcome of gynaecological surgery

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Abstract

Background: Hysterectomy (HT), urinary incontinence- (UI) and pelvic organ prolapse (POP) surgery are common surgical procedures in women with benign disorders and more than 16 000 procedures are performed annually in Sweden. To identify factors associated with a greater risk for an unsuccessful outcome is important and in particular factors that can be modified before surgery. The aim of this thesis was to analyse the influence of modifiable life-style factors such as high body mass index (BMI) and smoking on the outcome of hysterectomy, UI- and POP surgery.

Materials and Methods: Data was collected during the years 2004-2015 from the Swedish National Register for Gynecological Surgery including 6 308 midurethral sling procedures (MUS), 28 537 HT and 20 689 POP operations. The rate of obesity (BMI ≥30) ranged from 18-28% and smoking 9-18%. Multivariable logistic regression analyses were used to identify independent risk factors affecting per- and postoperative complications, change in UI status and subjective success with a follow-up of one year.

Results: In MUS, BMI ≥30 was associated with a higher risk of residual daily UI after surgery. In contrast, less peroperative complications were seen in women with BMI >25. In HT, obesity was associated with a higher risk of excessive bleeding, prolonged surgery, per- and postoperative complications and postoperative infections. Smoking was associated with a higher risk of postoperative infection in abdominal and vaginal HT. One fifth of the women who underwent HT experienced a change in continence status. Obesity, vaginal delivery and urinary urge were identified as riskfactors of UI after HT. In POP surgery obesity was associated with a higher risk of a vaginal bulge and UI after surgery. The studied life-style factors did not influence patient satisfaction.

Conclusions: Obesity was associated with a negative influence on all studied surgical procedures and particularly an increased prevalence of UI after surgery and complications with HT. Smoking was associated with postoperative infections after abdominal and vaginal HT. Preoperative counselling should include information on the influence of life-style factors on surgical outcome and offer life-style intervention programs.

Key-words; Body mass index, obesity, smoking, hysterectomy, mid-urethral sling procedures, pelvic organ prolapse, complications, urinary incontinence, vaginal bulge

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List of publications

This thesis is based on the following papers, which will be referred to in the text by their roman numerals.

I. Bohlin, K.S., Ankardal, M., Pedroletti, C., Lindkvist, H, Milsom, I.
The influence of the modifiable life-style factors body mass index and smoking on the outcome of mid-urethral sling procedures for female urinary incontinence.
Int Urogynecol J. 2015 Mar; 26(3):343-51

II. Bohlin, K.S., Ankardal, M., Stjerndahl, J-H., Lindkvist, H., Milsom, I.
Influence of the modifiable life-style factors body mass index and smoking on the outcome of hysterectomy.
Acta Obstet Gynecol Scand. 2016 Jan; 95(1):65-73

III. Bohlin, K.S., Ankardal, M., Lindkvist, H., Milsom, I.
Factors influencing the incidence and remission of urinary incontinence after hysterectomy.
Am J Obstet Gynecol. 2017 Jan; 216 (1):53.e1-53.e9.
doi:10.1016/j.ajog.2016.08.034

IV. Bohlin, K.S., Ankardal, M., Nüssler E., Lindkvist, H., Milsom, I.
Factors influencing the outcome of surgery for pelvic organ prolapse.
Submitted

Abbreviations

Adj OR	Adjusted Odds Ratio
AH	Abdominal Hysterectomy
ASA	American Society of Anesthiologists physical status classification
AUDIT	Alcohol Use Disorders Identification Test
BMI	Body Mass Index
CI	Confidence Interval
dU	De novo Urge
HT	Hysterectomy
LH	Laparoscopic hysterectomy
MD	Mean difference
MUI	Mixed urinary incontinence
NPR	National Inpatient Register
NRT	Nicotine Replacement Therapy
OR	Odds Ratio
PA	Physcial Activity
POP	Pelvic Organ Prolapse
POP-Q	Pelvic Organ Prolapse Quantification
RCT	Randomised Controlled Trial
RPR	RetroPubic Route
SSI	Surgical Site Infections
SUI	Stress Urinary Incontinence
TOR	Transobturator Route
TVT	Tensionfree Vaginal Tape
VH	Vaginal Hysterectomy
UI	Urinary Incontinence
UTI	Urinary Tract Infection
UUI	Urge Urinary Incontinence
WHO	World Health Organization

Contents

Introduction

Hysterectomy, pelvic organ prolapse (POP) and urinary incontinence (UI) surgery are the most common gynaecological surgical procedures and approximately 16 000 operations are performed in Sweden annually.[1] The majority of these surgical procedures are carried out on otherwise healthy women of working age. Elective surgery for benign indications is often optional for the patient, meaning that despite a severe reduction of quality of life, the disease or symptoms are not life threatening. Many women express concern before surgery. A bad result with a minor reduction of symptoms is not desirable. A complication related to surgery might cause severe consequences for the patient and to society with prolonged convalescence and sick leave. The most negative consequence is a complication with persisting symptoms. When a woman is seeking treatment for a benign gynaecological disease, several treatment options can often be considered before a surgical intervention. In addition, even if surgery is indicated there is time for both the patient and the doctor to overlook factors that can interfere with the results.

The objective of this thesis was to identify factors that are associated with a negative influence on the results of surgery and lead to an unsuccessful outcome for the woman. One important aspect is to identify factors that can be modified before surgery in order to reduce the risk of complications. Modifiable factors can be life-style related such as smoking, obesity, alcohol consumption and physical inactivity. According to reports from the Public Health Agency life-style factors have the greatest impact on the accumulated burden of illness in Sweden. Guidelines have been published in 2011 on effective methods to prevent diseases through changes in life-style.[2] These guidelines are also applicable and should be introduced in surgery, not least from a safety aspect. Life-style factors are in many ways as important riskfactors for perioperative complications and reduced success of

surgery as any medical risk factor. In addition, a perioperative life-style change can have a long-term effect on the general health of the indivual.

A large unselected cohort is required to render precision in estimates if risk factors affecting surgical outcome are to be studied. This thesis includes large cohort studies using data from the Swedish National Register for Gynaecological surgery, GynOp. GynOp has collected data since 1997 on the majority of performed hysterectomies, POP and UI surgery in Sweden. Life-style information can be obtained on smoking status and body mass index (BMI) in the register. The rate of smoking is gradually decreasing in Sweden, but obesity has reached epidemic proportions around the world. Gynaecological surgeons will be facing increasing life-style related issues and evidence on the influence of obesity and smoking on gynaecological surgery is still lacking.

Life-style factors and surgery in general

Overweight and obesity

Body mass index is often used as an objective measure of body weight in proportion to height and is calculated as kg/m^2. In the WHO classification the BMI groups are defined as: under-weight <18.5; normal weight 18.5-24.9; overweight 25-29.9; obesity I 30-34.9; obesity II 35-35.9 and obesity III ≥40.[3] In this thesis obesity is referred to as a BMI ≥30.

A high body mass index is one of the five leading causes of shorter life expectancy in Sweden. The proportion of obesity has tripled since the 80's and is continously rising. Between the years 2004-2013 obesity increased from 11 % to 14 % and today nearly 50 % of the population is overweight or obese. The greatest increase has been seen in the ages 45-64 years.[4] In the US the proportion of obesity reached epidemic proportions already in the beginning of the 21st century[5] and today it is a reality for Europe[6] as well. The worldwide obesity epidemic is a challenge for all medical specialities, including the surgical specialities.[6]

Obesity as a risk factor for different complications during and after surgery varies according to the type of surgery being performed. The most common complications associated with a high BMI are wound related complications, excessive bleeding and prolonged operating time.[7-10] The impaired healing of wounds is described to be an effect of excessive subcutaneous fat causing a lower regional blood perfusion, oxygen deprivation[11] and increased tension on the surgical incision. Other findings common in obese individuals and predictors of wound infections are elevated blood glucose levels,[12] impaired immunity[13] and longer operating time. Most of these conditions are found to be reversible after weight loss.[12,13]

Smoking

According to the National Board of Health and Welfare, tobacco smoking causes about 100 000 cases of smoking-related diseases and 12 000 deaths per year in Sweden.[2] Increased complications are seen within different surgical fields including major orthopedic surgery and abdominal surgery, but also in surgery of appendicitis, inguinal hernia repair and smaller skin incisions.[14] Wound related complications dominate with infections, wound dehiscence, hematomas and necrosis of flaps. The risk of pulmonary complications is elevated with pneumonia, broncospasm and desaturation. Tobacco can also be consumed as snuff, but no association with increased postoperative complications have so far been found.[15]

The pathophysiology of smoking and postoperative complications is thought to mainly depend on a chronic low oxygen tension in the periferal tissue.[11] This is supported by studies that show an improvement in tissue healing and reduction of surgical-wound infections with supplemental perioperative oxygen.[16] There is also a reduced immunocapacity. Abstinence from smoking is shown to reverse several of the underlying pathophysiological mechanisms. Prolonged wound healing recovers within 3-4 weeks, reduced immunological capacity within 2-6 weeks and lungdysfunction within 6-8 weeks.[14]

How smoking and obesity influence gynaecological procedures is discussed in each chapter of the surgical procedures.

Alcohol

The influence of alcohol on surgery is more powerful than smoking with the risk of mortal complications being doubled in hazardous drinking.[17,18] Despite this knowledge, not much notice is taken to alcohol consumption before gynaecological surgery. There is no information on alcohol consumption in GynOp and to include this information in the register would be of much value to patient safety measurements. Many patients who screen positive for alcohol misuse have no obvious health problems. Without screening nothing alerts the health care providers of drinking habits with a harmful effect on surgery.[19]

The prevalence of hazardous drinking for general surgical populations undergoing elective procedures is 7-49%.[19,20] Most of these studies are performed in males. According to the Public Health Agency of Sweden 12% of women have a hazardous drinking pattern which means drinking more than 9 alcohol units per week or at least four drinks at a time (with one drink equating 12 g of ethanol).[1] The incidence of hazardous drinking in a surgical population is often higher than in the general population because alcohol-related diseases are over-represented in a hospital population.[14] Hazardous drinking is related to increased postoperative infections, cardiopulmonary complications, bleeding episodes and increased stress response during surgery. These effects are seen in all types of surgery.[17,21] Studies on gynaecological surgery are limited. A Danish study on hysterectomy showed a complication rate of 80% in alcohol abusers (>60 g alcohol/day) compared to 27 % of moderate drinkers.[22]

Physical inactivity

Another interesting and important life-style factor that we were not able to analyse in this study is the impact of preoperative physical activity (PA) on the postoperative outcome. Physical inactivity is considered to be the fourth most important risk factor for overall death by the WHO[23] and increased PA in the population is of great importance leading to reduced risk of cardiovascular events and different types of cancer.[24] Physical condition and functional status have been shown to influence mental and physical health during hospitalisation and surgery. A poor physical condition may lead to reduced postoperative functional recovery and result in postoperative complications, death and restricted postoperative mobility in the elderly.[25,26]

Surgical procedures

Hysterectomy

Hysterectomy is one of the major surgeries in benign gynaecologic surgery, requiring general anesthesia, in-patient ward and a longer hospital stay than UI and POP surgery. In GynOp, more than 4 000 hysterectomies are registered annually, nowadays covering 90% of the performed hysterectomies in Sweden due to benign disorders.[27] The prevalence of hysterectomy is reported to be 11 % in Sweden[28,29] and the incidence 169/100 000 women[1] which is a low rate in comparison with other western countries. In the US, 30% of women by the age of 60 have had a hysterectomy and 590 000 procedures are performed annually.[30] 85-90% of hysterectomies on benign indication are due to abnormal uterine bleeding disorders or fibroids. Other diagnoses are pelvic organ prolapse, endometriosis and pain.

The three approaches of hysterectomy are abdominal hysterectomy (AH), laparoscopic hysterectomy (LH) and vaginal hysterectomy (VH). The minimal invasive hysterectomy methods, the vaginal and laparoscopic routes, were progressively introduced at the end of the 20th century implying smaller wounds, less wound related complications, shorter hospital stay and speedier recovery.

Abdominal hysterectomy is performed through a skin incision in the lower abdomen and in the majority of cases on benign indication as a horisontal incision.

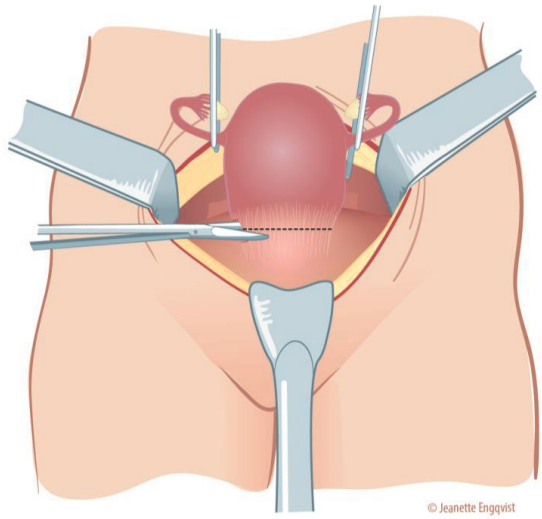


Figure 1. Abdominal hysterectomy (illustration ©Jeanette Engqvist)

Despite the general recommendation to perform VH in preference to AH whenever feasible,[31] the abdominal route is still dominating, but a wide variation is seen between clinics in Sweden.[32]

In vaginal hysterectomy uterus is removed via an incision in the upper vagina and without any skin incision. Shorter operating time, less bleeding, shorter hospital stay and faster recovery are the advantages of VH compared to AH.[31] VH requires a normal sized uterus reachable from the vagina. Even with a small uterine size intraabdominal adhesions in endometrios or previous intraabdominal surgery and no previous vaginal delivery aggravate the procedure and LH is usually preferred.

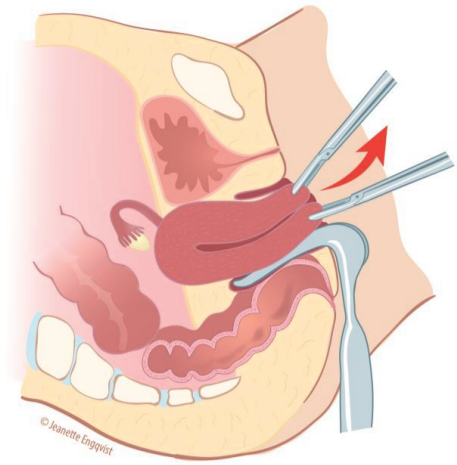


Figure 2. Vaginal hysterectomy (illustration ©Jeanette Engqvist)

In laparoscopic hysterectomy small skin incisions are made in the abdominal wall allowing the insertion of a camera and surgical instruments to detach the uterine attachments. The uterus is removed through the vagina or by morcellation into smaller pieces that can be evacuated through trocars in the incisions.

LH requires a longer operating time (MD 20.3 minutes compared to AH) and an experienced laparoscopic surgeon. Compared to AH the hospital stay is MD 2.0 days shorter and the postoperative recovery is MD 13.6 days shorter in LH.[31] In a total LH the whole procedure is done in the laparoscope. In a laparoscope-assisted VH, the surgery starts laparoscopically, but the last steps are performed vaginally. In this study, the route has been defined in regard to prime incision only.

There is also the choice of removing (total) or leaving (subtotal) the cervix uteri. Subtotal hysterectomy does not seem to have any advantages regarding sexual

function, urinary incontinence or genital prolapse development after surgery compared to total hysterectomy.[33] The risk of cyclic bleeding or discharge is increased after subtotal hysterectomy.[34]

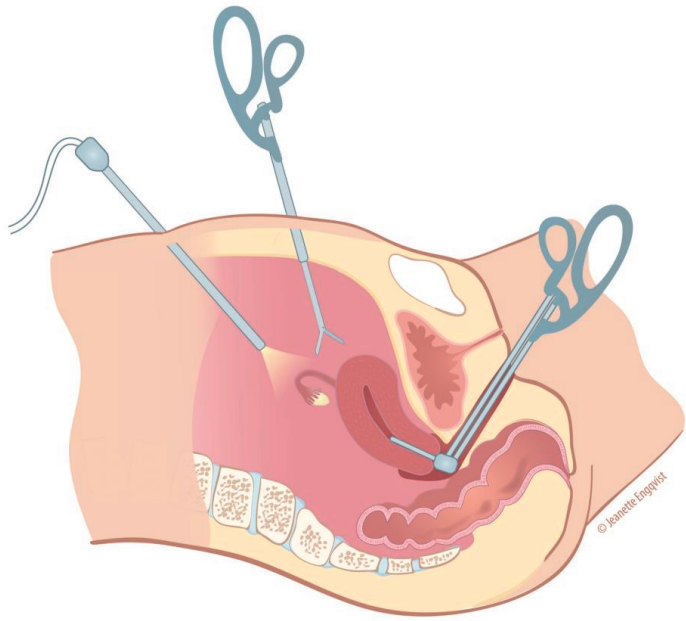


Figure 3. Laparoscopic hysterectomy (illustration ©Jeanette Engqvist)

Complications and hysterectomy

Infectious complications after hysterectomy for a benign condition are the most common complications ranging from 10.5-13% in AH, 8-13.0% in VH and 9-10 % in LH. Injury to the genitourinary tract is estimated to occur at a rate of 1-5% and injury to the gastrointestinal tract around 0.1-1%.[35-38]

The complication panorama differs according to the surgical route. The minimal invasive approaches are associated with lower rates of complications than the abdominal route. Randomised controlled trials on VH versus AH have found fewer febrile episodes or unspecified infections in VH, but no significant differences in

the need for blood transfusion, mean blood loss, haemoglobin drop, occurence of pelvic haematoma, vaginal cuff infection or UTI. The benefits of LH versus AH have been reported to be a smaller drop in hemoglobin, less wound or abdominal infections at the cost of more urinary tract injuries.[31] According to a report by Mäkinen et al a significant lower incidence of ureter and bladder injuries (0.5 and 0.8% respectively) was seen with an experienced laparoscopic surgeon (performed >30 LH) than those who had performed ≤30 operations (2.2 and 2.0% respectively).[37]

Not only the surgical approach to hysterectomy has changed in recent years. New concepts have influenced the perioperative care such as fast track surgery and enhanced recovery after surgery (ERAS) in order to improve the recovery of the patient and shorten the hospital stay.[39,40] Naturally this will have an impact on the prevalence of complications in hysterectomy as for any other surgery and the need for updated studies.

Urinary incontinence and hysterectomy

Another aspect of the outcome of hysterectomy is the change of UI status after surgery. Both de novo UI and remission of UI are reported after hysterectomy.[41-43] Different ways of studying this aspect have been carried out; either as measuring subjective and objective symptoms of UI or the prevalence of subsequent UI surgery. A nationwide study of Altman found a doubled risk of subsequent UI surgery among women with previous hysterectomy compared to non-hysterectomised women.[44] In two other cohort studies, VH was associated with an increased risk of surgery of the pelvic floor compared to a non-hysterectomised cohort.[45,46] Selection bias of a surgical cohort can play a role in these studies. Women having had surgery might be more prone to choose surgery again as a

treatment and thereby the cohorts might not be comparable. On the other hand, the results are supported by the Women's Health Initiative, an observational study on UI symptoms in which hysterectomy was associated with incident and residual UI both at baseline and after three years.[47] A meta-analysis of urinary symptoms and urodynamics after hysterectomy showed that UI symptoms were significantly reduced and the urodynamic diagnosis of detrusor overactivity was improved after hysterectomy. There was no significant reduction in the prevalence of urodynamic stress incontinence, which supports the evidence on increased risk of SUI surgery after hysterectomy.[41] In the study by Lakeman et al an increased risk of lower urinary tract symptoms was seen after hysterectomy and it was three times higher after VH compared to AH. An adjustment for the descent of the uterus, uterine size, parity and indication for hysterectomy was performed,[48] but in the other mentioned studies several confounders including BMI and smoking were not analysed.

Subtotal and total hysterectomy have been compared in the studies of the surgical aspects of hysterectomy and pelvic floor disorders. In a randomised study with a fourteen year follow up period subtotal and total abdominal hysterectomy were comparable regarding long-term objective and subjective pelvic organ prolapse and urinary incontinence.[49,50]

The complex genesis of UI imposes many difficulties when performing a study on hysterectomy and UI,[29] among many others the age of the study population. In a systematic review it was found that the odds of developing UI post-hysterectomy increased first after the age of 60 years.[43] In addition, there are reports indicating that a high BMI is associated with a risk of UI after hysterectomy.[51,52]

Life-style factors and hysterectomy

In gynaecological surgery, obesity is generally regarded as a surgical risk. Older studies on abdominal hysterectomy due to malignancy have found that obesity increases the risk of excessive bleeding, wound complications and postoperative infection as much as 5-10 times.[53-55]

The abdominal approach is still the most common way of performing a hysterectomy worldwide, but updated reports on AH and obesity on benign indication are surprisingly few. Two observational studies found a prolonged operative time in obese women for both vaginal and abdominal hysterectomy, but no significant difference in the length of hospitalisation, transfusion rate, and perioperative hemoglobin change.[56,57] Earlier Swedish studies from the GynOp register on hysterectomy have focused on postoperative infections and found BMI ≥30 to be a risk factor in both vaginal and abdominal hysterectomy.[58-60] In a Danish study from 2011 on more than 20 000 hysterectomies obesity increased the risks of infections and bleeding in AH, but not in VH or LH.

The main association of smoking and complications in hysterectomy is as a riskfactor for surgical site infections (SSI). In the above mentioned GynOp studies tobacco use was associated with a risk of postoperative infections in AH, but not in VH.[59,60] In 2014, an observational study on AH and LH found among other factors smoking and overweight and obesity to be predictors of SSI in AH, but not in LH.[61]

Midurethral sling procedures (MUS)

Urinary incontinence is a common condition in women. The reported prevalence rates of UI in women vary with different definitions, study population and study design. In most studies the prevalence of isolated stress UI (SUI) was 10-39%, the prevalence of mixed UI (MUI) 7.5-25%, and isolated urge UI (UUI) in 1-7%.[62] The most important riskfactors for UI are age, vaginal delivery and overweight.[63-65] Other suggested riskfactors are previous hysterectomy, smoking, chronic obstructive pulmonary disease, diabetes and neurological disease.[29,65-67] Depending on the type of UI, different treatment modalities are advocated and in this thesis surgical intervention was studied.

Midurethral slings (MUS) have since their introduction in the 1990s become the gold standard for treating SUI.[68,69] The GynOp register includes nowadays 90 % of the UI surgery performed in Sweden, with more than 3000 MUS each year.[27] They are quick, minimally invasive outpatient procedures, associated with a low morbidity and show good results in the long-term.[70,71]

The technique focuses on increasing the support of the urethra by stabilising the surrounding vaginal tissue. There is a variation of slings with different methods of placement and in this study the slings with the retropubic route (RPR) and the transobturator route (TOR) were analysed, while the single incision slings were excluded.

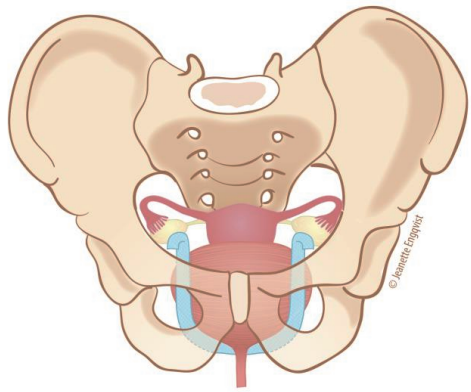


Figure 4. The retropubic route (RPR) (illustration ©Jeanette Engqvist)

The tension-free vaginal tape (TVT) is a RPR technique and was the first method to be introduced and is still the most common. In local anesthesia one small incision is made in the vaginal wall under the mid-urethra. A prolene sling is attached to two needles and the needles are passed through the incision on each side of the urethra through the retropubic space and up to the posterior surface of the symphysis. The sling is placed under the urethra without tension thus building a platform against which the urethra is compressed during abdominal straining. Routinely, a cystoscopy is then performed to check for bladder perforations.[69]

As an alternative, the sling can be inserted through the obturator foramen to avoid the blind passage of the retropubic space and reducing the risk of bladder and bowel injuries. The insertion of the needles can either start in the groin and exit in the vagina, as in the transobturator tape, (TOT),[72] or the inside-out technique is used as in the tension-free vaginal tape-obturator (TVT-O).[73]

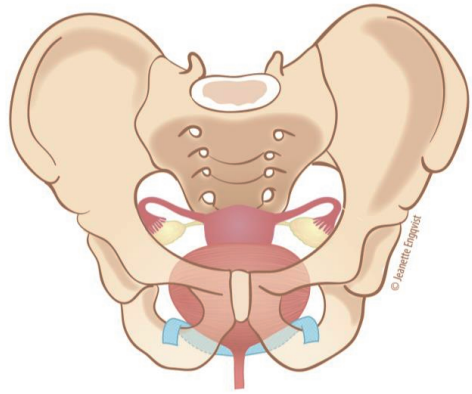


Figure 5. The obturator route (TOR) (illustration ©Jeanette Engqvist)

Irrespective of the routes traversed, the slings seem to be highly effective and the subjective short term (up to one year) cure rates range from 62%-98% in TOR and from 71-97% in RPR. Studies on long term follow ups (>five years) report cure rates of 43-92%.[74]

Complications and MUS

The overall complication rate is reported to be low. The most common adverse events in RCTs are groin pain and bladder perforations. A higher prevalence of groin pain is seen in TOR, 6.4% versus 1.3% in RPR and a higher rate of bladder perforations has been recorded in RPR, 4.5% vs 0.6% in TOR. Due to small wound incisions the rate of postoperative infections is low, mainly dominated by urinary tract infections.[74] In a nationwide analysis of complications associated with TVT procedures, Kuuva and Nilsson reported that 4.1%, 0.8%, and 0.7% of patients had a urinary tract infection, wound infection of the abdominal incision, and defective healing of the vaginal incision, respectively.[70]

Major vascular/visceral injury and operative blood loss are lower with TOR, which

is explained by the avoidance of the retropubic space. There is no need for cystoscopy which slighly prolongs the duration of surgery. RPR is on an average 7 minutes longer than a TOR. Major vessel injury and visceral organ injury are very rare and found in 0.07% and 0.04% respectively.[75]

Another bothersome adverse event of UI surgery is de novo urgency. Patients without previous urge complain on emerging urge with or without incontinence after surgery. The definition is not clearly set and thus the rate varies inbetween studies. The average rate of de novo urgency is reported to be 8.4%, with ranges varying between 3.1-25.9%.[70,76] The mechanism is unclear, although it is assumed to be caused by urethral obstruction or irritation by the mesh in most cases.[77] No significant difference between RPR and TOR has been found.[74]

Life-style factors and MUS

Most studies report MUS to be a safe procedure in obese women, but several of the previous studies have significant limitations including potential confounders such as concomittant surgical procedures,[78,79] short-term follow-up and small sample size.[80-83] There are reports on prolonged operating time and higher mean blood loss,[84] as well as a five-folded risk of surgical site infection in obese women compared to women of normal weight.[85] A higher incidence of postoperative urgency and UUI has also been demonstrated.[83] On the other hand, some of the most common complications such as bladder perforation[86] and groin pain in TOR show lower rates in obese compared to nonobese women.[87]

Several studies indicate lower cure rates related to obesity,[78,79,88,89] but data are inconsistent,[81,82,90,91] particularly concerning longterm data. In a study by Hellberg et al women with BMI ≥35 had a long-term cure rate of 52.1% with an average

follow-up time of 5.7 years. Moreover, this study revealed a significantly lower success rate in the elderly as well.[92]

Studies on the influence of smoking on complications and cure in MUS procedures are few and several of the studies analysing the life-style factor obesity have not included smoking in the analysis.[81,83,89,90,93] Richter et al found smoking and obesity to be independently associated with incontinence severity at baseline in women undergoing surgery for stress incontinence. There was no report on the outcome after surgery.[94]

Pelvic organ prolapse (POP) surgery

The prevalence of POP varies depending upon the definition. If based on symptoms the prevalence is 3-8%[95-98] compared with 41-50% when defined and graded on examination.[62,99,100] Early stages of prolapse are common and often asymptomatic.[99,100] POP is a consequence of damage to muscles, nerves and endopelvic fascia that form the pelvic organ support. It is a rare condition among women with no vaginal delivery and is strongly associated with childbirth[96,101] and an increasing number of births.[95,101] Other associated factors are prior hysterectomy,[102] age,[95,103] chronic obstipation,[96] physically demanding work,[103] chronic cough,[104] family history,[103] obesity[101,103] and smoking.[101,104]

The lifetime risk of undergoing surgery for prolapse surgery alone has been shown to vary between 5 and 19%.[68,105-108] Different surgical procedures are advocated depending on location of the prolapse and both native tissue and synthetic mesh

repairs exist.[109] In this thesis only simple transvaginal anterior and posterior colporraphy with or without mesh were studied, the most common techniques for POP surgery.

A typical anterior or posterior colporraphy is performed in local, general or regional anesthesia and preferably in a daycase setting. In short, an incision is performed in the vaginal wall to identify the defect in the underlying tissue. The native tissue is folded over the defect by sutures to create a new support of the vaginal wall to avoid the protrusion of the bladder (anterior) or the rectum (posterior).

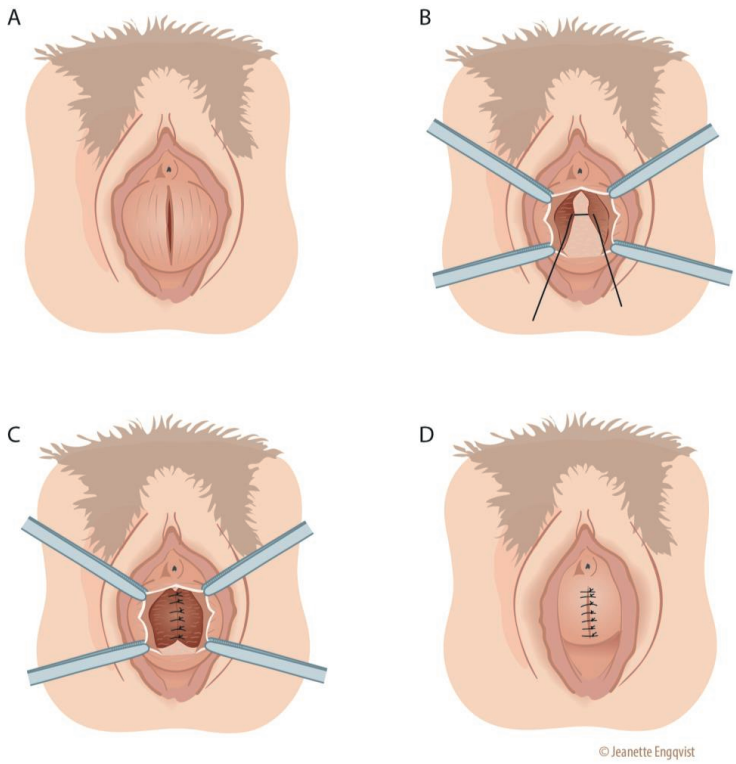


Figure 6. Anterior colporraphy in pevic organ prolapse surgery (illustration ©Jeanette Engqvist)

The problem of recurrent prolapse lead to the development of new surgical techniques in the 1990s. Mesh augmented surgery showed promising results and increased rapidly without proper longterm evaluation until alarming reports on an increased risk of adverse events arised in 2008.[110] Recently, new international guidelines recommened vaginal mesh repair to be performed by experienced specialists and reserved for high risk patients such as women with recurrent prolapse.[111] The need for the continued evaluation of the outcome of POP surgery is evident. Since POP surgery with mesh was introduced in Sweden it has been recommended to be used in repeat surgery only and according to a GynOp report from 2015 implants were used in 54.3% of repeat surgery and in 7% of primary surgery. [112]

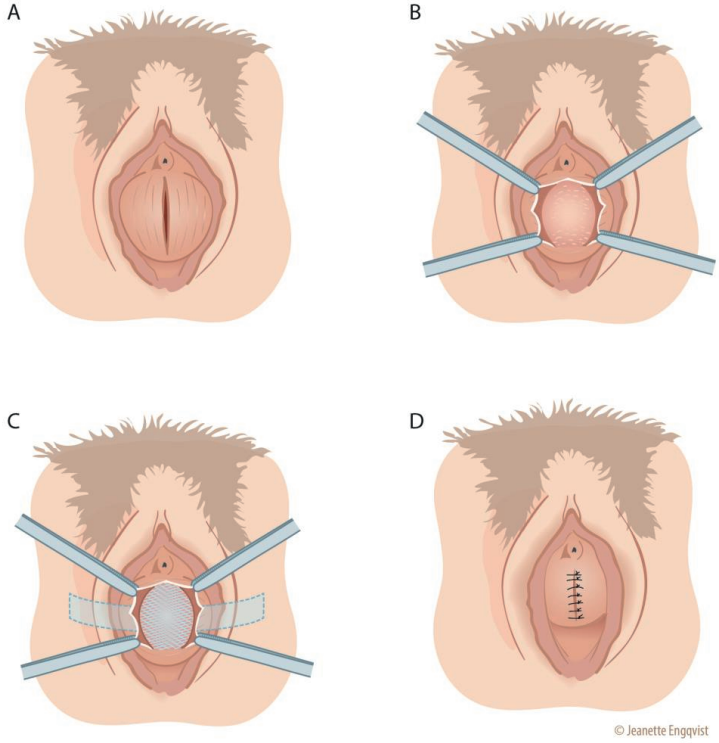


Figure 7. Anterior vaginal wall repair with mesh (illustration ©Jeanette Engqvist)

The surgical procedure with mesh repair starts with a incision of the vaginal skin. A dissection is performed between the bladder and the vagina for a cystocele and between the rectum and vagina for a rectocele. Sutures or tissue anchoring devices fix the mesh anteriorly either to the obturator membrane, to the pelvic sidewall or lateral to the bladder. Posteriorly, all types of mesh are fixed bilaterally to the sacrospinous ligaments using different techniques and then distally sutured to the perineum. The mesh is placed along the vagina between the points of fixation without further suturing. Sutures close the vaginal skin to cover the mesh.

The indication for POP surgery is bothersome symptoms and at least stage II prolapse. The stage of prolapse is most commonly defined according to POP-Q (the Pelvic Organ Prolapse Quantification system)[113,114] in which the most protruding part of the prolapse is measured in relation to the hymen.

The goal of surgery is to eliminate POP symptoms and to restore normal pelvic anatomy. Defining treatment success is difficult and varies in the literature depending upon what definition is used and if it is based upon anatomic or subjective success.[115] Prolapse stage ≥II used to be a measurement of surgical failure, but is probably a too strict anatomical criterion that corresponds poorly to a symptomatic prolapse. More recent studies use stage ≥III instead as a surgical failure where the most distal portion of the prolapse is >1 cm below the hymen. The strongest relationsship with subjective improvement and treatment success is found to be the absence of vaginal bulge symptoms.[115] To facilitate the comparison of studies the NIH Pelvic Floor Disorders Network has recommended that any definition of success after POP surgery should include the absence of bulge symptoms in addition to anatomic criteria.[109]

Prolapse of the anterior compartment is the most difficult to repair, and rates of recurrence are higher than at other vaginal sites.[116] Success rate ranges from 80-

100% in cases series to only 40-60% in RCTs.[117] Mesh in anterior POP results in better anatomical functional outcome, but is associated with more adverse events.[109,116] Posterior colporraphy results in success rates of 80-95%. Use of mesh has not been demonstrated to improve outcomes and there is no supportive evidence to recommened mesh in correcting posterior vaginal prolapse.[116]

It is important to clearly define primary surgery and repeat surgery. Primary surgery for POP is the first procedure required for the treatment of POP in any compartment. Repeat surgery is a repeat operation for prolapse recurrence in the same site as the first surgery. A new prolapse in a different compartment after previous prolapse surgery should be referred to as primary surgery.[118] The risk of reoperation is estimated to be around 13-29%,[107,119] but varies widely in the literature, partly because primary or repeat surgery has not been clearly defined until recently. In addition, regardless of an objective or subjective failure, many women choose not to undergo surgery again.[118]

Complications and pelvic organ prolapse

Peroperative complications in POP surgery are generally low, but increased in mesh augmented surgery due to the more invasive technique. Both awareness of prolapse and the rate of recurrence of anterior compartment prolapse on examination are reported to be reduced with the use of mesh compared to native tissue in RCTs. These benefits must be balanced against a longer duration of surgery, more bladder perforations, greater blood loss and increased rates of pelvic haemorrhage.[120,121] De novo stress UI is more common after mesh augmented POP surgery (5-10% versus 10%) and mesh erosions are seen in 10.4% of the women.[117]

Injury to neighbouring organs is unusal with native tissue repair and complications such as urinary retention and urinary tract infections are some of the most common complications. Concomitant procedures including hysterectomy or urinary incontinence surgery are reported to increase the risk of adverse events[122,123] and comorbidity is demonstrated to be strongly associated with postoperative complications.[124]

Urinary incontinence and pelvic organ prolapse

Olsen et al was first to show that symptomatic POP was associated with an increased risk of having urinary incontinence compared with women without POP. This was later confirmed in the EPIQ cohort study, by Lawrence et al 2008, that 57.4% of the women with prolapse reported UI.[97] The relationship between POP and UI is complex both with regard to pathophysiology and changes in relation to surgical correction of POP. POP surgery can result in cure of UI in up to one third of the women.[125] On the other hand an occult SUI can be unmasked by POP surgery.[126] De novo SUI is reported to occur in 10-12% after POP surgery.[126,127] The decision of whether or not to perform concomitant UI surgery in a POP repair or how to find an appropriate diagnostic preoperative test for occult UI is being discussed.[128] In Sweden, concomitant UI surgery is rarely performed in POP surgery as adverse events are likely to be higher[116,123,129] and the fact that UI symptoms can actually be reduced after POP surgery.[128]

Life-style factors and pelvic organ prolapse surgery

Although there are several studies showing an association between obesity and the development of POP,[130,131] data are conflicting regarding the associated symptomatology. Urinary incontinence and anal incontinence have been reported to

be the dominating pelvic floor symptoms in obese women rather than vaginal protrusion.[132,133] However other studies have reported an increase in the feeling of a vaginal bulge in obese women compared to nonobese women.[134] Reports on obesity and vaginal POP repair are scarce. Several of the excisting studies include both UI surgery and different methods of POP surgery. This results in conflicting data and difficulties in comparing surgical outcome and complications for each separate surgical method.[135] Most studies report POP surgery to be safe in the obese,[78] but the sample size of obese women is generally low in several studies.[136,137] An increased risk of postoperative infections has been demonstrated by Chen et al, even after the exclusion of abdominal site infections. Smoking was not included in the regression analysis.[85] Lowman et al have demonstrated smoking to be a riskfactor for mesh erosions.[138]

In a study reporting on native tissue anterior colporrhaphy in obese women the risk of anatomic recurrence was shown to be relatively higher in obese women compared to non-obese women.[139] This is in contrast to a study on anterior mesh repair surgery for advanced prolapse that reported no difference in the objective outcome between obese and non-obese women. However, obese women showed less improvement of subjective symptoms and sexual function.[140] Obesity has also been reported to be a riskfactor for urinary incontinence after POP surgery.[128]

Perioperative interventions of life-style factors

Smoking cessation

In recent years, randomised control trials (RCT) have shown that complications can be reduced with smoking cessation shortly before surgery. In 2002, a study on orthopedic knee and hip replacement surgery investigated smoking cessation 6-8 weeks before surgery. The complication rate was significantly reduced in the intervention group, with a rate of complications of 18 % compared to 53 % in the control group.[141] A Swedish study on smoking cessation 4 weeks before surgery and 4 weeks after surgery showed a doubled rate of complication in the control group compared to the intervention group.[142] A reduction of complications was also seen in acute fracture surgery with smoking cessation 6 weeks after surgery. In the intervention group the complication rate was 20% and in the control group 38%.[143] The intervention programs of the RCTs included nicotine replacement therapy (NRT) and repeated counselling with personnel specialised in tobacco cessation treatment. Smoking habits were analysed after one year and in the study on orthopedic surgery 22 % of the patients were still nonsmokers and in the Swedish study 33%.[144] This is in comparison with patient-induced NRT, without any other support for smoking cessation, that result in no more than 7-8% that remain free from smoking in the longterm.[145] An interview study of the patients in the RCTs found a high degree of disappointment among the patients being allocated to the control group. Many patients seemed to require support in preoperative smoking cessation and surgery can be seen as a golden opportunity to achieve a longterm change of smoking habits.[146]

In a Cochrane report from 2010, a comparison of brief and intensive interventions on short- and long-term smoking cessation was performed. Both types of intervention increased smoking cessation at the time of surgery. Only intensive

interventions showed a signficant effect on reducing complications and increasing long-term smoking cessation. The optimum preoperative intervention intensity remains unknown.[147]

Studies on the effect of intervention of smoking habits in gynaecological surgery are scarce. There is a need to highlight this matter for the gynaecologic surgeon in order to acquire better knowledge regarding in which surgical procedures smoking cessation should be emphasised in order to reduce complications.

Weight loss

Preoperative weight loss is routinely recommended prior to bariatric surgery and surgery on knee and hip replacement although robust evidence is lacking on the clinical effects.[148] In bariatric surgery data is inconsistent on the effect on peroperative complications and weight development over time, but the risk of postoperative complications is reduced.[149] UI in females has been studied in bariatric surgery with a remission rate of UI in women of 71% after surgery and after loosing >18 points in BMI.[150] The body mass reduction has also been shown to lead to improvement in fecal incontinence and quality of life, as far as the symptoms of pelvic organ symptoms were concerned.[151]

Several studies have demonstrated significant improvements in UI after weight loss. Hunskaar et al stated in 2008 that there is valid documentation for weight reduction as a treatment of UI in women.[152] A modest weight loss of 5-10% is sufficient to achieve significant improvement of UI.[153,154] Subak et al showed that a 6-month behavioral intervention targeting weight loss resulted in a mean weight loss of 8% and a decrease of 47% in the weekly number of UI episodes.[155]

In studies on obese women randomly allocated either to behavioral weight loss or to structured education programs there were few or no changes in the parameters of the POP-Q system with weight reduction.[156] Weight loss did not improve self-reported bothersome prolapse symptoms from the prolapse subscale question of the Urogenital Distress Inventory.[134]

Alcohol cessation

Most of the negative effects of alcohol are reversible. Infections and wound related complications are a result of reduced immunocapacity and lower concentration of proteins important in wound healing processes. One night of drinking 1 g ethanol/kg body mass results in measurable changes in immunomarkers, despite previous soberness for several weeks. The immunomarkers normalise within two weeks of soberness.[157] Alcohol has a toxic effect on cardiac function with the development of a subclinical cardiac insuffiency and arrhythmias leading to a reduced function in a stress situation such as surgery. Increased concentration of stress hormones are also seen which leads to an intensified stress response in surgery and may aggravate excisting alcohol induced organ dysfunction.[18] Without alcohol this response is diminished within 1-7 weeks. The negative effects on hemostasis are due to dysfunctional platelets and are reversed within a week of alcohol abstinence.[14]

Three RCTs on perioperative alcohol interventions exist. Two of the studies, performed in hip arthroplasty and colorectal cancer surgery, demonstrated a high effect of preoperative intensive alcohol cessation intervention 4-8 weeks before surgery. The compliance was high and there was a significant reduction in complications and alcohol intake.[158] The third study was a controlled trial in

general elective surgery and could not show any effect with brief intervention on postoperative complications.[159]

The lower limit of the amount of alcohol that leads to a negative effect on surgery is not known and thus all alcohol consumers can be at risk. The frequently used AUDIT (Alcohol Use Disorder Identification Test) identifies individuals with riskful drinking behaviour and problems related to addiction during the past year and not current consumption, which is more essential in surgery. Nondependent hazardous drinking or short-term hazardous drinking can be missed. To identify the level of alcohol consumption close to surgery and inform the patient of short term effects and reversibility are important. The recommended advice to patients with a riskful alcohol consumption facing surgery should be 4-8 weeks of alcohol cessation. The use of an intensive intervention program will significantly reduce the incidence of several complications.[14]

Physical activity prior to surgery

The degree of preoperative physical fitness and physical activity (PA) have been demonstrated to be independent predictors of improved short term mortality, length of hospital stay and discharge destination in abdominal oncology surgery.[160]

In breast and colorectal cancer surgery a higher preoperative level of PA has been associated with a faster physical recovery. The PA level was self-assessed according to the Saltin-Grimby Physical activity level scale.[161,162] In elective cholecystectomy regular PA was associated with less sick leave, better mental recovery and shorter hospital stay.[163]

RCTs on preoperative physcial therapy versus no physical therapy in elective cardiac surgery indicate that postoperative pulmonary complications and length of hospital stay are reduced.[164]

Aims

The overall objective of this thesis was to study the influence of life-style factors smoking and body mass index on the outcome of hysterectomy, urinary incontinence and prolapse surgery, while accounting for other factors which may influence the result.

The specific aims were:

Paper I To investigate the influence of body mass index, smoking and age on the cure rate, rate of complications, and patient satisfaction with the midurethral sling (MUS) procedures TVT and TVT-O/TOT.

Paper II To study the impact of body mass index and smoking on the outcome of hysterectomy and whether these factors vary between abdominal, laparoscopic and vaginal hysterectomy.

Paper III To assess the influence of body mass index, smoking and mode of delivery on the incidence and remission of urinary incontinence (UI) after hysterectomy while accounting for other factors which may influence UI.

Paper IV To study cure rates, complications and urinary incontinence (UI) status after primary and repeat surgery for cystocele and rectocele with and without mesh, and identify risk factors for the negative outcome of POP surgery.

Methods

The Swedish National Register for Gynecological Surgery

Data in the thesis were retrieved from the Swedish National Register for Gynecological Surgery, GynOp. GynOp was established in 1994 and started collecting data in 1997 on performed hysterectomies in Sweden. In 2006 the register was extended to include data on UI surgery and POP surgery. The addition of UI questions to the hysterectomy questionnaires was introduced as well.

Another quality register (GKR, Gyn-KvalitetsRegister) with similar variables as GynOp was used for the hospitals in the area of Stockholm. Since 2010 data from GKR are imported to GynOp and are included in the database which thus contain data from >90% of the Swedish gynaecological clinics. Recently the two registers have conjoined to one register, named GynOp.

GynOp has continuously been updated with new validated questions in the questionnaires. Online reports summarise valuable information to the participating clinics to increase the quality of care, but also to stimulate the use of the register to enhance the completeness and validity of data.

Data is gathered from patient questionnaires and doctor forms. When scheduled for surgery, a preoperative questionnaire and a health declaration are sent by post or e-mail to the patient and can be returned in the same manner. The electronic option is used by 50% of the patients. An advantage of the electronic forms is that the user is alerted if the questionnaire is incomplete. In accordance with the regulations for management of national quality registers, the patient receives written information about the register prior to surgery and has an opportunity to decline participation.

On admission the gynaecological surgeon gathers information from the questionnaires and is able to adjust any incomplete or inadequate data. Per- and postoperative forms are continuously filled in by the surgeon during the hospital stay. Eight weeks and one year after surgery the patient receives another questionnaire with questions on complications, cure and patient satisfaction. These questionnaires are later evaluated by the surgeon for any complication, whether the complications were mild/minor or severe and if any intervention was needed.

Classifications/Definitions

Body mass index (BMI) was calculated from the height and weight of the women according to the formula kg/m^2. BMI was categorised as normal (<25), overweight (≥25-29) and obese (≥30) according to the WHO classification (WHO 2006). In Paper I five BMI classes were included, but no differences in outcome could be found after stratification into fewer groups and thereby only three groups of BMI were used in the other studies.

Smoking status is recorded in GynOp as a smoker of 1-5 cigarettes, 6-20 cigarettes, >20 cigarettes, former smoker or nonsmoker. We tested if the intensity of smoking had any impact on the rate of complications, but could not find any correlation to number of cigarettes consumed daily. In Paper I smoking status was categorised into smoker, former smoker or nonsmoker, due to previous reporting that a former smoker has an increased risk of UI.[67] In the other three studies we only used the terms smoker och nonsmoker.

In Paper I age was encoded into ≤40 years, 41-60 years, 61-80years and >80 years of age. In Paper II-IV age was used as a linear variable.

Urinary incontinence was defined by the question “Do you experience urinary leakage or involuntary emptying of the bladder”. Leakage “1-3 times/week” or “daily leakage” was defined as bothersome UI and no bothersome UI was defined by the following answers “no urinary leakage”, “almost never leakage” or “1-3

times/month". Self-reported urinary leakage once a week has been shown to be considered as bothersome by 97.5% of women.[165] In paper I (MUS) the definition of cure was supposed to be defined in the same way as no subjective UI. It was noted after publication that the alternative 1-3 times/week was not included in "cure" and a correction has been made that cure included those without daily urinary leakage.

In Paper I the type of UI was included and was obtained from the assessment performed by the gynaecological surgeon who usually included a gynaecological examination, micturition lists, cough test, residual urine measurement and other relevant clinical data. Based on the history provided and this evaluation, the women were classified as having either stress UI or mixed UI according to the joint IUGA/ ICS definition.[166] De novo urgency (dU) was defined if the woman reported no urinary urgency preoperatively and one year after surgery reported urgency 1-3 times per week or daily.

In Paper II, the definition peroperative "excessive bleeding" was used and set at >1000ml for AH. Blood loss of >500 ml was applied in LH and VH since there is a lower tolerance for higher levels of blood loss in the LH and VH groups.[8,56] In Paper II-III uterine weight was categorised into three weight groups; <300 gram (g), 300-500g and >500 g. This classification was based upon the findings that minimal invasive hysterectomy techniques are recommended and associated with less complications for a uterus size similar to <12-14 gestational weeks, which corresponds to a weight of 250 g-280 g.[167,168]

In Paper IV symptomatic pelvic organ prolapse and symptom of recurrent prolapse were defined by the affirmation of the symptom "feeling a vaginal bulge" daily or 1-3 times per week.

The register includes information on the extent of the prolapse during maximal straining. These measures were transformed to POP-Q-stages I-IV and subsequently dichotomised into patients with stage I-II and stage III-IV prolapse. This dichotomisation is based on the study by Salvatore et al., which showed that stage III-IV prolapse is the only risk factor for recurrent prolapse.[169]
The answers from the question "Are you satisfied with the results of surgery?" were dichotomised into satisfied ("very satisfied" and "satisfied",) and not satisfied ("neither satisfied nor unsatisfied", "unsatisfied" and "very unsatisfied").

Exclusion criteria were surgery due to malignancy, concomitant UI and POP surgery in Paper I and IV and missing data on BMI and smoking in paper I-III. In Paper IV missing data on BMI and smoking were accepted in order to include more data on other confounders as the impact of BMI and smoking was found to be low.

Statistics

Categorical data were analysed by Pearson's chi-square or Fisher's exact test. Continuous variables were analysed using Student's t-test or ANOVA. A p-value <0.05 was considered to be statistically significant. Missing data was not included in the calculation of percentage.
Multivariable logistic regression models were created to allow calculation of odds ratio of risk factors for the different outcome variables while controlling for potential confounders. Crude odds ratio (OR) and the 95% confidence interval (CI) for possible confounders were calculated. Variables presenting an association with the dependent variables (p-value <0.05) were included in a multivariable logistic regression analysis. A stepwise approach was conducted in order to, one-by-one, exclude the variables demonstrated to be non-significant in the multiple testing. Adjusted odds ratio (adjOR) and the 95 % CI were calculated. The regression models require that there are no missing data for the dependent and the independent variables leading to a variation of the number of women included in each analysis.

The following variables were included in the regression analyses:

- Age, BMI and smoking status were included in all analysis
- *Paper I* Complications: parity, comorbidity, surgical method, previous prolapse surgery, hysterectomy and cesarean section. Additional variables included in the analyses for cure, dU and patient's degree of satisfaction with the operation: per- and postoperative complications, prolapse present, urinary retention, the assessment of urinary leakage, dU and postoperative daily urgency.
- *Paper II* Complications: co-morbidity indication for surgery, previous cesarean section, antibiotic prophylaxis, ASA score, route of hysterectomy, uterine weight, and bowel injury during surgery.
- *Paper III* De novo and remission of UI: mode of delivery, comorbidity, indication for surgery, preoperative daily urgency, route of hysterectomy, subtotal/total hysterectomy and uterine weight.
- *Paper IV* Complications: parity, mode of delivery, previous hysterectomy, preoperative daily urgency, chronic constipation, estrogen use, ASA class, comorbiditiy, preoperative feeling of a vaginal bulge, POP-Q stage >II, prophylactic antibiotics, anesthetics, type of surgery (anterior or posterior colporraphy) and the use of mesh. In analysis of subjective treatment success and UI the following additional variables were included: preoperative daily urgency, postoperative infection and severe complication.

All statistical analyses were performed using SPSS version 21, 22 or 23.

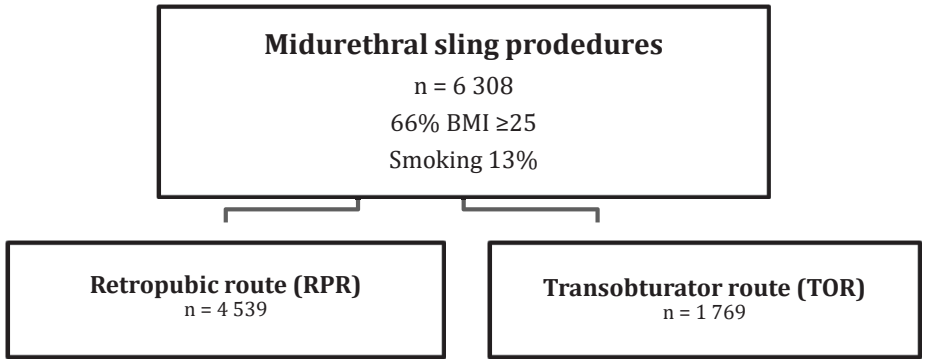
Ethical considerations

Ethical approval was obtained from the Ethics Committee at Sahlgrenska Academy, Gothenburg University (061-13). All women received written information about the register and had an opportunity to decline participation in the register.

Results

Paper I

The aim was to investigate the influence of body mass index (BMI), smoking and age on the cure rate, rate of complications, and patient satisfaction with the midurethral sling (MUS) procedures TVT and TVT-O/TOT.



6 308 women were included in the study of which 4 539 underwent a RPR procedure and 1 769 women underwent a TOR procedure. Current smokers did not differ between surgical groups and mean BMI was 26.5 for the RPR and 27.1 for TOR. In total there were 1 443 women with a BMI ≥30 and significantly more in the TOR group.

Peroperative complications were more common in RPR (4.7% vs 2.3% in TOR, p = 0.001), mainly due to bladder perforations. In the multiple regression analysis a retropubic approach was associated with increased adjOR of peroperative complications and BMI ≥25 compared to BMI <25 was associated with decreased adjOR of peroperative complications. At 8 weeks the rate of reported postoperative complications was 13 % for RPR and 14.3 % for TOR, without statistical

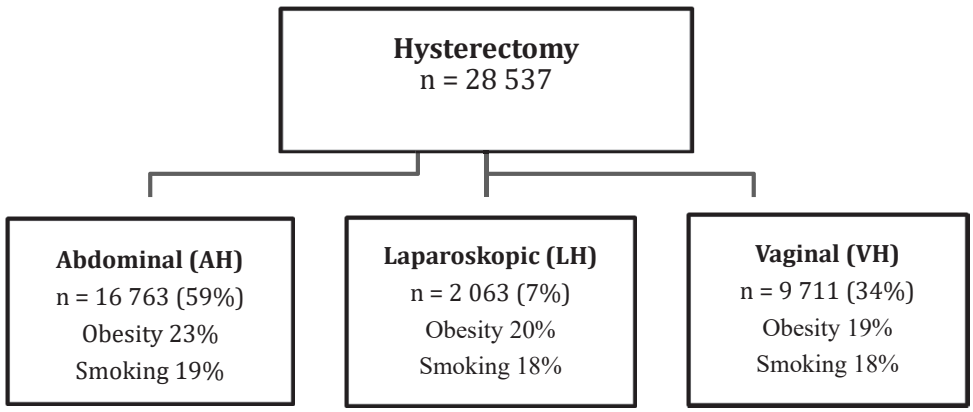
significance. No association was found between smoking and obesity for complications within 8 weeks after surgery.

Subjective 1 year-cure rate was 88.3% with RPR and 85.2% with TOR (p = 0.002). Subjective preoperative daily urinary leakage and urgency were more frequent with increasing BMI. After surgery symptoms were markedly reduced for all patients, but to a lesser extent in the higher BMI-groups. The cure rate in BMI ≥30 was 80% for RPR and 74.2% in TOR (p = 0.03). In the multivariable regression analysis higher risk of remaining daily UI was seen in women with a BMI ≥30 (adjOR 2.05; 95% CI 1.37-3.07), in diabetics (adjOR 1.98; 95% CI 1.35-2.89) and in women aged >80 years (adjOR 5.53;95 % CI 1.95-15.64).

De novo urgency (dU) was reported by 259 women among 2550 women who had no urgency preoperatively. The rate of de novo urgency (dU) one year after surgery was 9.8 % for RPR and 11.2 % (p =0.29) for TOR. dU was more frequently reported among smokers and in women with increasing BMI, however in the multiple regression analysis these factors were not significantly associated with dU. The rate of satisfaction with surgery after one year was 78% in RPR and 75% in TOR (p =0.002). Smokers compared to former smokers and nonsmokers reported lower rates of satisfaction and this could also be seen with increasing BMI. However, in the multiple regression analysis surgical route, BMI and smoking were no predictors of dissatisfaction. Identified riskfactors of dissatisfaction were postoperative complications, daily urinary leakage, daily urgency and de novo urgency.

Paper II

The aim was to study the impact of body mass index (BMI) and smoking on the outcome of hysterectomy and whether these factors vary between abdominal (AH), laparoscopic (LH) and vaginal hysterectomy (VH).



The study consisted of 28 537 women who underwent hysterectomy due to a benign disorder in 2004-2013. The majority of the surgery was performed as an abdominal hysterectomy (59%), one third with a vaginal approach and 7% laparoscopically. 18% were current smokers, the mean BMI was 26.3 and 21% had a BMI ≥30. There were small differences in smoking status between the hysterectomy groups, but there were more obese women in the AH group.

The indication for surgery and patient characteristics varied between the surgical groups. In AH fibroids and abnormal bleeding disorders dominated and previous caesarean section was more common compared to the VH group in which prolapse was more often an indication and the patients were older with higher parity. In LH the indication was more often pain and there was a higher prevalence of endometriosis. For both minimal invasive surgery groups (VH and LH) uterine

weight was lower and the rate of complications was generally lower compared to AH. Among organ lesions peroperative bladder perforations were more frequent in the VH group and postoperatively diagnosed ureter lesions were more common in the LH group.

A multivariable analysis was performed comparing VH and LH to AH including eventual confounding factors. Minimal invasive surgery was associated with several of the tested outcomes. LH was associated with lower adjOR for excessive bleeding >1000ml 0.27 (95% CI 0.13-0.54) and complications before discharge 0.76 (95% CI 0.62-0.94), but higher adjOR for duration of surgery>120 minutes 4.53 (95 % CI 4.01-5.12) and postoperative infections 1.51 (95% CI 1.28-1.79). VH was also associated with a lower adjOR of excessive bleeding >1000ml 0.72 (95 % CI 0.54-0.95), but in contrast to LH there was a lower adjOR for duration of surgery>120 minutes 0.58 (95% CI 0.51-0.65). The adjOR was more than doubled for reoperation in VH. The results in the final models were adjusted for age, BMI, smoking, uterine weight, indication for surgery and previous cesarean section. The postoperative variables were also adjusted for duration of hospital stay.

All hysterectomy procedures were analysed taking into account BMI and smoking. Operating time >120 minutes, excessive bleeding >1000ml, peroperative complications and complications at 8 weeks and postoperative infections were significantly more prevalent with higher BMI. Current smokers had a shorter hospital stay, more postoperative complications and more postoperative infections.
The subanalysis of postoperative infections into surgical site infections in the abdominal wall and vagina according to smoking and obesity is demonstrated in Table 1. Smoking was associated with higher crude odds of postoperative infection in both the abdominal wall and vagina than non-smokers. Obesity was associated with almost tripled odds of abdominal wall infection compared to normal weight.

Table 1. Surgical site infections in hysterectomy reported in the 8 week questionnaire according to smoking status and BMI.

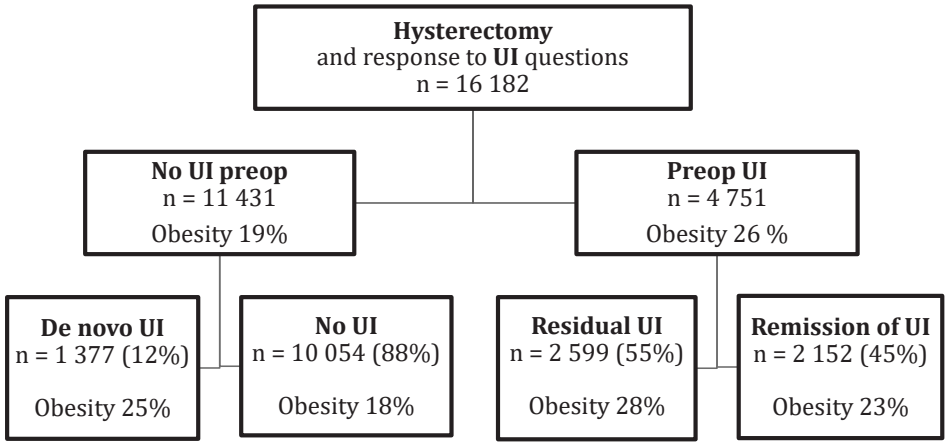
8 week questionnaire	**Vaginal infection**	OR CI 95%	**Abdominal wall infection**	OR CI 95%
Non-smoker	378 (1.8)	1	557 (2.6)	1
Smoker n (%)	122 (2.6)	1.48 (1.21-1.82)	191 (4.1)	1.59 (1.34-1.87)
BMI n (%)				
<25	204 (2.0)	1	199 (1.9)	1
25-29.9	176 (1.7)	0.89 (0.72-1.09)	256 (2.5)	1.33 (1.11-1.61)
≥30	120 (2.2)	1.13 (0.90-1.42)	293 (5.4)	2.92 (2.43-3.50)

The different complication variables were analysed in a multivariable logistic regression analysis stratified according to BMI class, smoking status and hysterectomy method. BMI 25-29.9 and BMI ≥30 were compared to BMI <25 and smoking versus no smoking. Overweight and obesity was demonstrated to have the strongest impact on complications in the AH group with a higher risk of bleeding >1000 ml and operative time >120 minutes in women with a BMI ≥25. Women with BMI ≥30 had increased odds of peroperative complications (adjOR 1.54 95% CI 1.26-1.88), postoperative complications (adjOR 1.21 95% 1.08-1.34) and postoperative infections (adjOR 1.73; 95% CI 1.50-1.99).

In VH the negative effect of BMI ≥30 could be seen in excessive bleeding >500ml (adjOR 1.63 95% CI 1.22-2.17) and operative time >120 minutes (adjOR 2.00 95% CI 1.60-2.50). In LH, BMI ≥30 increased the odds for prolonged surgery (adjOR 1.71 95% CI 1.30-2.26). Smoking was a riskfactor for postoperative infection in both AH (adjOR 1.23 95% CI 1.07-1.40) and VH (adjOR 1.21 95% CI 1.02-1.43), but not in LH (adjOR 1.31 95% CI 0.93-1.84). In the final models the results were adjusted for age, uterine weight, previous cesarean section, indication for surgery and duration of hospital stay.

Paper III

The aim was to assess the impact of body mass index, smoking and mode of delivery on the incidence and remission of urinary incontinence after hysterectomy.



Out of 28 537 hysterectomies in paper II 16 182 women had answered the question about urinary incontinence both before and after surgery. Firstly, the women with different UI status preoperatively were analysed. The women with UI before surgery (n = 4 751) had a higher mean BMI of 26.7 compared to 25.9 (p <0.001) in women without UI (n = 11 431). Previous vaginal delivery, daily urge and a uterus weight >500 g were more common in the UI group compared to the non UI group.

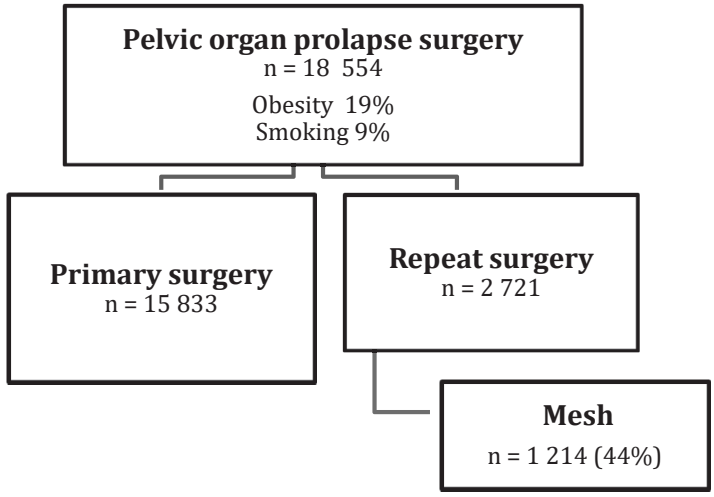
Secondly, analysis of the women who developed de novo UI after surgery was analysed (n = 1 377). These women more often had a vaginal delivery and 25% of the women had a BMI ≥30 compared to 18% of the women who did not develop UI. The prevalence of de novo UI increased with increasing BMI class. In the multivariable regression analysis of de novo UI, a BMI ≥30 was associated with

63% higher odds compared to a BMI <25, preoperative daily urge with 77% higher odds compared to no daily urge and at least one vaginal delivery with 40% higher odds compared to cesarean section. A large uterine weight was associated with a lower risk of de novo UI. The women with de novo UI were less satisfied with surgery compared to the women who did not develop UI (84% versus 93 % p = <0.001) and 7.9% of the women stated that their condition had worsened one year after surgery compared to 1.1% of the women without de novo UI (p = <0.001).

Thirdly, the women with UI before surgery (n = 4 751) were analysed according to UI (n = 2 599) or no UI (n = 2152) one year after surgery. 45.3% had a remission of UI and there was a lower rate of BMI ≥30 in this group compared to the group of women with residual UI. There were more nulliparous women and women delivered by caesarean section only with remission of UI. Mode of delivery was not a statistically significant factor for remission of UI in the multivariable regression analysis. Factors associated with remission of UI were BMI <25 (1.22; 95 % CI 1.01-1.47), a uterine weight >300g (1.98; 95 % CI 1.69-2.33), fibroids (1.33; 95 % CI 1.09-1.62) and pelvic organ prolapse (2.25; 95 % CI 1.60-3.18) as indication for surgery and no daily urge before surgery (1.51; 95 % CI 1.29-1.76). Vaginal hysterectomy was associated with a decreased remission of UI (0.70; 95% 0.57-0.87). Smoking did not influence UI status after hysterectomy.

Paper IV

The aim was to assess cure rates, complications and urinary incontinence (UI) status after primary and repeat surgery for cystocele and rectocele with and without mesh, and identify risk factors for the negative outcome of POP surgery.



18 554 women were included in the study of which 15 833 underwent primary surgery and 2 721 had repeat surgery due to a prolapse recurrence in the same site. Only simple anterior and/or posterior colporraphy were included. Mesh augmented surgery was performed in 44.6% of the women undergoing repeat surgery.

The rate of obesity was 19% and smoking 9% with no differences between the groups. Previous vaginal delivery was seen in >98% in both surgical groups and previous hysterectomy was more common in repeat surgery than in primary surgery. The rate of complications was low, but more common in mesh augmented

repeat surgery. All complication variables were tested in relation to BMI and smoking, but no differences could be found.
There cure rates between primary or repeat surgery were similar, but higher rates of cure and patient satisfaction were reported among women who underwent repeat surgery with mesh.
In the multivariable regression analysis of feeling a vaginal bulge one year after primary surgery BMI ≥30 versus BMI <25 was an independent predictor of no cure, but not after repeat surgery.

Among the women with preoperative UI up to 49% had a remission of UI after surgery. It was more likely that residual UI and de novo UI occurred in repeat surgery and de novo UI was even more pronounced in the mesh group. The rate of UI eight weeks after surgery did not differ compared to one year after surgery, except for de novo UI, which was less prominent after 1 year in mesh augmented surgery. Overweight and obese women reported more often UI after surgery compared to women at a healthy weight.

Multivariable regression analysis identified increasing age, overweight and obesity to be predictors of residual UI in primary surgery. BMI ≥30 had 50% higher odds of residual UI than BMI <25. Women who underwent an anterior colporraphy had half the odds of residual UI after surgery compared to no anterior colporraphy. UI, but not BMI was a predictor of decreased satisfaction after surgery, in contrast to the factor “surgery with mesh” that rendered higher patient satisfaction and subjective surgical success.

Discussion

Methodological considerations

Quality registers permit a systematic control of health care systems. The number of quality registers in Sweden is increasing and studies originating from national registers are becoming more common. The study designs used in register-based studies may vary and include observational studies (cohort or case control) or register based RCTs. This thesis includes cohort studies using the Swedish National Register for Gynecological surgery, GynOp.

A register usually provides a large sample size, which enhances precision in estimates and allows the study of rare exposures and outcomes. Data is collected for several purposes and often, as in this study, it is already available, minimising time consumption and reducing costs. Another advantage of using a register is that collection of register data has been done independently of the present study, and this often reduces various types of bias such as recall and non-response bias. The main limitations are that necessary information may not be available and confounder information is missing. Observational studies do not allow conclusions or causal associations. Moreover, the data collection is done by several different individuals and not by the researcher, which can lead to poorer data quality. RCTs are often mentioned as the gold standard, particularly when comparing different surgical methods. However, RCTs are often performed in highly selected populations which limit generalisability. An observational study design based on a register with good coverage may therefore present benefits regarding study directness compared to a RCT.

In GynOp, patients are included at the time of surgery and independently of any study. The patients are informed that data can be used in research and they can

decline participation. Both patients and gynaecological surgeons provide information to the register in order to achieve as complete a data set as possible. A potential report bias in the register could be that the surgeons often assess their own complications, which can lead to bias due to both an underreporting and an overreporting of complications. However, the registered complications cannot be officially linked to a specific surgeon and thereby a bias of underreporting complications is thought to be minimised. The reports of severe complications in GynOp seem to be adequate and according to the results in this thesis in accordance with other studies. The term mild or minor complication represents a heterogenous sample of non-severe complications and the rate is usually higher compared to complications rates in other studies. This indicates that complications are probably not underreported in the register.

Internal validity of GynOP

A control of completeness of registered data is routinely done in the register and most perioperative information is complete to >90%.[27] The follow-up questionnaires replace the follow-up visit and identify those patients in need of a follow-up. A previous study from GynOp showed that questionnaires provided a more complete collection of post-treatment information than traditional follow-up visits. 75 % of the patients in the study stated no need of any medical contact after surgery. The questionnaires were well understood and there was no reporting on any major problems in completing the questions.[170]

There is a guide on complications linked to the forms completed by the surgeons that facilitates a more reproduceable evaluation of a severe complication. This, however, is unfortunately not specified according to the Clavien Dindo classification,[171] which would have enhanced the comparison of complications

internationally and within different surgical fields. This classification has recently been included in the register. So far most studies on gynaecological surgery and complications do not use the Clavien Dindo classification.[172] In this thesis, transformation of the variables was prioritised to enhance a comparison with similar variables used in previous studies and not with the intention to mimic the Clavien Dindo classification.

External validity of GynOp

Data completeness is validated annually with audits at clinics and data are concurrently randomly checked with medical records as a reference. Each year data is also compared to the National Inpatient Register (NPR), considered the gold standard register and it is mandatory for Swedish hospitals to report data to NPR. Matching cases between NPR and GynOp are around 89% and the coverage was in 2013 and 2014 more complete in GynOp than in NPR.[173]

There is a risk of decreased interest to supply a register if the register creates extra work.[174] GynOp data can be converted into text that can be used in medical records to avoid time-consuming administration of both filling in register forms and creating a medical record. The disadvantage of this system is that studies on the external validity of the register are more difficult to perform. If there is inadequate information in the register it will be copied to the medical record and no comparison can be done between the register and the records.

The external validity of some of the complication variables have been evaluated and reported on www.gynop.org. In a report from 2014, patient-reported severe complications were compared to surgeon-reported severe complications. 2641 women out of 30 000 (8.7%) women who underwent a hysterectomy had reported a

severe complication. In 705 of these cases patient-reported severe complication were later judged by a doctor as no complication. These cases were later analysed in the register. A majority of the women displayed other parameters that indicated an abnormal postoperative period. 68 patients were judged as having had a nonregistered severe complication. In conclusion, 0.2% of 30 000 hysterectomies had not been given the correct diagnos of a severe complication. In a report from 2015, patient reported infections treated with antibiotics were compared to medical records. If information was missing in the medical record a telephone interview was performed. Of 213 studied patients 5 patients (2%) had not given the correct information. This results in a validity of the studied variable of ≥90% with a trend towards a small underreporting of antibiotic treatment, but no differences between clinics could be seen.

Strengths and limitations

The main strengths of this thesis are the inclusion of a large cohort of women covering the majority of the clinics involved in gynaecological surgery in Sweden and a high response rate to the questionnaires up to one year after surgery. The study provides a survey over complications and outcome in the most common gynaecological procedures and identified riskfactors. Two of the most important lifestyle factors, smoking and obesity, were possible to study in the register. Additionally, it confirmed the validity of the register that the collected data on surgical outcome was in comparison with previous studies.

Some of the limitations of the study are due to missing information in the register. Socio-economic factors and the life-style factors alcohol consumption and physical activity are not included in the register and their role as confounders could not be studied. In addition the follow-up time is limited to one year. Another limitation is lacking information concerning mesh erosions in POP and UI surgery. A study including a new questionnaire on the longterm outcome of POP surgery has

therefore been developed and distributed to POP surgery patients and within the near future results will be published (also mentioned in “Future perspecitves”).

Another limitation of the study is that the definitions of surgical success in MUS (Paper I) and POP (Paper IV) were only based on self-reported measurements and not on any objective parameters. However, previous reports have demonstrated that self-reported symptoms are reliable and adequate when they are collected at the time of the study.[175-177] Subjective improvement is one of the most important outcomes in surgery and cannot be replaced by any objective measurement. For example, the strongest relationship with subjective improvement and treatment success is found to be the absence of vaginal bulge symptoms.[115] The register also provides data on UI and vaginal bulge before and after surgery, which promotes a comparison of any perioperative alteration of these variables.
The severity or bothersomeness of UI symptoms was not measured and we did not specify the subtype of UI. However, the aim of the study was not to specify UI type and we assumed that the loss of urine is a highly disturbing issue if it occurs daily or several times a week irrespective of the type of UI.

The UI-questions were introduced into the register in 2006 and thereby the women with hysterectomy 2004-2006, included in Paper II had to be excluded. It might have been adviseable to exclude one or two more years since clinics in Sweden were adding the UI questions in different degrees after 2006. Instead we chose to analyse the non-responders. The main reason for not responding was probably that no questions had been included yet. Non-response was age-dependent and younger women may have been less motivated to answer questions regarding UI as UI is less common in younger age. This is probably also true for women undergoing LH who responded to a lower extent to the postoperative UI questions.

Results and comments

The influence of obesity in gynaecological surgery

Obesity had an impact on outcome in all surgical procedures in the thesis. The most explicit association was found between obesity and UI. A higher rate of UI pre-and postoperatively was seen for each surgical method with increasing BMI.

Table 2. The association between obesity and urinary incontinence (UI) in multivariable regression analysis described as adjusted odds ratio (adjOR).

	BMI≥30 vs BMI<25 adjOR 95% CI
MUS	
Residual UI	2.05 (1.37-3.07)
Hysterectomy	
Residual UI	1.22 (1.01-1.47)
De novo UI	1.63 (1.37-1.94)
POP	
Residual UI	1.49 (1.25-1.77)
De novo UI	1.65 (1.33-2.04)

Obese women had doubled odds of residual UI after MUS. Increasing BMI was correlated to an increase in de novo UI and residual UI and a decrease in remission of UI in women undergoing hysterectomy and POP surgery. In hysterectomy, obesity was associated with 63% higher odds of de novo UI and 22% higher odds of residual UI compared to BMI <25. POP surgery in obese women was associated with 65% higher odds of de novo UI and 49% higher odds of residual UI compared to women with BMI <25. Thus, the impact of obesity on UI seems to be of equal magnitude after hysterectomy as POP surgery (Table 2).

The highest prevalence of obesity was found in women undergoing UI surgery compared to women undergoing hysterectomy or POP surgery. Although, when analysing the women with UI after hysterectomy the mean BMI and the rate of obesity were even higher than in the MUS cohort (Table 3).

Table 3. The different rates (%) of obesity and mean BMI in the studied procedures.

	Hysterectomy				**MUS**	**POP**
	All hysterectomies	Remission of UI	De novo UI	Residual UI		
	(Paper II)	*(Paper III)*			*(Paper I)*	*(PaperIV)*
BMI, mean	26.3	25.9	26.9	27.3	26.8	26.2
		All women *Paper III*: 26.3				
Obesity %	21	18	25	28	24	18
		All women *Paper III*: 21				

Surgical failure after POP surgery was also influenced by obesity, but to a lower degree than surgical failure in MUS.

The results illustrate the importance of obesity as a riskfactor for UI in different surgical procedures, but also as a factor associated with pelvic floor disorders in general. The longterm results of UI after MUS have been reported to be continuously worsening in obese women,[92] also confirmed in a study in 2016,[178] and emphasises the importance of weight reduction as an additional treatment of UI. A RCT on weight loss interventions showed that women who lost 5-10% of baseline weight reduced their UI episodes with 50% and the authors stated that weight reduction should be considered a first line treatment of UI.[155] Even though most studies on the effect of weight loss and POP do not result in less symptoms of vaginal bulge, other prolapse related symptoms are shown to ameliorate.[134,156] Additional positive side effects of moderate weight loss are improvement of

hyperglycemia, hyperlipidemia, hypertension and quality of life.[179,180] A preoperative discussion concerning weight loss before pelvic floor surgery should be implemented to avoid surgery or to improve outcome after surgery.

The strongest association between obesity and complications in the thesis was seen in hysterectomy. High BMI was associated with excessive bleeding, prolonged surgery and overall complications (Table 4). Bleeding over 500ml, prolonged surgery and blood transfusion are known riskfactors of surgical site infections (SSI).[181] We could confirm that BMI ≥30 was associated with postoperative infections with almost tripled odds of abdominal wound infection when compared to women with BMI <25 (Table 1).

Table 4. The association between obesity and complications in multi-variable regression analysis described as adjusted odds ratio (adjOR).

	BMI≥30 vs BMI<25 adjOR 95% CI
MUS	
Peroperative complications	0.51 (0.35-0.74)
Hysterectomy	
Excessive bleeding	2.80 (2.21-3.55)
Prolonged surgery	2.40 (2.14-2.64)
Peroperative complications	1.46 (1.22-1.75)
Postoperative complications	1.11 (1.01-1.21)
Postoperative infections	1.47 (1.31-1.64)

SSI is the most common cause for unplanned readmission after hysterectomy.[182] Patients who develop a SSI are five times more likely to be readmitted to hospital, 60% more likely to spend time in an intensive care unit and twice as likely to die than patients without SSI.[183] In addition, they are more likely to require radiology

testing and medical treatment, thus leading to higher health care costs and inconvenience for the patient.[184]

The association between complications and obesity was more evident in abdominal hysterectomy than in minimal invasive procedures in Paper II. Most studies on this topic conclude that minimal invasive methods are preferable in the obese to avoid higher risk of adverse effects. Contrary to these recommendations, previous studies including our study, revealed that the rate of AH increased as BMI increased.[31,185,186] Why the abdominal route is chosen may be due to a larger uterine size in the obese,[187] but more likely a selection by the surgeon who may have concerns about difficult surgery and an increased risk of conversion.[188] The surgeon should be aware of these facts when considering surgical method and strive for the use of minimal invasive methods also in obese women. The addition of robotics in laparoscopic surgery is gaining importance, particularly in the obese, although more research is needed.[189] Nevertheless, to initiate a weight loss prior to hysterectomy seem most reasonable, for example while evaluating conservative treatment against bleeding disorders.

Obesity and midurethral sling procedures *(Paper I)*

Obesity and complications in MUS

Paper I and Paper IV demonstrated that the negative influence of obesity is mainly on the outcome of urinary incontinence after pelvic floor surgery than on complications. In contrast and in agreement with studies of others, obesity was a protector of the bladder from being injured by the trocar in RPR slings. The increased amount of fatty tissue around the bladder in overweight and obese patients protects the bladder from injury. The rate of bladder perforations has previously been reported to be 4.5%[86,190] and a similar rate was found in our study (3.2%).

Another common complication of MUS, and particularly in TOR, is groin pain, with a rate of 6.4%.[74] A higher rate of postoperative pain 8.6 % could be noted in TOR in our study, but pain in the groin has not been specified in the register until recently. Injuries to visceral organs and major vessels were expected to be low and urinary tract infections were also reported in accordance with previous publications.[70]

Several prior studies have been limited by small sample size[80,82,83] and heterogenous surgical procedures,[78,79] but they mainly support our results that MUS seem to be safe procedures in obese women.

The most common long-term complication after MUS is de novo urgency, known to be associated with a negative impact on quality of life. There is no clear objective definition of dU and therefore rates vary widely in the literature from 3-30%.[191,192,76] Often the definition is based on symptoms rather than objective measurements[192,193] or on non-validated questionnaires.[194] In Paper I we chose to define de novo urge (dU) as new symptoms of urge one year after surgery in women who preoperatively had reported no urge. dU was found in 259 women (10.5%) and was more frequently reported among smokers and in women with increasing BMI. These variables were not shown to be independent predictors in the multivariable analysis. The results may have been affected by the fact that smokers and women with a BMI ≥30 had a higher degree of urgency before surgery. When all women were assessed, an increasing frequency of daily urgency with increasing BMI-class was recorded one year after surgery and might better reflect urgency problems after MUS in the obese. In a secondary analysis of a RCT from 2016 on RPR versus TOR a higher prevalence of bothersome urgency was reported in obese women compared to non-obese (45.8% versus 22.4% $p = 0.01$), similar to the prevalences in our study (38% versus 25% $p = <0.001$).[195]

Obesity and cure in MUS

Several studies have presented good results in women with obesity for both RPR and TOR,[81,196] but the cure rates are often lower compared to their non-obese counterparts.[79,88,195]

The present studies comparing cure rates in RPR versus TOR in obese women have not found any significant differences according to surgical method. Although the size of the obese study populations was small and probably only powered to detect large differences.[93,197] A conclusion on whether to use RPR or TOR in obese women cannot be drawn from our study design, however we could demonstrate higher cure rates after RPR than TOR (80% vs 74.2% in TOR, $p = 0.03$). The adjOR of cure for all slings was significantly lower in obesity, but surgical method was no independent riskfactor in the multivariable regression analysis.

Obesity and hysterectomy *(Paper II and III)*

Obesity and complications in hysterectomy (Paper II)

Duration of surgery increased with BMI regardless of surgical approach in consistency with two previous reports.[198,199] The intraabdominal fat intrudes on the intraabdominal space and covers anatomical structures which presumably aggravate the procedure. The cut off time of prolonged surgery was set at 120 minutes and it might have been advisable to use another cutoff in LH as the mean operating time was longer than the other hysterectomy routes. However, we could still detect a higher adjOR for prolonged surgery in obese compared to the non-obese and this limit has also been used in a previous study on LH and obesity.[8] Mean operating time or operating time >60 or >90 minutes rendered similar results.[56,185] As in our study, previous studies have found no other associated risk of complications in LH and obese women.[8,185,199]

The association of obesity and increased risk of infection in AH is supported by other studies, but in VH the results are contradictory. A large Danish observational study found no association between postoperative infections in the obese and VH, although the infection rate was low.[185] In a recent study by Shah et al on >50 000 women undergoing hysterectomy, an association between increased wound infections and obesity could be seen in VH, but to a lower magnitude than in AH.[199] Similar results were demonstrated in a GynOp study on data from earlier years than in our study and with corresponding rates of postoperative infections. In AH, the adj OR of BMI ≥30 versus BMI <25 was comparable (1.59 95% CI 1.29-1.98)[59] to our study (adjOR 1.73 95 % CI 1.50-1.99), but we could not reproduce the results of Kjölhede et al[60] or Shah et al[199] in VH. The reason could be that the rate of infections or included confounding factors differed, concomitant POP surgery was excluded in our study and we did not specify wound infections. In the study by Shah et al[199] smoking was included as a confounder. Osler et al[185] only adjusted for smokers in LH and did not include smoking in the regression model for infections. Kjölhede et al found an association between smoking and infections in AH[59], but not in VH[60]. The same argumentation as for VH in obese and infections can be applied for the differences in results of smoking.
We demonstrated a higher frequency of ureter lesions in LH as previously reported[31] and there was no association found between obesity and ureter lesions.

In the multivariable regression analysis there was a higher adjOR of obesity and excessive bleeding in AH (>1000ml) and in VH (>500ml), but not in LH. Osler et al found more bleeding complications in obese women undergoing AH, but not in VH or LH. Excessive blood loss was defined as >1000ml.[185] Rasmussen et al reported increased blood loss in VH but not in AH, even though the peroperative blood loss limit was set at 500ml.[56] Rafi et al and Harmanli et al could not demonstrate any change in perioperative hemoglobin or increased transfusion rates in obese women compared to women of normal weight.[57,200,201] The blood loss is

expected to be lower in VH and it seems reasonable to use a lower limit for excessive bleeding than in AH. A bleeding around 500ml does not render any major intervention or bloodtransfusion and is thereby not classified as a complication, leading to lower rates of perop complications in minimalinvasive hysterectomy. In obese women versus normal weight women higher odds of peroperative complications could only be found in AH. This was presumably due to more bleeding complications, supported by the fact that a higher rate of blood transfusion was reported in AH and in BMI ≥30 compared to BMI <25 (3.8 % versus 2.0% p = <0.001). No association between obesity and increased blood loss was found in LH in accordance with previous publications.[8,202]

Bladder lesions were more common in women with a BMI <25. As in MUS the bladder is well protected by the fatty tissue and bladder injuries were less common with increasing BMI. In most studies all organ lesions are grouped into one variable and therefore no comparison of this finding could be found in the literature. Moreover, complications during hospital stay and reoperations were more common in women with a BMI <25. Complications discovered within 1-2 days before discharge are usually postoperative bleeding complications which might require reoperation. This can explain both the higher rate of complications during hospital stay and reoperation in non-obese women compared to obese women. Intraabdominal pressure is higher in obese women caused by the fatty tissue and might cause a sufficient compression of the vessels in the pelvis to lower the risk of postoperative bleeding. Another more uncertain speculation is that surgery is prolonged in the obese group and there is more time for the bleeding to be revealed.

Obesity and UI after hysterectomy (Paper III)

The adverse effects of lower urinary tract symptoms after hysterectomy have been reported previously in different study designs, although results are

inconsistent.[44,47,48,203,204] A systematic review came to the conclusion that there was an increase in odds for incontinence in women with hysterectomy, but also pointed out a lack of potential confounders in several of the analysed studies.[43] In our study data on UI was collected prospectively, before and one year after surgery and we were able to include several important confounders. Vaginal delivery, obesity, daily urge without incontinence and uterine weight were associated with both de novo UI and remission of UI. Mode of delivery and obesity are well known riskfactors for the development of pelvic floor disorders[96,98] and obviously these factors also influence UI after hysterectomy. To our knowledge the influence of mode of delivery on UI after hysterectomy has not been previously demonstrated.

There was a dose-response relationship between de novo UI, increasing BMI and vaginal delivery, which could not be seen in women with no vaginal delivery. Both vaginal delivery and obesity cause permanent muscle and nerve injuries and when adding the potential risk of surgical nerve injuries these women seem to be more prone to UI. Uterine weight had the strongest positive impact on continence status of all factors indicating that hysterectomy of a large uterus is likely to cause an improvement in UI.

Remission of UI (13.3%) was almost as likely to occur as residual UI (16.1%) after hysterectomy and de novo UI was found in 8.3% of the total cohort. Accordingly one fifth of the women experienced a change in continence status. When analysing only the women with preoperative UI, 45% had a remission of UI. De novo UI is a negative consequence of hysterectomy and remission of UI can be seen to be a positive development following surgery, also reflected in the degree of satisfaction being reduced in women with UI post hysterectomy. These results, including the knowledge on potential riskfactors, are of great importance when counselling women who are to undergo a hysterectomy.

Obesity and pelvic organ prolapse surgery *(Paper IV)*

The lowest prevalence of obesity was noted in the women undergoing POP surgery compared to the other surgical cohorts. Surgery seemed to be safe in obese women with no increased rates of complications or patient dissatisfaction with POP surgery in accordance with previous studies.[78,137,140]

Obesity was demonstrated to be a predictor of symptoms of recurrence after primary surgery in Paper IV. Kawasaki et al reported an increased risk of anatomic recurrence already within two months in obese women who underwent native tissue anterior colporrhaphy.[139] Lo et al found improvement with regard to anatomic outcome, although obese women experienced less improvement of POP symptoms after sacrospinosus ligament fixation and anterior mesh repair.[140] On the other hand Clark et al. studied 376 women for 5 years following surgery for POP and/or UI and there was no association between BMI and risk of reoperation.[119] In our study no increased rate of obese women was noted in repeat surgery compared to primary surgery and no influence of obesity could be seen on the feeling of a vaginal bulge one year after surgery in repeat surgery. Obesity is presumably weakly associated with repeat surgery, however there might be a selection of patients by the surgeon or that the obese woman is reluctant to undergo repeat surgery.

Instead we found obesity to be associated with a higher risk of both residual UI and de novo UI one year after POP surgery. Almost half of the study population experienced a remission of UI, but the odds of residual UI were 50% higher for the obese woman. There is only one previous study that has evaluated riskfactors of UI after simple POP surgery (without concomitant UI surgery) and BMI was identified as an important riskfactor.[128]

The influence of smoking *(Paper I-IV)*

Smoking has gradually been decreasing in Sweden during the last decade.[4] In a recent study by Lindh et al four cohorts of 19-year-old women were studied

regarding reproductive health and the relationship to socio-economic status. Smoking habits decreased successively from 41% in 1981, 34% in 1991, 28% in 2001 to 19% 2011. In the cohorts of 1981 and 1991 there were more smokers in low socio-economic status areas, but in the more recent cohorts of 2001 and 2011 smoking habits were no longer related to socio-economic status.[205]

There are numerous possible explanations for the decrease in the prevalence of smoking. The availability of a standardised health care system with a long experience of preventive healthcare is one important factor. The lowest prevalence of smoking among women is during the childbearing ages of 30-44 years where the health promoting work of the maternal and child health care centers have played an important role. According to Folkhälsorapporten 2014 the highest prevalence of smoking is found in the ages of 45-64 (14 %),[4] which is during the years when most hysterectomies are performed. The reason for a higher smoking prevalence in the hysterectomy cohort (18%) compared to the general population of today is that data was included since 2004 in the study. In 2004 the prevalence of smoking was 23% in this age group.[206] There is no indication that smoking causes increased menstrual bleeding disorders[207] and a increased need of hysterectomy. On the contrary, it is associated with a decreased risk of fibroids[208] and early natural menopause.[209]

Table 5. The rate of smoking and mean age in Paper I-IV.

	Hysterectomy		**MUS**	**POP**
	All hysterectomies	Hysterectomy and UI		
	(Paper II)	*(Paper III)*	*(Paper I)*	*(PaperIV)*
Age mean	50	51	55	65
Smoking %	18	17	13	9

The rate of smoking differed between the surgical cohorts (Table 5). In the hysterectomy cohort where the highest rate of smokers was reported, complications were more common and the impact of smoking on complications was more evident. The odds of vaginal or abdominal wall infection were 48 and 59% higher than for the non-smokers (Table 1).
In the MUS cohort 13% were smokers and the mean age was 55 years and in POP surgery the mean age was 65 years and the rate of smoking 9%. This illustrates both the age-dependent development of disorders indicating surgery and that smoking habits change during life. Many smokers wish to quit and according to these figures it appears that 50% succeeded in smoking cessation after 50 years of age.

The combination of low rates of complications and smoking in the UI and POP surgery cohorts aggravated the analysis of the influence of smoking in these procedures. In addition, the most common smoking related complication in POP surgery has been linked to mesh erosion,[138] however information on mesh erosions in GynOp is lacking. Smoking was also recently reported to be a riskfactor of erosions of the polyprolene tape in MUS[210] and a study from 2015 found that smoking was associated with an increased risk of a second surgery for SUI within two year.[211] Several of the previous mentioned studies on MUS and obesity did not include smoking as a confounding factor.

Thus, this thesis could only demonstrate an association between smoking and hysterectomy related complications. Should smoking cessation be enforced in all types of gynaecological surgery or is it too resource demanding in relation to the outcome of the intervention? This thesis cannot more than hypothesise on the effect of smoking intervention on all procedures. The study design would preferably be a

randomised controlled study (RCT), which is actually an ongoing registerbased RCT in GynOp and described in chapter "Future perspectives".

The direct effect of smoking cessation on the outcome of surgery in POP and UI surgery is probably low considering the low rates of complications. On the other hand, to offer a smoking cessation program cannot be disputable as abstinence from smoking would be one of the major benefits for the woman's general health. Surgery is shown to be a window of opportunity to introduce life-style changes. There is a higher rate of maintained smoking abstinence one year after perioperative smoking cessation intervention compared to nicotine replacement therapy at any time.[144,145]

The influence of previous vaginal delivery *(Paper I-IV)*

Vaginal delivery is another life-style factor associated with the development of pelvic floor disorders.[96,98] In Table 6 the prevalence of previous vaginal in the different surgical procedures in this thesis is depicted.

Table 6. The prevalence of vaginal delivery in Paper I-IV.

	Hysterectomy					**MUS**	**POP**
	All hyster-ectomies	No pre/postop UI	De novo UI	Remission of UI	Residual UI		
	(Paper II)	*(Paper III)*				*(Paper I)*	*(Paper IV)*
Vaginal Delivery %	85	83	88	89	92	96	98

The requirement of POP- and UI surgery seems to be strongly associated with the longterm consequences of vaginal delivery as >96% of the women had experienced a vaginal delivery in the POP- and UI surgery cohorts. The rate of nulliparous women in the ages of 60-65 years in the general population is according to the Medical Birth Register 12.3-14.1%.[212] This is in comparison with vaginal delivery rates of 85% in women undergoing hysterectomy in Paper II.

When analysing UI after hysterectomy in Paper III previous vaginal delivery was more common in women who developed de novo UI. Among women with residual UI after hysterectomy the prevalence of vaginal delivery was even higher. Altman et al found that the risk for multiparous women to undergo POP- or UI surgery after hysterecomy was 11-16 times higher compared to women with no vaginal delivery.[44,102]

Route of hysterectomy can also be linked to previous vaginal delivery. Women with previous vaginal childbirth are more likely to undergo VH. In our study >96% of the women undergoing VH had experienced a previous vaginal delivery compared to 81% in LH and 80% in AH. This is important to bear in mind when discussing if and how the different routes of hysterectomy influence the risk of later pelvic floor surgery.

Hysterectomy and subsequent pelvic floor disorder *(Paper I,III, IV)*

The prevalence of hysterectomy in Sweden has been estimated to be 10-11%.[29] In Paper IV, a history of hysterectomy prior to POP surgery was 19.5% in primary surgery and 27.5% in repeat surgery. In the MUS procedures in Paper I the prevalence of previous hysterectomy was also considerably higher than expected; in RPR 18.6% and in TOR 26.1%.

The development and risk of subsequent surgery due to pelvic floor disorder has been demonstrated to be higher after hysterectomy[43,47,101] irrespective of hysterectomy technique.[44] VH has been associated with a higher risk than the abdominal approach.[45,46,48] It is probably not due to the vaginal approach *per se,* but rather the selection of the patients to vaginal surgery, with regard to indication for surgery, previous vaginal delivery, obesity and comorbidity. [101,213,214]

In paper III, VH was associated with lower odds of UI remission compared to AH. Indication for surgery due to prolapse was associated with doubled adjOR of UI remission compared to bleeding disorders. Most women with prolapse undergo VH and the results might seem inconsistent. However, UI is more prevalent in women with prolapse and therefore women undergoing hysterectomy due to prolapse are more likely to experience UI remission. This may also indicate that a hysterectomy on prolapse indication should be performed before incontinence surgery in women with both prolapse and incontinence.

In Paper IV prior hysterectomy was an independent predictor of feeling of a vaginal bulge one year after surgery, but we could not find any association between prior hysterectomy and residual or de novo UI after POP surgery.

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Future perspectives

The Swedish National Register of Gynecological surgery, GynOp is a quality register of great value considering the participation of the majority of Swedish clinics and the high response rate amongst patients in the follow-up questionnaires. It opens up many opportunities to perform clinical research.

Randomised register study

One novel study method is to perform a randomised study in a register. The randomisation process is programmed into the register, which automatically identifies new patients eligible for inclusion in the study. The method facilitates clinical randomised studies and makes them less expensive.[215]

Paper II showed an increase of postoperative infections among smokers undergoing hysterectomy, in accordance with other studies on smoking and surgical complications. Peri-operative smoking cessation is known to decrease smoking related postoperative complications and is important to implement in clinical practice according to national guidelines. An ongoing study in GynOp analyses how the register can be used as an informatic tool for both the patient and the surgeon to enhance the implementation of smoking cessation. In addition, questions on smoking cessation in the follow up questionnaires after surgery provide information on the outcome of smoking intervention.

In time for surgery the woman completes a health declaration form and two months after surgery a follow up questionnaire. In addition the surgeon fills in several perioperative forms. This potentially allows the addition of information to these questionnaires and forms on the importance of smoking cessation. In GynOp 50% of the patients answer the GynOp questionnaires on the internet and these patients

are included in the study. If smoking is reported in the health declaration the patient is automatically randomised in the data program to one of four alternatives. Either she receives a text message with information on smoking cessation in the questionnaire or her smoking status will be alerted to her surgeon to request smoking cessation. In the third group both the patient and her surgeon will be alerted. The fourth group will receive no information about smoking cessation. In the postoperative questionnaire the patient will be asked to participate in a research study including questions about smoking cessation.

If it is shown that perioperative smoking cessation can be enhanced by information via a quality register it should be used in clinical practice. Furthermore, the register can be utilised by the participating clinics to evaluate the effect of perioperative smoking cessation. Likewise, it is important to assess the functionality of a randomised study in a national register to address other future important issues. A similar study could be carried out on weight loss before surgery or alcohol cessation before surgery.

Other life-style factors of importance

Other interesting factors of importance to study in the surgical field are both alcohol use and physical activity. Information on these factors is at present not available in the register despite the fact there is evidence to support its inclusion.

5-year follow-up study on POP

There is a need for longterm follow up after POP surgery and particularly after mesh augmented surgery. There is also lacking information on mesh erosions in GynOp. New questions have been developed to improve the analysis of mesh erosions. These questions have been included in a questionnaire sent to women five years after POP surgery as a longterm follow-up study. This study is in cooperation with Emil Nüssler.

Conclusions

- GynOp generates large surgical cohorts and permits the study of the outcome of gynaecological surgery
- Obesity (BMI ≥30) was found to be the life-style factor most strongly associated with a negative outcome in all studied surgical procedures
- After UI surgery obese women had a poorer outcome with decreased cure rates, more often persistent daily urinary leakage and urgency symptoms than their non-obese counterparts *(Paper I)*
- A BMI ≥30 was associated with higher risk of complications in all hysterectomy techniques *(Paper II)*
    - In abdominal hysterectomy: excessive bleeding, prolonged surgery, peroperative complications, postoperative complications and infections
    - In vaginal hysterectomy: excessive bleeding and prolonged surgery
    - In laparoscopic hysterectomy: prolonged surgery
- After hysterectomy one fifth of the study population experienced a change in continence status *(Paper III)*
    - Obesity was associated with higher risk of de novo UI and residual UI
    - Previous vaginal delivery was shown to be an important factor in the development of UI after hysterectomy
- In POP surgery obesity was associated with higher risk of vaginal bulge after one year and higher risk of de novo UI and residual UI *(Paper IV)*
- Smoking was associated with higher risk of postoperative infections in abdominal and vaginal hysterectomy *(Paper II)*
- Life-style factors should be considered when counselling a woman prior to gynaecological surgery for overall health benefits and to improve outcome of surgery.

Sammanfattning på svenska

Hysterektomi, prolaps- och inkontinenskirurgi är de vanligaste kirurgiska ingreppen till följd av benign gynekologisk sjukdom. I Sverige opereras mer än 16 000 kvinnor årligen. I de flesta fall uppnås goda behandlingsresultat, men ingreppet kan efterföljas av komplikationer och även ge upphov till nya besvär. Det är av betydelse att identifiera faktorer som kan inverka negativt på operationsresultatet och särskilt de faktorer som kan förändras innan operationen. Livsstilsfaktorer som övervikt och rökning är exempel på förändringsbara faktorer. Ohälsosamma levnadsvanor bidrar i stor utsträckning till den samlade sjukdomsbördan i Sverige och samtal om levnadsvanor med patienter i olika sammanhang är betydelsefullt för patients hälsa. Inför planerad kirurgi är patienten ofta mer benägen till förändring av olika riskfaktorer avseende hälsan. Förändring av ohälsosamma levnadsvanor kan således förbättra möjligheten till ett bra kirurgiskt resultat, likväl möjligheten att efter operation leva ett hälsosammare liv.

Syftet med avhandlingen var att undersöka hur övervikt/fetma och rökning inverkar på komplikationsfrekvensen samt operationsresultatet vid operation av urininkontinens, prolaps samt hysterektomi. För att kunna bedöma enskilda livstilsfaktorer analyserades även andra möjliga riskfaktorer.

Studierna baserades på data insamlat från 6 308 inkontinensoperationer, 28 537 hysterektomier och 20 689 prolapsoperationer under 2004-2015 i nationella kvalitetsregistret för gynekologisk kirurgi, GynOp. Förekomsten av per- och postoperativa komplikationer, urininkontinens samt nöjdhet efter ingreppet studerades upp till ett år efter operationen. I prolapsgruppen ingick även symtom på prolapsrecidiv ett år efter operationen.

Vid slyngplastik mot urininkontinens uppnåddes ett lyckat resultat i 87% av operationerna. Majoriteten av kvinnorna som ingick i studien var överviktiga (BMI 25-29) eller obesa (BMI ≥30). Med stigande BMI-klass var dagliga urinträngningar

och urinläckage mer förekommande både innan och efter operationen. BMI ≥30, diabetes och ålder>80 år identifierades som riskfaktorer för kvarstående daglig urininkontinens efter operationen. Dagliga urinträngningar och dagligt urinläckage ökade risken att inte vara nöjd med operationen.

Vid abdominell hysterektomi var BMI ≥30 en riskfaktor för stor blödning och komplikationer under operationen, längre operationstid, postoperativa komplikationer och infektioner. Vid laparoskopisk och vaginal hysterektomi ökade BMI ≥30 risken för förlängd operationstid och stor blödning. Rökning innebar högre risk för postoperativa infektioner efter abdominell och vaginal hysterektomi.

Risken för nytillkommen urininkontinens efter hysterektomi var högre om kvinnan hade BMI ≥30, tidigare genomgått en vaginal förlossning eller besvärades av urinträngningar innan operationen.

Vid prolapsoperation av obesa kvinnor sågs en högre förekomst av urininkontinens före och efter operation. Det var också vanligare med symtom på ny prolaps ett år efter operationen samt nytillkommen urininkontinens redan 8 veckor efter operationen. Obesitas påverkade inte komplikationsfrekvensen eller nöjdhetsgraden. Operation med nät innebar högre risk för komplikationer, men patienterna var nöjdare med operationen och symtom på ny prolaps var mindre ett år efter operationen. Mer än 96% av kvinnorna som genomgått prolaps-eller urininkontinensoperation hade tidigare fött barn vaginalt vilket talar för att vaginal förlossning är en betydande riskfaktor för behov av bäckenbottenkirurgi. Det framkom ingen negativ effekt av rökning på resultat vid dessa operationer.

Sammanfattningsvis hade BMI ≥30 en negativ inverkan på utfallet för alla operationstyper. Det sågs en ökad risk för komplikationer efter hysterektomi och ökad risk för kvarstående eller nytillkommen urininkontinens efter såväl hysterektomi som prolaps-och urininkontinensoperation. Rökning ökade risken för infektioner efter hysterektomi, men inverkade inte på någon av de övriga studerade faktorer.

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