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The Manchester-Fothergill procedure versus vaginal hysterectomy with uterosacral ligament suspension in the treatment of vaginal apical prolapse

From a clinical and economic perspective

PhD Thesis Cæcilie Krogsgaard Tolstrup

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The Manchester-Fothergill procedure versus vaginal hysterectomy with uterosacral ligament suspension in the treatment of vaginal apical prolapse

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Contents

Preface

This thesis is written based on research conducted at the Department of Obstetrics and Gynecology, Herlev and Gentofte University Hospital from July 2015 to June 2018 where I was employed as a research fellow. I was enrolled as a PhD-student at the Graduate School at the Faculty of Health and Medical Sciences, University of Copenhagen.

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Abbreviations

VH	Vaginal hysterectomy
MP	Manchester-Fothergill procedure
POP	Pelvic organ prolapse
POP-Q	Pelvic organ Prolapse Quantification system
USL	Uterosacral ligament
CL	Cardinal ligament (Mackenrodt's ligament)
SSL	Sacrospinous ligament
ALL	Anterior longitudinal ligament
RCT	Randomized controlled trial
BMI	Body Mass Index
ASA	American Society of Anesthesiologists score
DugaBase	Danish Urogynecological Database
DHHD	Danish Hysterectomy and Hysteroscopy Database
DAD	Danish Anesthesia Database
DKK	Danish kroner
EUR/€	Euro
US$	American dollars
AU$	Australian dollars
PACU	Post-anesthesia care unit
HR	Hazard ratio
OR	Odds ratio
SD	Standard deviation
CI	Confidence interval

Introduction

Pelvic organ prolapse (POP) is a very common condition affecting millions of women worldwide. Vaginal apical prolapse is a subtype of POP in which a descent of the cervix, uterus or vaginal vault is present (1). Even though apical prolapse is a benign condition it can affect quality of life substantially. Usually conservative treatment with vaginal pessaries is first line of treatment but for those women whose symptoms cannot be cured, surgical treatment is next. POP surgery aims to restore the normal vaginal anatomy and thereby reduce symptoms. Numerous surgical procedures for treatment of apical prolapse are performed worldwide including vaginal hysterectomy (VH) and the Manchester-Fothergill Procedure (MP), which are among the most common in Denmark.

The entire number of POP-operations done has been increasing over the last decade (2)(3) with around 5,400 POP surgeries annually in Denmark (4), and 350,000 in the US of which around 50% include repair of apical prolapse (5). This number will increase further in the future due to the aging population and growing obesity rate in many developed countries. The extensive surgical activity in this field imposes a burden on the affected women as well as a substantial economic burden on health care budgets. Despite the large number of surgeries performed worldwide, no consensus exists on the best surgical procedure for repair of apical prolapse, and only little attention has been paid to this topic so far. VH has been the most common surgical treatment of apical prolapse for years, and still holds the prime position as the preferred procedure worldwide (6)(7)(8).

It is the aim to ensure all women the most satisfactorily postoperative outcome with the least risk of complications, recurrence of symptoms and need for re-intervention. To do so, consensus on the best surgical method for apical prolapse repair needs to be reached. As the economic resources used on health care are increasing, durable treatments at reasonable costs are in great demand.

Scientific papers included in the PhD thesis

Paper I

Tolstrup CK, Lose G, Klarskov N. **The Manchester procedure versus vaginal hysterectomy in the treatment of uterine prolapse: a review**. Int Urogynecology J. 2017 28:33-40. (1)

Paper II

Tolstrup CK, Husby KR, Lose G, Kopp TI, Viborg PH, Kesmodel US, Klarskov N. **The Manchester-Fothergill procedure versus vaginal hysterectomy with uterosacral ligament suspension: a matched historical cohort study**. Int Urogynecology J. 2018 29:431-440. (2)

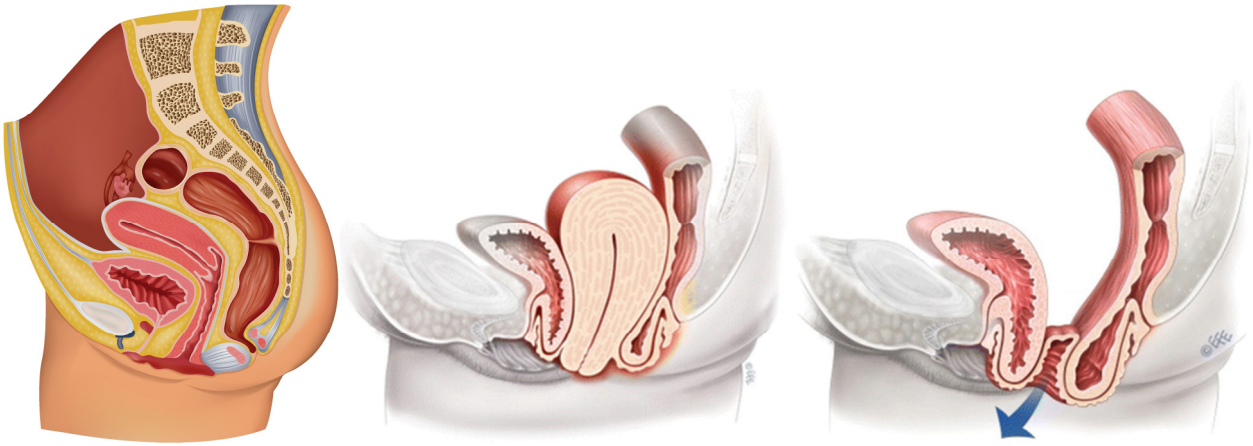
Paper III

Husby KR, Tolstrup CK, Lose G, Klarskov N. **Manchester-Fothergill procedure versus vaginal hysterectomy with uterosacral ligament suspension: an activity-based costing analysis**. Int Urogynecology J. 2018 Feb 26. doi: 10.1007/s00192-018-3575-9. (3)

Background

Pelvic organ prolapse

POP can be defined by symptoms, signs and clinical investigations (1). The diagnosis should be based on a combination of POP symptoms, signs of POP and possible clinical investigations.
Symptoms of POP can generally be related to the urinary, bowel or sexual function. The cardinal symptom of POP is vaginal bulging. Other frequently reported symptoms include pelvic pressure, low backache, incomplete bladder emptying/urinary retention, incomplete defecation, splinting, rectal urgency, dyspareunia and obstructed intercourse (1). Symptoms of POP are often non-specific and the correlation to objective findings is weak (9)(10). Most patients experience POP symptoms when the prolapse reaches the hymen or below (ie POP-Q stage ≥ II) (11)(12)(13). As POP is a benign condition, it does not affect mortality but quality of life is moderately to severely affected in 75% of women who consult a gynecologist due to POP-symptoms (14).
Signs of POP are descent of one or more of the anterior, apical or posterior compartment. Descent in the anterior compartment is seen as a descent of the anterior vaginal wall, which is usually caused by a cystocele or uretrocele, while descent in the apical compartment is due to descent of the cervix, uterus or vaginal vault in case of previous hysterectomy. Descent in the posterior compartment is observed as a descent of the posterior vaginal wall, most frequently due to a rectocele or enterocele (Fig.1 and 2). The most common is descent of the anterior vaginal wall (15) followed by descent of the posterior vaginal wall, though POP frequently occurs as a combination of descent in more than one compartment.



A **B** **C**

Fig. 1 Pelvic organ prolapse (apical prolapse)

A Normal anatomy. *B* Uterovaginal-prolapse. *C* Vaginal vault prolapse.

Reprinted with permission from colourbox.dk (A) /An International Urogynecological Association (IUGA) / International Continence Society (ICS) joint report on the terminology for female pelvic organ prolapse (POP), 2016, Int Urogynecol J, Springer (B, C)

A **B**

Fig. 2 Clinical manifestations of POP

A Stage III Uterine prolapse. *B* Stage IV Vaginal prolapse (complete eversion).

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POP is most commonly graded according to the Pelvic Organ Prolapse Quantification system (POP-Q) (Fig. 3) which classifies POP into five stages according to the relation between the most distal point of the prolapse and the hymen at maximum straining (1) :

Stage 0: No prolapse
Stage I: > 1 cm above the hymen
Stage II: ≤ 1 cm above or below the hymen
Stage III: > 1 cm below the hymen but the eversion is at least 2 cm less than the entire vaginal length
Stage IV: Complete eversion of the vagina or an eversion at least within 2 cm of the entire length of the lower genital tract

Signs of POP (POP-Q stage ≥2) are found on anatomical examination in more than 50% of women aged more than 40 years (16). For apical prolapse (POP-Q stage ≥1) the corresponding number is 14.2% in postmenopausal women (17).

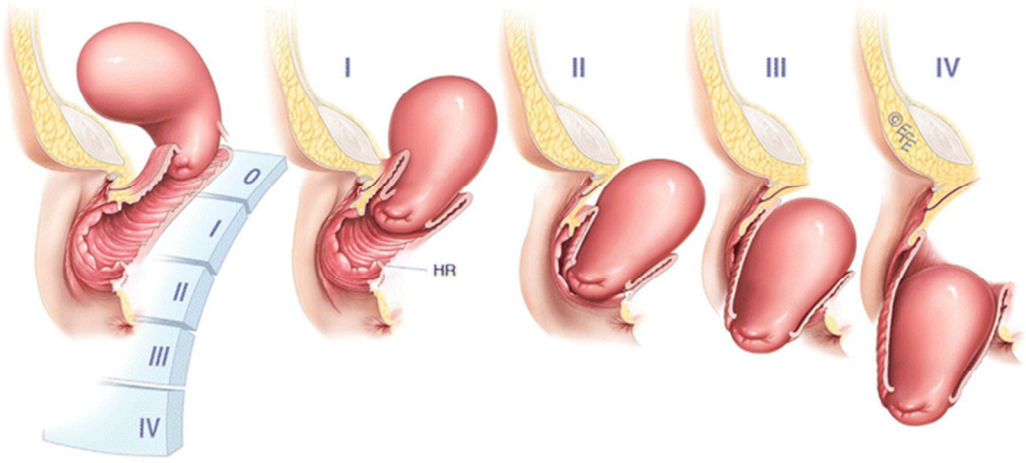

Fig. 3 POP-Q: Prolapse staging 0, I, II, III, IV
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Clinical investigations include urodynamics, ultrasound imaging, magnetic resonance imaging (MRI) and computed tomography (CT). Investigations are optional, as they are not required in POP diagnostics.

Development of POP is multifactorial. A recognised theoretical model explaining the multiple causes in development of POP has been developed (18). In this model factors are described as predisposing, inciting, decompensating or promoting. Predisposing factors affect the connective tissue and can be hereditary, racial or genetic, whereas inciting factors include delivery mode, parity, increased birthweight and pelvic surgery. Decompensating factors concern the effect of aging and the postmenopausal decrease in sex hormones. Promoting factors are mainly related to life style and other physical conditions as obesity, heavy occupational work and conditions with chronically elevated intraabdominal pressure (e.g. cronic cough, constipation etc.) (19)(20)(21). The pelvic organs are held in position by attachment to the pelvic walls by the endopelvine fascia. The vagina is suspended in the anterior-posterior level by the pubocervical fascia which attach the cervix to the posterior surface of the pubic symphysis, the uterosacral ligaments attaching the cervix to the sacrum (Fig. 4), and laterally by the cardinal ligaments situated along the inferior border of the broad ligament connecting the lateral sides of the cervix and vaginal fornixes to the lateral pelvic walls (Fig. 4). Injuries to any of these ligaments can result in prolapse of the uterus, cervix or vaginal vault after hysterectomy. In case of cervical elongation, symptoms of POP can occur even in the absence of descent of the uterus meaning that injuries to the suspending ligaments are not always the pathophysiological explanation to symptoms.

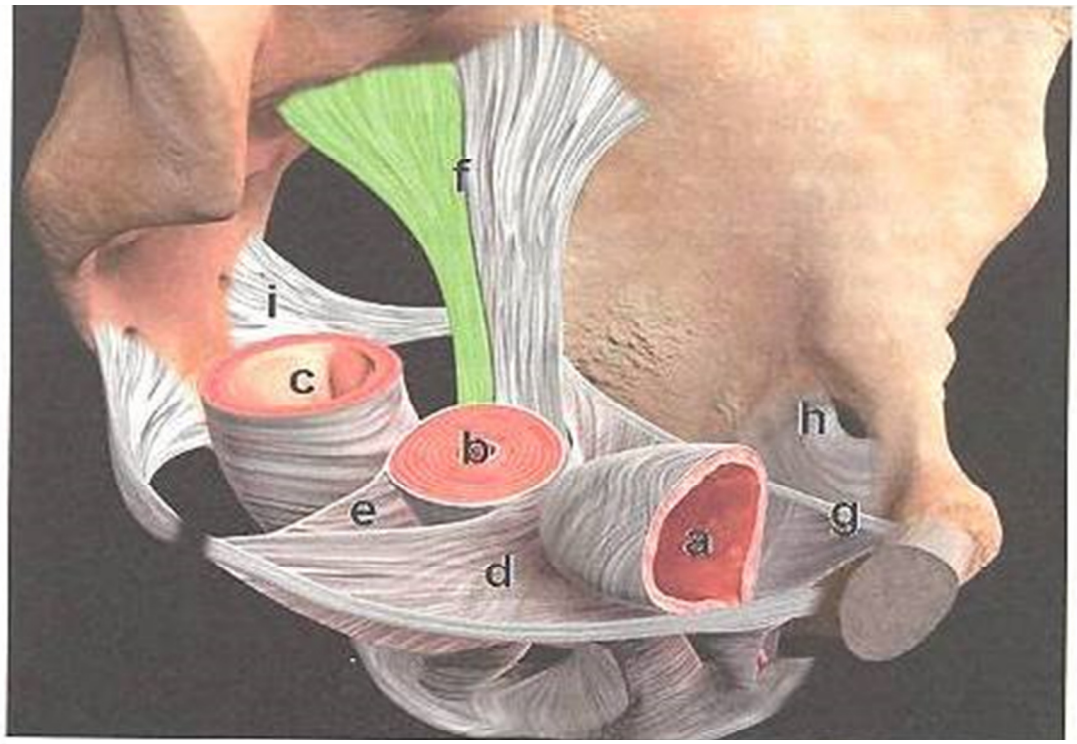

Fig. 4 The utero-vaginal suspension

a Bladder. *b* Cervix. *c* Rectum. *d* Pubocervical fascia. *e* Rectovaginal fascia. *f* Uterosacral ligament (green part) and cardinal ligament (grey part). *g* Arcus tendineus fascia pelvis. *h* Obturator foramen. *i* Sacrospinous ligament.

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Treatment of POP

At all times uterine prolapse seems to have affected women. The first descriptions of attempts of treatment date back to the Egyptian papyri, and ever since a wide selection of potential treatments have seen the light of day. At the time of Hippocrates the leading thought was that the uterus acted like an animal which could be controlled by odours. Hence, delightful odours were placed at the woman's head and bad odours close to the prolapsed uterus to allure the uterus back into its normal position. In a similar manner the uterus could be threatened to retreat by a red-hot iron. Other treatments tested were application of different astringents and oils to the prolapsed part, and halved pomegranates served as pessaries. If treatments were not successful, the woman would undergo succussion whereby she was tied upside down and bounced until her prolapsed uterus was withdrawn. Subsequently the woman was left bed bound for days with her legs tied together. During the Renaissance anatomic dissections became popular providing cutting-edge knowledge of the anatomy of the female genital tract, including the uterine suspension. By the

end of the 16th century the use of pessaries became recognised. The first pessaries produced were made of metal, wood and waxed cork. A real break-through came in 1844 when Charles Goodyear was granted a patent for invention of vulcanised rubber, resulting in a true boom in pessaries made by this new material. Surgical treatment of uterine prolapse has evolved concurrently with other treatment modalities. The earliest records originate form the second century C.E. where surgical removal of a gangrenous prolapsed uterus was described. Due to lack of knowledge of asepsis and poor anesthesia, surgery remained risky business for centuries. In the late 19th century standard surgical treatment of uterine prolapse included narrowing the vaginal vault, perineorrhaphy, colpocleisis and cervical amputation, among others. Hysterectomy as a treatment of uterine prolapse was not reported until 1861 (22).

Conservative treatment

Conservative treatment includes lifestyle interventions, pelvic floor muscle training (PFMT), and the use of vaginal pessaries. Lifestyle interventions (e.g. weight loss) aim to decrease the intra-abdominal pressure, whereas PFMT is capable to improve POP symptoms (23)(24) by reinforcing the pelvic floor muscles.

A wide selection of vaginal pessaries exists (Fig. 5). When inserted into the vagina, the pessary provides mechanical support to the vaginal walls and the uterus (25)(26).

Fig. 5 Vaginal pessaries

Clockwise from top left: Ring with central support, cube, gellhorn and donut.

Picture taken by the author

Surgical treatment

When conservative treatment fails to reduce symptoms, or when it is not well tolerated by the patient, surgical repair is required. In Denmark the lifetime risk of POP surgery is 19% for women aged 80 years (27) but the rate differs between countries. The peak incidence of POP surgery is in women aged 60-69 years (42.1 surgical procedures/10,000 women)(5).
Surgery should solely be performed on a clear indication and reserved for cases where POP symptoms affect the quality of life notably.

Surgical repair of vaginal apical prolapse – what do we know so far?

The surgical strategy for repair of apical prolapse varies highly internationally. Vaginal hysterectomy has been the most common surgical treatment of apical prolapse for years (6)(7)(8), and in the US uterine prolapse is the most frequent indication for hysterectomy in women aged more than 55 years (28). Correspondingly, in 2005 57.4%, 45.0% and 40.1% of all hospital admissions for POP surgery in Germany, France and England included a hysterectomy (29). VH and the MP are among the most common procedures in Denmark, whereas sacrocolpopexy and hysteropexy are rarely used despite being frequently performed elsewhere. However, numerous other common surgical techniques exist.

Surgery for apical prolapse can basically be done through the vaginal or abdominal route, though the vaginal route is by far the most common currently. The abdominal approach is dominated by laparoscopy (robot-assisted or not), though the traditional open access (laparotomy) can be used too. Procedures can be divided into uterine-preserving and non-preserving, including different techniques for suspension of the vaginal vault or cervix (in case of subtotal hysterectomy) at the time of hysterectomy or in previously hysterectomised patients. In most procedures, the uterus/cervix/vagina is suspended and fixated to one or more ligaments (Table 1). The fixation can be done by sutures, or with the use of graft or mesh. Augmentation of native tissues with various types of mesh (usually polypropylene) is an established strategy to obtain durability by increasing fibrosis and providing a barrier to recurrence. However, the use of mesh carries a risk of mesh-related complications, and consequently the benefits must be weighed against the risk of serious adverse events. The ligaments most commonly used for fixation are the anterior longitudinal ligament (ALL), the uterosacral ligaments (USL) (Fig. 4), the sacrospinous ligaments (SSL) (Fig. 4) and the cardinal ligaments (CL) (Fig. 4). When indicated, surgery for

apical prolapse can be accompanied by one or more other procedures for repair of concomitant prolapse in another compartment (often anterior/posterior colporrhaphy).

Table 1 Ligament suspension procedures

Ligament suspension procedure	Uterus intact	Uterus removed	Mesh	Route
ALL				
Sacrohysteropexy	x		+	abd/vag
Sacrocolpopexy		x	+	abd
Sacrocervicocolpopexy		x	+	abd
USL				
Suture hysteropexy	x		-	abd/vag
Low USL suspension		x	-	abd/vag
High USL suspension		x	-	abd/vag
Posterior intravaginal slingplasty		x	+	vag
SSL				
Sacrospinous hysteropexy	x		-	abd/vag
Sacrospinous fixation		x	-	vag
Uphold™	x	x	+	vag

ALL Anterior longitudinal ligament. *USL* Uterosacral ligament. *SSL* Sacrospinous ligament. *Abd* Abdominal. *Vag* Vaginal.

Anterior longitudinal ligament (ALL) suspension

In **sacrohysteropexy** the prolapsed uterus is fixed to the ALL through the abdominal route either laparoscopically or by an open access. The technique was first described in 1957 by Arthure and Savage (30), and their technique is very similar to the sacrohysteropexy done today. The peritoneum over the sacral promontory is incised, and the ureteres identified. The broad ligaments are opened, the vesico-uterine peritoneum incised, and the bladder reflected distally. The arms of a Y-shaped mesh are introduced through openings created in the broad ligaments and fixed to the anterior and posterior side of the uterus. The other end of the mesh is then fastened to the ALL over the sacral promontory (31).

With regards to laparoscopic sacrohysteropexy a symptomatic recurrence rate of 2% was seen only 10 weeks after surgery (32). This finding was confirmed in another study showing a re-operation rate of 2% due to symptomatic recurrence at a mean follow-up of 2.1 years (33). Another study compared laparoscopic sacrohysteropexy with VH and found that 8% of patients needed re-surgery due to recurrence after laparoscopic sacrohysteropexy compared to 20% after

VH (34). Buttock pain occurred in 8.7% after laparoscopic sacrohysteropexy. The pain resolved spontaneously in eight patients but one (0.9%) had to undergo suture cutting and concomitant VH due to persistent pain (35). Adhesions between exposed mesh and bowel loops causing abdominal pain with need for laparoscopic treatment was found in 2-3.9% after laparoscopic sacrohysteropexy (33)(32).

Sacrocolpopexy (a.k.a. abdominal sacrocolpopexy) is by many considered the gold standard in apical suspension (36). It can only be performed through the abdominal route via an open access or laparoscopically (robot-assisted or not) (1), and it is mainly performed as a treatment of vaginal vault prolapse (36) but can be done as a prophylactic procedure at the time of hysterectomy as well. The first steps in the development of sacrocolpopexy was taken back in the early decades of the 20th century, and in 1949 one of more abdominal procedures anchoring the vagina to the abdominal wall was described (37). In 1957 gynecologists started attaching the posterior uterine fundus to the ALL due to a high rate of postoperative enterocele. Five years later Lane suggested the use of an intervening graft between the vagina and sacrum to avoid excessive tension on the vagina (38).

In sacrocolpopexy the anterior side of the sacral promontory is carefully dissected to identify the ALL. The peritoneum is opened from the promontory to the pouch of Douglas, and the posterior dissection goes down to the ventrolateral side of the levator ani muscle. Then the paravaginal fascia is dissected down to the lower third of the vagina, to just below the bladder trigone. The posterior arm of a Y-shaped mesh is distally attached to the levator ani muscle and proximally to the vaginal apex/cervix. The anterior arm is placed underneath the bladder and sutured to the caudal part of the vagina and apex. The other end of the mesh is finally fixed to the ALL at the level of the promontory (39)(Fig. 6).

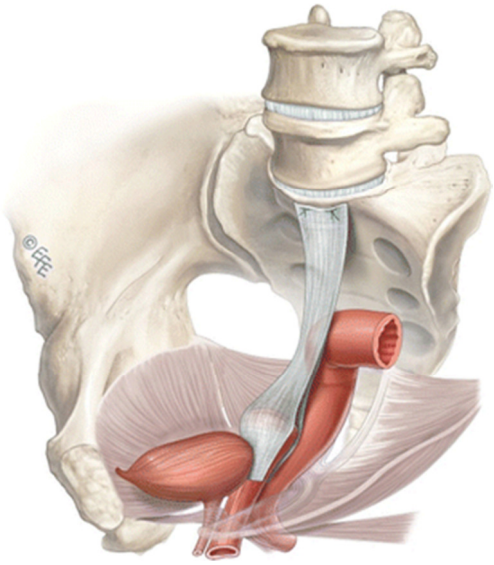

Fig. 6 Sacrocolpopexy

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Sacrocolpopexy is a widely performed procedure, recognised for its low recurrence rates. A re-operation rate of 2.3% due to recurrence was found at a follow-up of up to 27 months in a systematic review not differentiating between laparoscopic and open sacrocolpopexy (40). In accordance with this a recent study showed a re-operation rate of 3.5% for recurrence, and a subjective cure rate of 95.3% 60 months after laparoscopic sacrocolpopexy (39). The laparoscopic and open approach yield equal outcomes regarding success rate and improvement in quality of life (41)(42). When compared to vaginal sacrospinous colpopexy, lower rates of recurrent apical prolapse were seen after sacrocolpopexy (43)(44). Though not common, presacral hemorrhage is the potentially most serious perioperative complication related to fixation to the ALL. In a large systematic review hemorrhage or transfusion, or both were found in 4.4% of patients after sacrocolpopexy (45). In another study mesh erosion occurred at a rate of 2.9% at a follow-up of 60 months after laparoscopic sacrocolpopexy (39).This is in agreement with a total mesh erosion rate of 3.4% shown in a systematic review assessing all surgical approaches of sacrocolpopexy. In this review 3% of patients underwent re-operation due to mesh erosion or infection. In addition ureteral injury was found in 1%, and 1.1% of patients underwent re-operation due to small bowel occlusion caused by adhesions between exposed mesh and bowel loops (45).

Sacrocervicocolpopexy (a.k.a. sacrocervicopexy) is most commonly performed as a preventive matter at the time of subtotal hysterectomy but it can be done in patients who have previously had a subtotal hysterectomy too. The remaining cervix is suspended to the ALL by mesh or graft in a way similar to laparoscopic sacrocolpopexy (46).

Uterosacral ligament (USL) suspension

In **suture hysteropexy** the uterus is suspended by plication of the USLs which are re-inserted into their original site of insertion on the posterior side of the cervix (47). High rates of repeat surgery was found after laparoscopic suture hysteropexy where 16% underwent re-surgery for apical prolapse at a follow-up of less than 20 months (47). Ureteric occlusion had to be surgically corrected in 4.7% after laparoscopic suture hysteropexy because of medial ureteral kinking in close proximity to the plicated USLs (47). Another potentially serious complication to laparoscopic suture hysteropexy occurred in 2.3% where laparotomy and blood transfusion were required due to laceration of a uterine artery (47).

Low USL suspension (a.k.a. McCall suspension/culdoplasty) and high USL suspension can be undertaken as preventive procedures at the time of hysterectomy or in already hysterectomised women. They can be performed either via a vaginal or abdominal access (usually by laparoscopy). In low USL suspension the vaginal vault is sutured to the left USL and subsequently the peritoneum of the cul-de-sac is plicated followed by fixation to the right USL. Finally additional sutures can be put through the posterior vaginal wall, the USL and back through the vaginal wall (48).

By **high USL suspension** the vaginal vault is sutured to the USL bilaterally (Fig. 7) before the anterior and posterior arm of each suture is fixed to the rectovaginal and pubocervical fascia (49). A recent RCT comparing high USL suspension to sacrospinous fixation failed to show any difference in anatomical, functional and adverse outcomes at a follow-up of two years (50). Low and high USL suspension have been shown to have equal outcomes (51).

Posterior intravaginal slingplasty is described in the paragraph on transvaginal mesh repair.

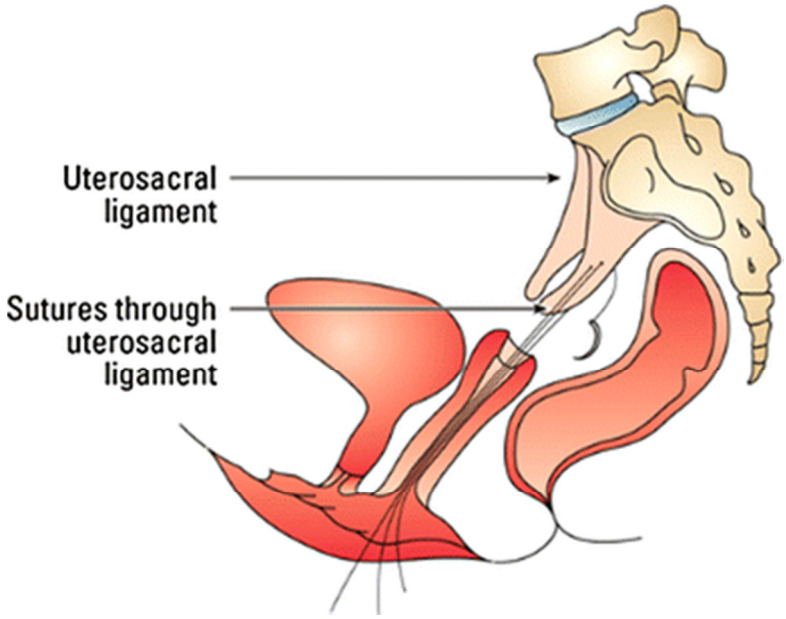

Fig. 7 high USL suspension

The uterosacral ligaments are re-attached to the vaginal vault.

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Sacrospinous ligament (SSL) suspension

Sacrospinous hysteropexy was not described until 1989 where a case series on vaginal sacrospinous hysteropexy was published. This technique quickly gained popularity, and today it is one of the best studied techniques for repair of apical prolapse. By this procedure a unilateral or bilateral fixation to the SSL is done (1). Fixation by *the vaginal route* is done through a midline incision in the posterior vaginal wall, which is separated from the rectum. The ischial spine is localized and through blunt dissection the ligament is identified through the pararectal space. Sutures are placed (unilaterally or bilaterally) through the ligament approximately two cm medial to the ischial spine and through the posterior side of the cervix in the midline, and tightened. Finally the vaginal wall is closed (52)(53).

A re-operation rate of 2.3% due to apical prolapse recurrence after vaginal sacrospinous hysteropexy has been shown (54). In a recent systematic review and meta-analysis no difference was found between vaginal sacrospinous hysteropexy and VH in the rate of repeat surgery because of apical prolapse recurrence (55), however the studies included in this review are very heterogenous and hence, comparability is limited. One of two RCTs included in the review showed an anatomical recurrence rate (POP-Q ≥II) of 27% for the apical compartment after vaginal sacrospinous hysteropexy compared to 3% after VH. On the other hand no differences in quality of life and urogenital symptoms were discovered (53). The other RCT found no re-

operations due to apical recurrence after vaginal sacrospinous hysteropexy whereas 2% were seen after VH (35). The outcomes regarding anatomic recurrence, functional outcome and quality of life were equal between VH with USL suspension and vaginal sacrospinous hysteropexy at 12 months follow-up (35). Buttock pain, a well-known complication to hysteropexy, was experienced by 15-18.1% of patients after vaginal sacrospinous hysteropexy, and consequently up to 1.5% underwent surgery (54)(56).

Sacrospinous fixation (a.k.a. sacrospinous colpopexy or sacrospinous ligament fixation) (Fig. 8) is technically similar to sacrospinous hysteropexy, and can be performed as a preventive procedure at the time of hysterectomy or in already hysterectomised. Sacrospinous fixation consists of a fixation of the vaginal vault to the SSL (Fig. 8), and the technique can vary depending on whether fixation is unilateral or bilateral (1).

Uphold™ is described in the next paragraph on transvaginal mesh repair.

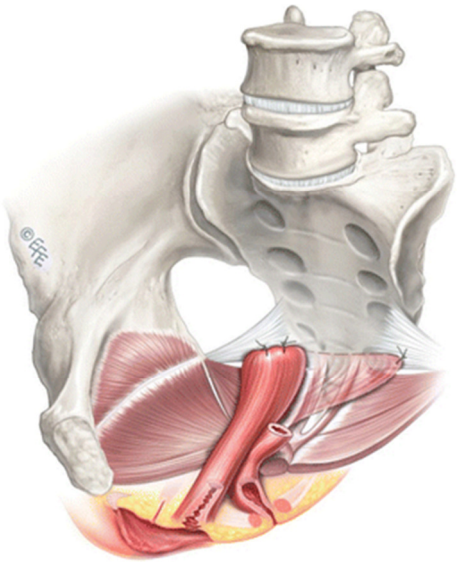

Fig. 8 Sacrospinous fixation (sacrospinous colpopexy/sacrospinous ligament fixation)
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Transvaginal mesh repair

There is an ongoing pursuit of developing the ideal procedure for apical prolapse repair, as all existing surgical procedures carry an inherent risk of recurrent prolapse. During the last two decades numerous prefabricated mesh kits for apical prolapse repair have been developed and promoted, providing a minimally invasive alternative to the conventional surgical treatments.

Among the previously most popular kits are the Apogee™/Perigee™ system (American Medical Systems Inc., Minnetonka, MN, USA), introduced in 2004 and the Gynecare Prolift™ system (Ethicon Women's Health and Urology, Somerville, NJ, USA), introduced in 2005. Within a few years after the introduction of prefabricated mesh kits serious adverse events including mesh erosion and pain, became apparent. This ultimately lead to the FDA notification on mesh-use in 2008 (57), with an update in 2011 (58). A few years later a scientific committee (SCENIHR) under the European Commission declared the use of meshes for POP repair only appropriate as a second choice after failed primary surgery (59). In the wake of this, a number of mesh kits were withdrawn from the market, including the Apogee™/Perigee™ and the Gynecare Prolift™ systems. Since then, much attention has been paid to the use of synthetic meshes in prolapse repair, and consequently The National Institute for Health and Care Excellences in England in December 2017 issued a recommendation stating that the use of transvaginal mesh for anterior or posterior prolapse repair should be restricted to research purposes due to serious safety concerns (60). This was followed by a ban of synthetic meshes for prolapse repair by the authorities of Australia and New Zealand.

The current available prefabricated mesh kits are second generation kits, including the **Uphold™ Lite Vaginal Support System** (Boston Scientific). In this second generation the mesh is light-weight and the size reduced thereby limiting the mesh load to avoid mesh related complications.

The Uphold™ procedure is done through a horizontal incision in the anterior vaginal wall at the level of the bladder neck. The SSLs are identified extraperitoneally by digital dissection along the obturator muscle and paravesical/vaginal space. After identification of the ischial spine, the suture-mesh arm device is delivered into the SSL approximately two cm medial to the ischial spine by palpation. In non-hysterectomised the superior mesh edge is sutured to the paracervical ring and in hysterectomised to the vaginal apex. Apical suspension and positioning of mesh across the anterior compartment is provided by the tension of the mesh arms. Finally the vaginal incision is closed (61).

A recent prospective multicenter study on the Uphold™ procedure showed an anatomic success rate (POP-Q<II) of 83.3% at five years follow-up. In accordance with this 86.8% reported no symptom, or symptom without bother when asked about the presence of a bulge in the vaginal area (62).Correspondingly a previous study found 93% of patients to be satisfied with the result at a median follow-up of 12 months (61). In the multicenter study 19.7% underwent additional pelvic surgery during follow-up, of which 23.1% was due to apical prolapse recurrence (62).

The rate of mesh erosion ranged from 2.6% at a median follow-up of 12 months (61) to 1.4% after five years (62), while mesh removal due to pain was necessary in another 1.4% (62). In comparison mesh erosion or infection was discovered in 5.8% in an earlier study pooling data for various mesh types including the Apogee™ and Gynecare Prolift™ systems (40).

Posterior intravaginal slingplasty (PIVS) (a.k.a. infracoccygeal sacropexy) is another minimally invasive procedure for suspension of the vagina. It was frequently performed previously but has now been withdrawn from the market due to frequent vaginal erosions. The suspension relied on creation of new USLs using a polypropylene tape which ran along the native USLs. The procedure was done through a vertical incision in the posterior vaginal wall just below the vault/cervix. The ischial spines were identified, and two short skin incisions were made in the perianal area below the ischial tuberosities. An IVS tunneller was placed through the incisions up to the level of the ischial spine on one side. The tunneller was turned medially and guided through the vaginal incision. The procedure was repeated on the other side. The polypropylene tape was fixed to the posterior fornix or vaginal vault, and the vaginal incision was closed at last (63).
A study with nine years follow-up found an anatomic success rate after posterior intravaginal slingplasty of 93.2% (POP-Q ≤I for the C and Bp point), and an improvement in quality of life was confirmed by all participants who would recommend the surgery to others too (63). Similarly, anatomical recurrence (POP-Q >II) appeared in the apical compartment in 7% in another study with 13 months follow-up (64). Re-operation because of recurrence of apical prolapse was found to be more frequent after transvaginal mesh repair in general (all procedures pooled) (2.9%) compared to after abdominal (1.5%) and laparoscopic (1.8%) sacrocolpopexy, and even native tissue repair (2.3%) in a large register study with at least two years follow-up (65). The rate of vaginal tape erosion after posterior intravaginal slingplasty PIVS ranges between studies. An erosion rate of 8.7%, and related re-operation rate of 4% was found in a large register study despite a median follow-up of only seven weeks (66). Another study disclosed a substantially lower rate of tape erosion of 2.3% at nine years follow-up (63). When transvaginal mesh repair procedures are pooled, the rate of mesh removal/revision is 5.1% compared to 1.2% after abdominal sacrocolpopexy and 1.7% after laparoscopic sacrocolpopexy (65).

Intraoperative complications occurred in 2.8%, including bleeding with need for blood transfusion in 1.6%, and rectal injury in 1% (66). A similar rate of rectal injury was seen in another register study where rectal perforation occurred in 2.4% (64).

For all the previously described surgical mesh-procedures, the mesh is generally re-peritonised to avoid future adhesions to bowel loops or other adjacent viscera.

Obliterative procedures

Colpocleisis is an obliterating procedure (1), and one of the oldest surgical treatments of apical prolapse still in use. The procedure performed today has only undergone minor modifications from the original procedure described by LeFort in 1877. The technique differs according to if the uterus is intact or not, as a colpocleisis is performed in non-hysterectomised and a colpectomy at the time of hysterectomy or in previously hysterectomised patients. As it puts an end to the ability of sexual intercourse, colpocleisis and colpectomy are only suitable for women with no wish for future coitus.

Colpocleisis aims at closure of the vaginal vault while drainage of uterine discharge is sustained. Rectangular strips of vaginal mucosa are removed from the anterior and posterior vaginal wall thereby creating a canal of approximately three cm bilaterally. The denuded part of the vaginal walls is approximated to each other and sewn together with rows of interrupted stitches, obliterating the lumen permanently. Uterine discharge is able to be expelled through the lateral bilateral vaginal canals (67).

In **colpectomy (total colpecleisis)** there is no need for uterine drainage, allowing a complete closure of the vaginal lumen. A circumscribing incision is made through the vaginal mucosa, in the anterior wall in an ample distance of the urethral opening, and in the posterior wall approximately one cm from the introitus, and laterally at the level of the hymen. A total excision of the vaginal mucosa is done, and the denuded surface of the prolapse is squeezed into the pelvis by purse-string sutures, which are finally tied. If possible, the sutures are then attached to the endopelvic fascia. At the end the introital flaps are approximated by horizontal sutures (67). Whether or not to preserve the uterus at the time of colpocleisis has been a controversial issue, but a recent decision analysis did not show any benefits from concomitant hysterectomy at the time of colpocleisis (68).

Colpocleisis and colpectomy are highly effective procedures with long term anatomical success rates > 90% and great patient satisfaction (69)(70)(67). After colpocleisis 95% of patients report

being either “satisfied” or “very satisfied” with the result (71)(72)(73). Intraoperative complications, as bleeding and visceral injury is seen in < 2% of patients in most studies, and the most prevalent complication is urinary tract infection occurring in approximately one third of patients (74)(75).

Vaginal hysterectomy (VH)

VH was performed for the first time in 1813 by Langenbeck. It was originally developed and undertaken as an effort to treat uterine and cervical malignancies (76) but soon gained popularity as a treatment of apical prolapse. By 1937 VH had become the leading treatment in apical prolapse in the US (77). As vaginal vault prolapse rapidly became an apparent complication to hysterectomy, attempts to fixate the vaginal vault has been done since the 1890s (22), and currently a selection of different techniques for fixation are available of which three are described in the preceding paragraphs. In Denmark the most frequent fixation techniques are low and high USL suspension.

In VH a circumcision is made around the cervix thereby creating an access to the pouch of Douglas. The uterus is removed after cutting the cardinal ligaments and the USL. After suspension of the vaginal vault, the mucosa is closed. Recurrence in the form of vaginal vault prolapse frequently occurs after VH, requiring surgical repair in 6-8% of all women (78). Though, a recent systematic review showed a lower risk of symptomatic apical recurrence (POP-Q≥II) for VH compared to uterine-preserving procedures when data for all preserving procedures was pooled (RR 10.61; 95% CI 1.26–88.94; p = 0.03). However, the surgical technique varied considerably between the included studies.

Ureteral lesion, or obstruction caused by accidental suturing, are well-known complications related to VH. Occlusion was seen in 3.2% of patients who had the vaginal vault fixated by USL suspension (53) and 2.9% after sacrospinous fixation (79)(80). When VH is compared to uterine-preserving techniques in general, it entails larger blood loss and longer surgery time (81)(82)(83)(84)(85).

The Manchester-Fothergill procedure (MP)

The MP is a uterus preserving procedure developed by the Manchester gynaecologist Archibald Donald, who first performed it in 1888. The original MP consisted of an amputation of the cervix combined with a perineorrphaphy and an anterior and posterior colporrhaphy (86).

Later the procedure was modified by Fothergill, who introduced an essential step in the procedure in which the uterine support was efficiently shortened by plication of the cardinal

ligaments at the anterior aspect of the cervix (86). In this way the procedure known as the Manchester-Fothergill procedure evolved. In the MP an anterior colporrhaphy is done, followed by a circumcision of the cervix. The bladder is dissected from the cervix, and the cardinal ligaments are identified by palpation at the lateral sides of the cervix, cut and marked. The cervix is then amputated. The size of the amputation depends on the degree of cervical elongation, and usually ranges from one to three cm, though the crucial point is the plication of the cardinal ligaments, not the amputation itself. The cervical epithelium is dissected from the cervix to ensure a sufficient application of epithelium to the remaining cervical piece after suturing. The cardinal ligaments are then plicated and sutured to the anterior side of the cervical piece, pulling it up and backwards (Fig. 9). The cervical piece is re-epithelialised with Sturmdorf sutures, creating a neoportio. Finally a posterior colporrhaphy is performed if needed (81)(87).

The MP has been shown to be an efficient and durable treatment with a patient satisfaction rate of 95% one year postoperatively, and a five-year re-operation rate of 2.8% due to symptomatic apical recurrence (88). Cervical stenosis is a complication unique to the MP. A frequency of 11% was found in a single study (89), though no cases were detected in other studies (90)(91). In addition, a recent study found a rate of severe complications of only 0.2% after the MP compared to 1.9% after VH (92).

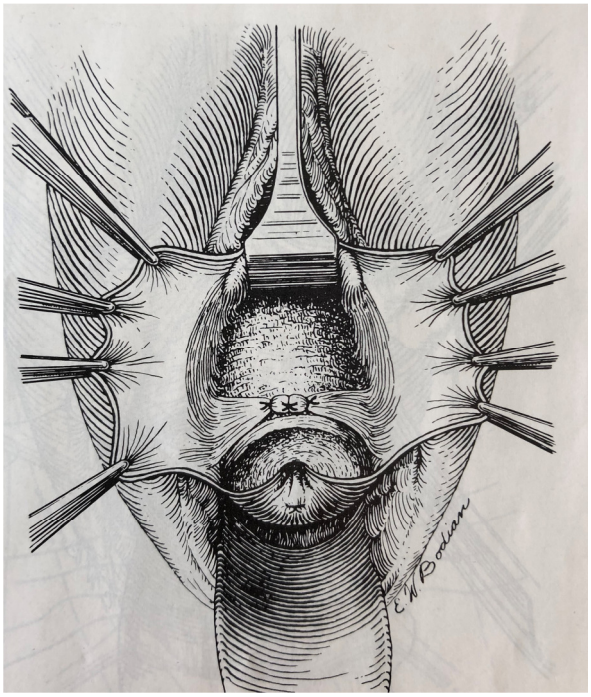

Fig. 9 The Manchester-Fothergill procedure

Figure shows the position of the plicated cardinal ligaments which are sutured to the anterior side of the remaining cervical piece.

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Health care financing in Denmark

Health care budgets are currently under increasing pressure among others due to ongoing development of new treatment modalities, improvement of existing treatments and the aging population in many developed countries.

Models of health care financing vary from country to country. In general, health care services can be financed directly by user fees or indirectly by a third part. In third-party financing there is a third part between the patient and the health care provider, thus there is no direct cash flow from the patient to the provider. The third part can be a government (i.e. a public health care system), a social insurance fund, a private insurance company or an aid organization/NGO (altruism) (93). In accordance with the Scandinavian welfare model, health care in Denmark is a public responsibility financed by taxes, and specific services are provided by public and private providers. Specialty planning by the Danish Health Authority aims at securing preconditions for equal and high quality all over Denmark (94)(95).

In order to shorten waiting times, activity based financing (ABF) was implemented in the 1990s. In ABF patients with similar conditions are grouped together in Diagnosis Related Groups (DRGs) by an electronic 'DRG-grouper' utilizing patient data on age, gender, diagnosis and interventions performed. The average costs of treatment per patient in each DRG are calculated based on information on the public hospitals' costs related to treatment of patients in each group. In this way, average costs for all available in-patient and out-patient treatments are calculated. This serves as the basis for calculation of the number of DRG-points/DKK for in-patient treatments and DAGS-points/DKK for out-patient treatments (DAGS: Dansk Ambulant GrupperingsSystem). Based on this information and information on each clinical department's production of DRG-points, economic resources were allocated to providers (i.e. hospitals and clinics) based on activity level measured in DRG/DAGS-points/DKK (96).

Economics of prolapse surgery

Annually a high number of POP surgeries are performed worldwide requiring significant economic resources. Because of the aging population, the share of women in the US with symptomatic POP will increase by 46% from 2010 to 2050 (97). Likewise, it is forecasted that the annual costs related to POP surgery in the US and Europe will grow at twice the rate of population growth during the next decades (98). In 2005 the total costs of hospital admissions involving POP surgery were 81,030,907 €, 83,067,825 € and 144,236,557 € in England, France and Germany, respectively (29). There is a lack of cost-effectiveness data on POP surgery in general, as only a minority of studies evaluating POP surgery do actually examine the economic costs. A number of economic analyses exist in relation to surgical repair of apical prolapse, mainly assessing sacrocolpopexy. In a cost-effectiveness analysis vaginal reconstructive surgery was shown to be more cost-effective in the treatment of post-hysterectomy vaginal prolapse than open sacrocolpopexy and robot-assisted laparoscopic sacrocolpopexy (99). When compared to sacrospinous fixation in a recent comparative analysis of surgery without concomitant hysterectomy, the mean index costs of open sacrocolpopexy (12,763 US$) and laparoscopic sacrocolpopexy (13,647 US$) were significantly higher compared to sacrospinous fixation (10,993 US$, $P<0.0001$ for both). The same applied to the follow-up costs, in total 15,716 US$ for open sacrocolpopexy and 16,838 US$ for laparoscopic sacrocolpopexy compared to 13,916 US$ for sacrospinous fixation, $P<0.0001$ for both (100).

Open sacrocolpopexy was confirmed to be associated with a significantly higher cost (6450 AU$) than sacrospinous fixation (4575 AU$) ($P<0.01$) in another study (101). When the

traditional open sacrocolpopexy was compared to laparoscopic sacrocolpopexy and robot-assisted laparoscopic sacrocolpopexy in a cost-minimizing analysis, a significantly lower in-patient cost of open sacrocolpopexy (13,149.99 US$) was seen than for laparoscopic sacrocolpopexy (19,308.94 US$) and robot-assisted laparoscopic sacrocolpopexy (24,161.48 US$) (P=0.0004). Futhermore, the in-patient costs of laparoscopic sacrocolpopexy were lower compared to the costs of robot-assisted sacrocolpopexy (102). The same conclusion was reached in another cost-minimizing analysis (103). A significantly lower mean total cost of laparoscopic sacrocolpopexy compared to total vaginal mesh was found (mean difference 4013.07 US$, 95% CI: 3107.77-4918.37 US$) (104). Based on the existing literature vaginal repairs seem to be less costly than abdominal. To our knowledge no studies comparing the financial costs of VH and the MP exist.

Study I

The Manchester procedure versus vaginal hysterectomy in the treatment of uterine prolapse: A review

Objectives

To provide a systematic review of the literature comparing VH to the MP as a treatment of apical prolapse, and to examine if VH and the MP are equal regarding:

- Symptomatic and anatomic outcome.
- Quality of life score and functional outcome.
- Conservative and surgical re-intervention rate.
- Risk of complications and operative outcomes.

Materials and methods

A systematic review was done according to the MOOSE guidelines. The scientific question and eligibility criteria were pre-specified. Studies eligible of inclusion either compared VH to the MP only, or consisted of a comparison of more surgical procedures for treatment of apical prolapse, provided that data for VH and the MP was available for individual analysis. Publication date was not restricted, and we did not apply any limitations regarding language or study design. The primary outcome was anatomic and symptomatic outcome in the same or another compartment. The secondary outcomes were quality of life score, functional outcome, operative outcomes, re-operation and conservative re-intervention rate and complications. A literature search was conducted in Pubmed, EMBASE and the Cochrane databases with the following search strategy:

("hysterectomy, vaginal"[MeSH Terms] AND ((((Manchester[All Fields] AND ("surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "operation"[All Fields])) OR (Manchester[All Fields] AND ("wound healing"[MeSH Terms] OR ("wound"[All Fields] AND "healing"[All Fields]) OR "wound healing"[All Fields] OR "repair"[All Fields]))) OR Manchester-Fothergill[All Fields]) OR (Manchester[All Fields] AND ("methods"[MeSH Terms] OR "methods"[All Fields] OR "procedure"[All Fields]))))) AND ((("uterine prolapse"[MeSH Terms] OR "uterine prolapse"[MeSH Terms]) OR "pelvic organ prolapse"[MeSH Terms]) OR ("uterine prolapse"[MeSH Terms] OR ("uterine"[All Fields] AND "prolapse"[All Fields]) OR "uterine prolapse"[All Fields] OR ("uterus"[All Fields] AND "prolapse"[All Fields]) OR "uterus prolapse"[All Fields]))

MESH terms were used in Pubmed and subject headings in EMBASE. Reference lists and books were searched manually. The last search was undertaken on June 10th 2016.

Results

A total of 65 studies were identified. After screening by abstract and full-text, nine studies met the eligibility criteria (Fig. 10) however, not all outcomes were assessed in all included studies. Anatomic recurrence in the apical compartment was seen in 4-7% after VH compared to none after the MP. The re-operation and conservative re-intervention rate due to symptomatic recurrence showed a similar pattern with a higher rate after VH (9-13% and 14-15%, respectively) than after the MP (3-10% and 10-11%, respectively). No difference was shown between the two procedures regarding postoperative prolapse related quality of life scores and urinary incontinence. Operating time was longer, the perioperative blood loss tended to be larger, more bladder lesions and infections where related to VH, and the postoperative blood loss was greater too.

Conclusion

The evidence is very scarce, and no studies have evaluated the economic costs related to the two procedures. Though, the literature is in general in favour of the MP. There is an urgent need for further studies to gain evidence in this field. Consequently, we designed and conducted study II and III.

Fig. 10 Flow chart showing literature search

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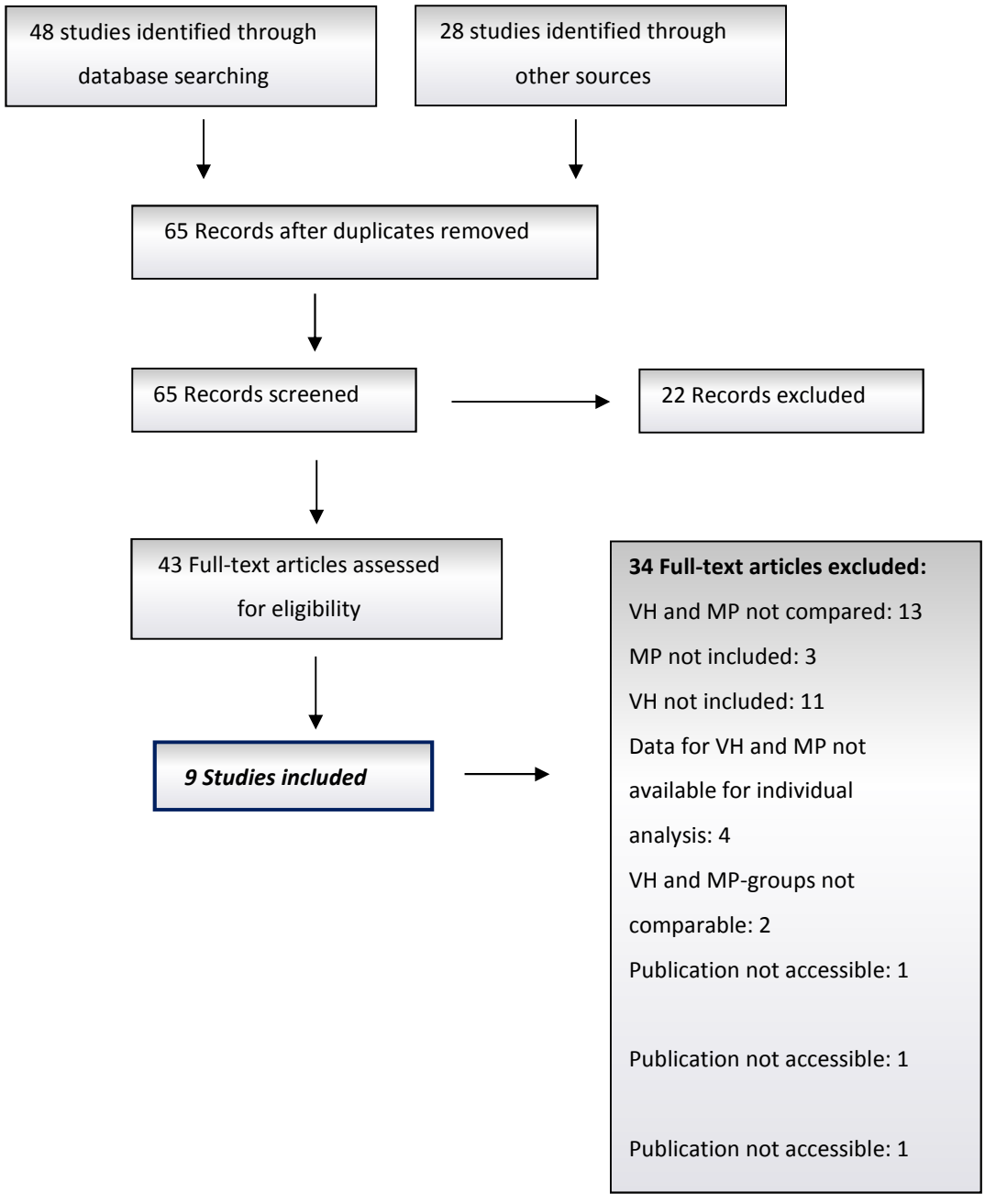

Study II and III

The Manchester-Fothergill procedure versus vaginal hysterectomy with uterosacral ligament suspension: a matched historical cohort study (study II)

Manchester-Fothergill procedure versus vaginal hysterectomy with uterosacral ligament suspension: an activity-based costing analysis (study III)

Objectives

Study 2

For each of the surgeries:

- To estimate the rate of recurrent or de novo POP in any compartment.
- To estimate the rate of recurrent or de novo POP for each compartment specifically.
- To estimate the rate of perioperative and postoperative complications.
- To go through the pathological evaluation of the tissue removed.

Study 3

To compare the hospital costs of VH and the MP in relation to:

- Costs of the primary surgery.
- Costs of recurrences.
- Costs of complications.
- Costs of postoperatively developed urinary incontinence.
- Costs related to uterus-preservation in the MP-group.

Materials and methods

These studies were conducted based on the same matched historical cohort. The cohort included women who underwent a VH or MP due to a prolapse in the apical compartment in one of four public hospitals in the Capital region of Denmark in 2010-2014 (both included). The patients were followed from the date of operation till recurrence, de novo POP or hysterectomy (for the MP-group only) or August 31st 2016, whichever came first. In addition, all patients were followed regarding postoperative complications until data collection was finalized on August 31st 2016. Exclusion criteria included previous apical POP surgery, indications for VH concurrent to

POP, connective tissue disease, concomitant surgical procedures at the time of MP/VH (e.g. midurethral sling or rectal surgery), and MP accompanied by hysteropexy. Matching on preoperative POP-Q stage in the apical compartment and age was carried out by an independent statistician (a difference in age up to five years was accepted). Owing to exclusions after the initial matching, a second matching was done to ensure as many included pairs as possible. All partners to excluded patients re-entered the pool available for matching. In total 295 matched patient pairs were included (Fig. 11).

Data collection from patient records was approved by The Danish Health and Medicines Authority (3-3013-1397/1 and 3-3013-1397/2) and data storage by the Danish Data Protection Agency (2012-58-0004).

Fig. 11 Flow chart showing matching of participants

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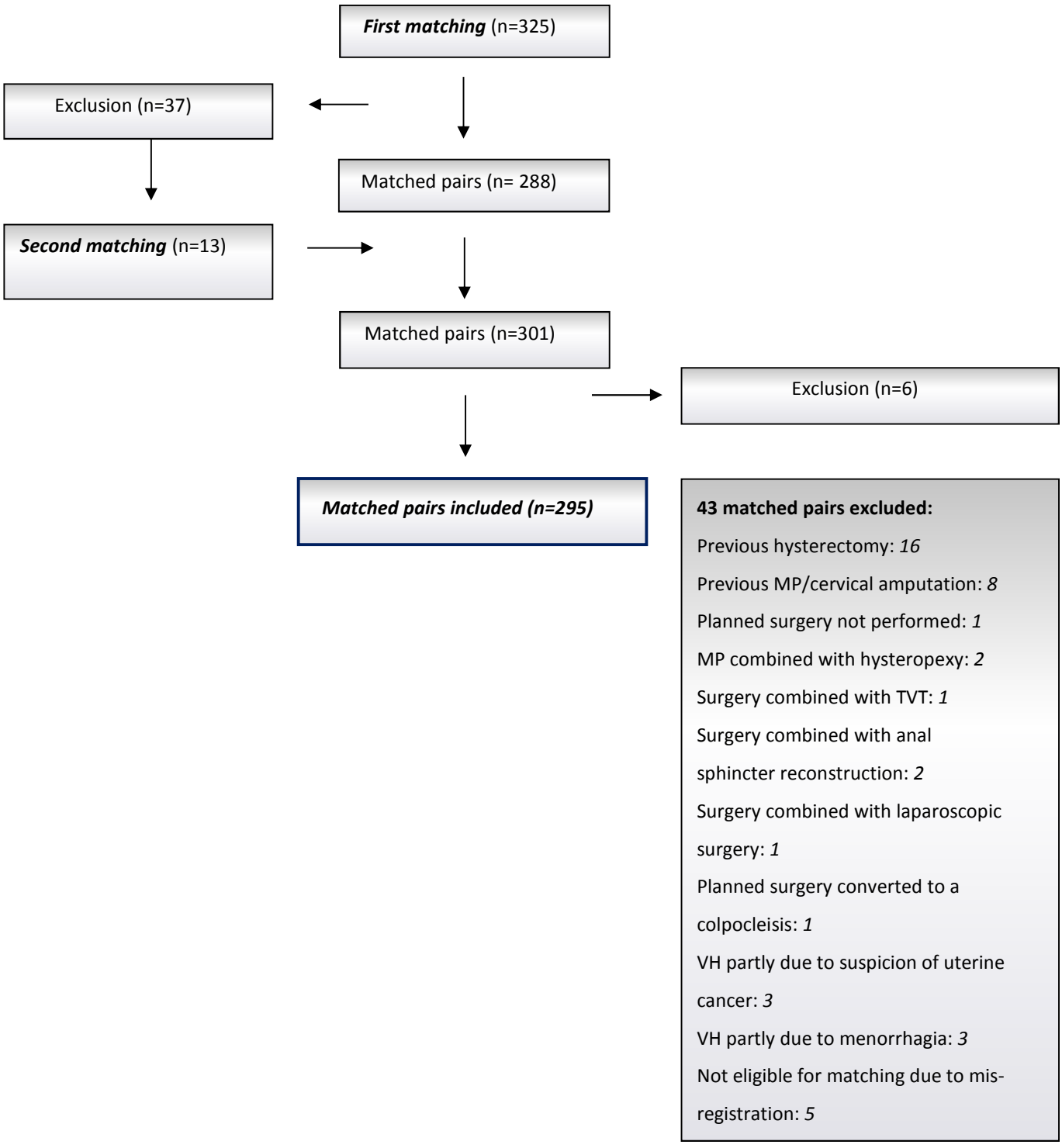

Study II – Clinical outcomes

The study population was identified through the Danish Urogynecological Database (DugaBase) which includes data on all prolapse and incontinence surgeries done in public and private hospitals in Denmark. From the Dugabase we collected information regarding age at surgery, preoperative POP-Q stage for all compartments (estimated by the simplified technique revised by Swift et (105)), ASA-score, BMI, smoking status, weekly alcohol consumption, a preoperative short-form questionnaire on objective examination and patient characteristics (completed by the gynecologist), surgeon experience level with each procedure, and hospital referral. We used the Danish Hysterectomy and Hysteroscopy Database (DHHD) to identify and exclude patients registered with concurrent indications to VH, as DHHD holds data on all hysterectomies undertaken in public and private hospitals in Denmark. The Danish Anaesthesia Database (DAD) contains data on all anesthesia-requiring surgeries in Denmark. When data on BMI and ASA-score in the Dugabase were missing or unlikely (BMI <15 or >50 and ASA>4) data were replaced with data from DAD. According to the Danish recommendations, three months postoperatively patients either had an out-patient visit or a phone interview. In case of relapse of symptoms, new symptoms or any kind of problems related to surgery, the patient was invited for an examination. Reporting of data to the registries is mandatory by law ensuring a high data completeness (106)(107)(108). Information on pathological evaluation of the tissue removed by the two procedures was collected from The Danish National Pathology Registry and Data Bank which covers all pathological evaluations in Denmark no matter if performed in public or private hospitals. Furthermore, for the MP-group data on any tissue removed from the uterus or cervix during follow-up was obtained. Data from the registries were merged using the personal identification number from the Danish Civil Registration System.

The electronic patient record for all patients was reviewed and data assembled regarding patient characteristics, the surgical procedure and concomitant surgery. For the follow-up period, data for any compartment was compiled with respect to recurrence, de novo POP, surgical or pessary treatment due to recurrence or de novo POP, pelvic floor muscle training, and perioperative and postoperative complications.

The *primary outcome* was recurrent or de novo POP in any compartment. *Secondary outcomes* were recurrent and de novo POP in each compartment, perioperative and postoperative complications, pathological evaluation of the uterus/cervix removed and uterine/cervical samples taken during follow-up (for the MP-group only).

Recurrent and de novo POP were defined as one or more of the following:

- **POP treated with surgery or pessary**
- **POP-Q stage II with POP symptoms**
- **POP-Q stage ≥ III independent of POP symptoms**

Statistics

We considered a difference clinically important if 15% of patients had recurrence or de novo POP in any compartment in one group while 25% were affected in the other. From this point of view, a sample size calculation was done using McNemar's Z-test with two-sided equality. The power (1-p) was set to 0.8 and α to 5% which equals a total sample size of 253 pairs. We used a Cox Proportional Hazard model to examine the association between each procedure and recurrent or de novo POP. The hazard ratio (HR) is interpreted as a cause-specific hazard due to competing risk (ie hysterectomy for the MP-group). P-values for the HR and two-sided 95% confidence intervals (CI) were calculated using Wald's test of the Cox regression parameter. Cumulative Hazard Plots illustrated the risk of having an event at any given time. The risk (odds ratio) of a postoperative complication related to surgical procedure was analyzed by logistic regression to address the matching, whereas Fischer's exact test was applied to the analysis of perioperative and postoperative complications in general. P-value ≤0.05 was considered significant. Statistical analyses were performed with SAS® Enterprise Guide 7.11 (SAS, North Carolina, USA).

Study III – Economic outcomes

From DAD durations of surgery, anesthesia, and recovery in post-anesthesia care unit (PACU) was obtained. In case this information was missing, a median time was applied estimated on stratification due to procedure, suspension technique for VHs, ASA-score and surgeon experience level with the current procedure. Information on all procedures, examinations, contacts, and uterus related activities was collected from patient records. The cost analysis addresses hospital resource use only and presumes equal resource use elsewhere for the two groups. All costs to uterine or cervical pathological analyses for the MP-group were included, even for tissue samples taken outside hospital. Since all patients had at least 20 months follow-up, the primary cost analysis was based on this. For the entire follow-up period (up to 80 months) a secondary analysis was conducted (figure 2) in which costs were weighted by the

number of observed patients at the time. Unit costs were achieved from hospital administration, relevant departments, calculated or estimated by local experts. A list of unit costs and salaries is provided in Appendix 1 in study III (109). The cost of each procedure was approximated based on duration of surgery, staff wages, utensils, pathological tests, time in the operating theatre and nights spend in hospital. It was expected that one nurse anesthetist and two operating nurses attended during anesthesia and surgery, and one junior and senior gynecologist during surgery. Additionally, half an hour of work was added for the gynecologists to prepare for the surgery. A senior anesthetist was assumed to be in charge of two operating theaters at a time, and one nurse cared for two patients in PACU simultaneously. From the hospital administration salaries, costs of one night of hospitalization and hourly cost of the operating theatre were obtained. Unit costs of utensils, blood products, pathological tests, radiological procedures, and ring pessaries were achieved from relevant departments. For subsequent contacts costs were based on wages and assumed durations. Successive procedures because of complications were split into *minor* (e.g. cystoscopies and suture removal), *medium* (e.g. vaginal surgery) and *major* (e.g. intra-abdominal surgery). Based on experts' advice costs of minor complications were equivalent to 25% of the cost of a MP, medium complications to 50%, and major complications were considered equivalent to VH with high uterosacral ligament suspension. Costs of operations due to recurrence were presumed to be proportional to the costs of the primary surgeries (for details see Appendix 1 (109)). Costs of recurrences were included when patients approached with symptoms. Costs to pathological sampling were included in the sensitivity analysis even if performed outside hospital. The reimbursement rates paid to private gynecologists by the regional health authorities were applied as unit costs.

Statistics

A sensitivity analysis was conducted for the costs regarding overnight hospital stay, operating theatre and pathological sampling, and for the percentage of working time in which staff are involved in direct patient contact. Additional sensitivity analyses were performed in which patients with missing information on duration of surgery and/or anesthesia and/or stay in PACU or patients costing more than 300% of the median costs of MP and VH, respectively, were excluded. Paired t-tests were applied to the analysis of costs of the primary surgery, the total 20-month costs, and used as sensitivity analysis. On the remaining categories Wilcoxon signed rank sum was used, and Mann Whitney to the analysis of durations. P-value ≤ 0.05 was considered significant. Statistical analyzes were conducted using SAS® 9.4 (SAS, North Carolina, USA).

Results

The only significant difference in baseline characteristics was in use of preoperative local estrogen treatment which was more frequent in the VH-group (Table 2). The distribution of apical compartment prolapse stage was as follows: Stage I: 4 pairs, stage II: 208 pairs, stage III: 76 pairs and stage IV: 7 pairs. More details on baseline characteristics are described in study II (110). A vaginal vault suspension procedure was performed for all VHs (83.4% low and 16.6% high uterosacral ligament suspension). The distribution of VH and the MP was uneven between the participating units as two units mainly performed VHs whereas the other two primarily did MPs (Table 3). Follow-up ranged from 20 to 80 months.

Table 2 Baseline characteristics of participants

Characteristic	**MP-group [n]**	**VH-group [n]**	***P value***
Age at surgery (years), mean (±SD)	59.6 ± 13.0 [295]	61.1 ± 11.4 [295]	0.2*
Body Mass Index (kg/cm^2), mean (±SD)	25.7 ± 4.0 [287]	25.4 ± 3.8 [295]	0.4*
Local estrogen treatment, n (%)	121 (41.01) [285]	157 (53.22) [291]	0.006†
Preoperative POP-Q stage apical compartment, n (%)	[295]	[295]	1.0†
I	4 (1.3)	4 (1.3)	
II	208 (70.5)	208 (70.5)	
III	76 (25.8)	76 (25.8)	
IV	7 (2.4)	7 (2.4)	
Preoperative POP-Q stage anterior compartment, n (%)	[293]	[294]	0.3†
0	35 (11.9)	23 (7.8)	
I	35 (11.9)	37 (12.6)	
II	89 (30.1)	78 (26.5)	
III	125 (42.4)	145 (49.3)	
IV	9 (3.0)	11 (3.8)	
Preoperative POP-Q stage posterior compartment, n (%)	*[288]*	*[293]*	*0.1*†
0	*97 (33.7)*	*107 (36.5)*	
I	*124 (43.0)*	*97 (33.1)*	
II	*50 (17.4)*	*70 (23.9)*	

III	*16 (5.6)*	*17 (5.8)*	
IV	*1 (0.3)*	*2 (0.7)*	
Previous colporrhaphy, n (%)	[295]	[295]	
No	261 (90.3)	268 (90.8)	0.4†
Anterior colporrhaphy	21 (7.3)	22 (7.5)	1.0†
Posterior colporrhaphy	13 (4.5)	10 (3.4)	0.7†
Surgeon experience level with each procedure, n (%)	[289]	[294]	0.6†
≤ 25 surgeries	47 (16.2)	54 (18.3)	
26-100 surgeries	32 (11.0)	38 (12.8)	
>100 surgeries	210 (72.6)	202 (68.6)	
Concomitant surgery, n (%)	[295]	[295]	
Anterior colporrhaphy	245 (83.1)	242 (82.0)	0.8†
Posterior colporrhaphy/ Enterocele	60 (20.3)	96 (32.5)	0.001†
Perineorrhaphy	27 (9.2)	43 (14.6)	0.06†

MP Manchester-Fothergill procedure. *VH* Vaginal hysterectomy. *[n]* total number of participants.

SD Standard deviation. *T-test. †Fischer's exact test.

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Table 3 Distribution of surgeries

Hospital	**Total no. of surgeries, *n (%)***	**No. of MPs, *n (%)***	**No. of VHs, *n (%)***
1	17 (2.9)	17 (5.8)	0 (0)
2	244 (41.3)	182 (61.7)	62 (21)
3	190 (32.2)	49 (16.6)	141 (47.8)
4	139 (23.6)	47 (15.9)	92 (31.2)
In total	590 (100)	295 (100)	295 (100)

MPs Manchester-Fothergill procedures. *VHs* Vaginal hysterectomies.

Study II – Clinical outcomes

Recurrence or de novo POP

Recurrence or de novo POP was significantly more frequent after VH both in any and each compartment individually (Table 4 and Fig. 12). For VH 83.3% of all recurrences in any compartment appeared within 20 months of surgery, whereas the corresponding number for the MP was 78.2%, indicating a sufficient follow-up period.

Table 4 Recurrence or de novo POP

Recurrence/de novo POP	**MP-group [n]**	**VH-group [n]**	***P* value***
Any compartment, n (patients), %	*23 (7.8) [295]*	*54 (18.3) [295]*	*0.0002*
Risk of recurrence/de novo POP, HR (95%CI)	1.0 (ref.)	2.5 (1.3 - 4.8)	
Apical compartment, n (%)	*1* (0.3) *[295]*	*15* (5.1) *[295]*	*0.0004*
Risk of recurrence, HR (95%CI)	1.0 (ref.)	10.0 (1.3 - 78.1)	
Surgical treatment, n (%)	0 (0) [295]	8 (2.7) [295]	0.007
Pessary treatment, n (%)	1 (0.3) [295]	9 (3.1) [295]	0.02
PFMT†, n (%)	0 (0) [295]	2 (0.7) [295]	0.5
No treatment, n (%)	0 (0) [295]	2 (0.7) [295]	1.0
Anterior compartment, n (%)	*12 (4.1) [295]*	*33 (11.2) [295]*	*0.002*
Risk of recurrence/de novo POP, HR (95%CI)	1.0 (ref.)	3.5 (1.4 - 8.7)	
Recurrence (previously operated), n (%)	11 (4.1) [266]	22 (8.3) [264]	0.05
De novo POP, n (%)	1 (3.4) [29]	11 (35.5) [31]	0.002
Surgical treatment, n (%)	6 (2.0) [295]	19 (6.4) [295]	0.01
Pessary treatment, n (%)	5 (1.7) [295]	13 (4.4) [295]	0.09
PMFT†, n (%)	7 (2.4) [295]	10 (3.4) [295]	0.6
No treatment, n (%)	2 (0.7) [295]	3 (1.0) [295]	0.7
Posterior compartment, n (%)	*14 (4.7) [295]*	*38 (12.9) [295]*	*0.0007*
Risk of recurrence/de novo POP, HR (95%CI)	1.0 (ref.)	2.6 (1.3 - 5.4)	
Recurrence (previously operated), n (%)	1 (1.4) [73]	9 (8.5) [106]	0.05
De novo POP, n (%)	13 (5.9) [222]	29 (15.3) [189]	0.02
Surgical treatment, n (%)	6 (2.0) [295]	25 (8.5) [295]	0.0006
Pessary treatment, n (%)	1 (0.3) [295]	10 (3.4) [295]	0.01
PFMT†, n (%)	9 (3.1) [295]	11 (3.7) [295]	0.8
No treatment, n (%)	5 (1.7) [295]	2 (0.7) [295]	0.5

MP Manchester-Fothergill procedure. *VH* Vaginal hysterectomy. *[n]* total number of patients. *Fischer's exact test. *HR* Hazard ratio. *CI* Confidence interval. †Pelvic floor muscle training.

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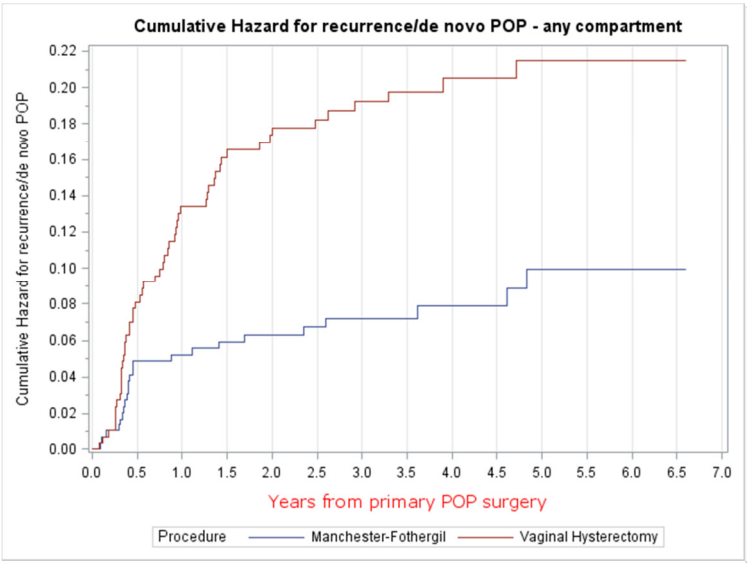
A



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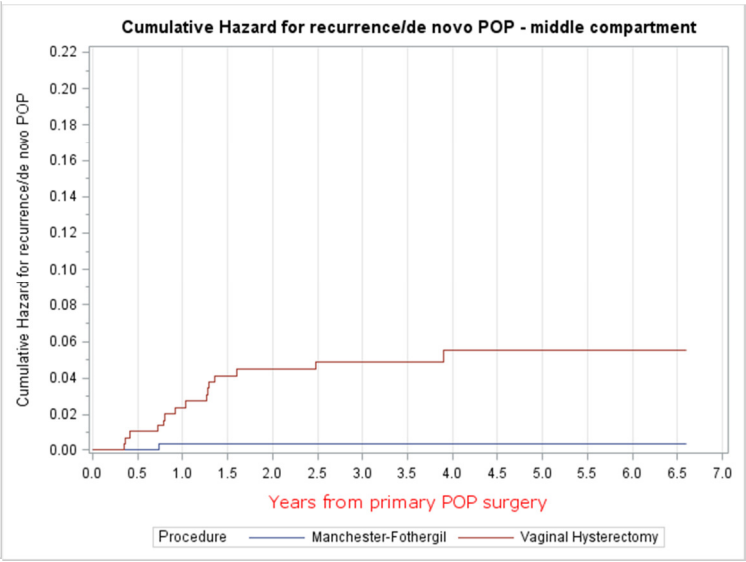

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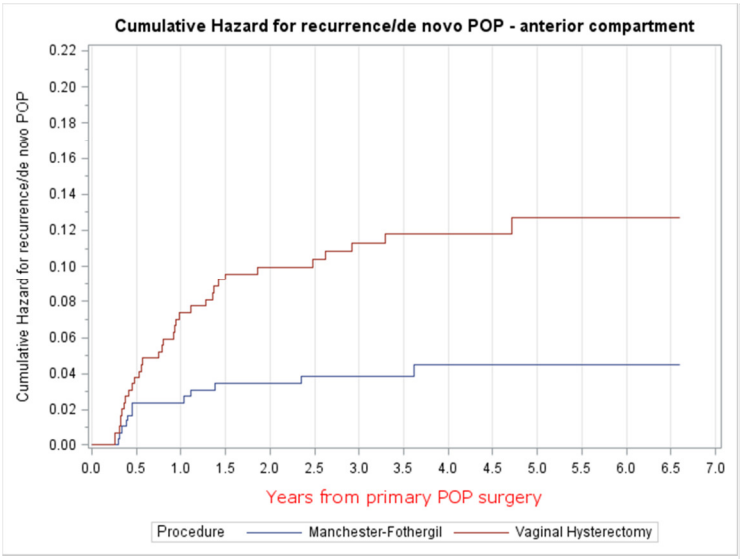

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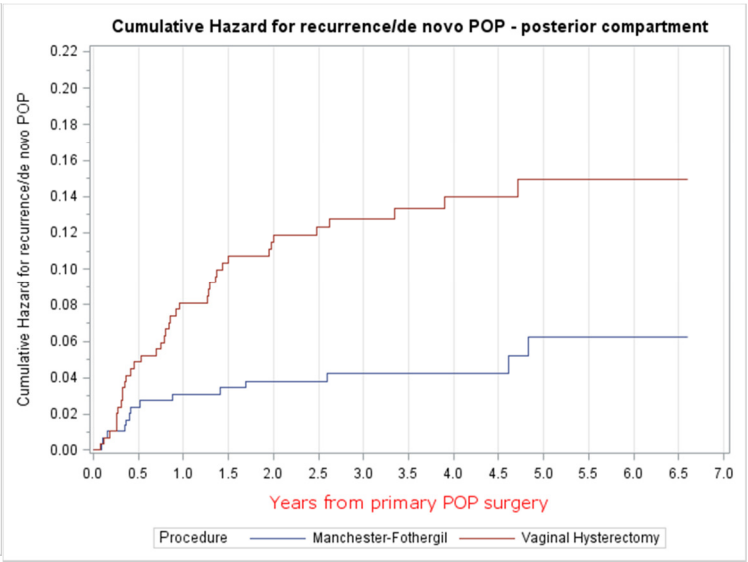

Fig. 12 Recurrence or de novo POP in relation to follow-up time

Cumulative Hazard Plots showing the cumulative hazard of recurrence or de novo POP as a function of time from surgery in any compartment (A), the apical (B), anterior (C) and the posterior (D) compartment.

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Complications

Perioperative complications were more frequent after VH, and there was a trend towards more postoperative complications as well, though this difference was not significant (Table 5). Minor complications (e.g. hematomas and pain) accounted for the majority of postoperative

complications. Six patients in the VH-group had an intra-abdominal bleeding with a blood loss of ≥ 1000 ml (median 1700 mL, range 1000- 3700 mL)), all requiring surgical treatment within 24 hours. In three patients laparoscopy was converted to open surgery to stop the bleeding. In the MP-group one patient had a hematometra and later a pyometra, which was seen in another patient too. Hospital administered antibiotic within 30 days from surgery was equally frequent in the groups (urinary tract infections not included). One patient in the VH-group was treated due to a vaginal infection and three patients in the MP-group were treated because of vaginal or cervical infection and one had an infected vaginal mucosal defect. In a patient from the MP-group an unacknowledged obstruction of the left ureter was discovered because of urosepsis and hydronephrosis. An acute nephrostomy was required, and later a JJ-catheter was inserted and removed six months postoperatively, and normal renal function gained. In the VH-group a suture removal was done in local anaesthesia and a suture was loosened in general anaesthesia.

Table 5 Complications

Complication	**MP-group n=295**	**VH-group n=295**	***P value*** [*]
Perioperative complications*, n patients* (%)	*0 (0)*	*8 (2.7)*	*0.007*
Suture cut/loosened perioperatively due to obstruction of ureter	0 (0)	4 (1.4)	
Organ lesion [†]	0 (0)	1 (0.3)	
Other [‡]	0 (0)	1 (0.3)	
Bleeding > 500 mL	0 (0)	2 (0.7)	
Postoperative complications*, n patients* (%)	*50 (16.9)*	*63 (21.4)*	*0.2*
Risk of postoperative complication, OR (95% CI) [##]	1.0 (ref.)	1.3 (0.9 - 1.9)	
Unaknowledged obstruction of ureter requiring surgery, n (%)	1 (0.3)	0 (0)	
Urinary retention, n (%) [§]	7 (2.4)	9 (3.0)	0.8
Hematometra/pyometra, n (%)	3 (1.0)	0 (0)	
Antibiotic treatment in hospital, n (%)	5 (1.7)	3 (1.0)	0.7
Bleeding, total n (%)	2 (0.7)	8 (2.7)	0.1
Superficial, n (%)	2 (0.7)	2 (0.7)	
Intra-abdominal, n (%)	0 (0)	6 (2.0)	0.03
Other complication requiring surgery, n (%)	0 (0)	3 (1.0)	

Minor complications, n (%)	50 (16.9)	57 (19.3)	0.5

MP Manchester-Fothergill procedure. *VH* Vaginal hysterectomy. [*]Fischer's exact test. [†]Bladder lesion. [ǂ]Missed surgical napkin removed laparoscopically during ongoing anesthesia.*CI* Confidence interval. [##]Logistic regression. [§]Urinary retention: Retention requiring treatment with intermittent catheterization/indwelling catheter.

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Pathological evaluation

As it is intended to leave a cervical stump of approximately one cm when performing a MP, no difference in cervical length was found for the amputated cervices for the MP-group (mean length 24.9 mm, range: 4-60 mms, n=270) and the cervices attached to the removed uteri for the VH-group (mean length 34.3 mm, range: 15-80 mms, n=136). Thus, a potential difference is expected to be insignificant. In the VH-group a small lymfocytic lymphoma was found in the removed uterus, nevertheless the patient had previously undergone examinations because of an increased M-component, and no further treatment was required.

During follow-up these cases occurred in the MP-group: One patient was diagnosed with a stadium IA endometrial adenocarcinoma which was surgically treated. Another patient had a complex endometrial hyperplasia with atypia not requiring any treatment by the end of follow-up. In addition, three more patients underwent hysterectomy. One because of suspicion of endometrial carcinoma, another due to symptomatic fibromas, and a third was a concurrent prophylactic procedure because of suspicion of ovarian cancer. No uterine malignancy was detected in any of the cases.

Study III – Economic outcomes

The total average costs at 20 months follow-up were 3,514 € after VH compared to 2,318 € after MP, corresponding to a difference of 1,196 € (95%CI: 927-1465 €) (Table 6). For VH costs related to the primary operation, complications, recurrences, and the total costs were significantly higher than for the MP. The cost of the primary surgery accounted for 80% and 82% of the total cost for VH and MP, respectively. Salaries (52.3% for VH and 56.9% for MP), costs of overnight hospital stay (21.5% for VH and 12.7% for MP), and costs related to use of the operating theatre (13.5% for VH and 14.6% for MP) constituted the main expense of the cost for the primary surgery. Time in operating theatre, duration of surgery and at PACU, and nights of hospitalization were all significantly longer for VH than for MP (Table 7).

When surgeries were analyzed according to the preoperative POP-Q stage in the apical compartment, it was seen that the average cost of surgery for POP-Q stage I and II was 2207 € for MP versus 3502 € for VH (P< 0.0001), and 2603 € versus 3545 € (P= 0.0075) for POP-Q stage III and IV for the MP and VH, respectively.

The cost difference seemed to be reasonably constant when looking at the entire follow-up of 80 months (Fig. 13).

The sensitivity analyses underline the conclusion that the MP is less expensive than VH (Fig. 14), as the cost difference between the operations is highly significant (P< 0.0001) in all the analyses.

Table 6 Total costs within 20 months of the primary surgery

	Total costs (€) VH-group	**n**	**Total costs (€) MP-group**	**n**	***P value***
Primary surgery	**825,630**	**295**	**560,680**	**295**	**<0.0001 ¤**
Surgeons (time of surgery + 30 minutes before/after surgery)	191,159	295	143,203	295	<0.0001 *
Operation nurses (time at operating theater)	94,799	295	69,670	295	<0.0001 *
Anesthetic nurse + 0.5 anesthetist (time at operating theater)	128,176	295	94,199	295	<0.0001 *
0.5 PACU nurse (time at PACU)	17,361	295	12,084	295	<0.0001 *
Operating theater	111,188	295	81,714	295	<0.0001 *
Overnight stays	177,648	259	71,386	117	<0.0001 *
Utensils	22,795	295	19,719	295	<0.0001 *
Pathological evaluations	66,867	295	50,976	295	<0.0001 *
Contacts (control visits)	14,941	252	17,729	260	0.04 *
CT urography related to primary operation	698	3	0	0	0.25 *
Complications	**91,661**	**74**	**58,518**	**56**	**0.02 ***
Postoperative bleeding (superficial or deep)	36,110	8	3,211	2	0.02 *
Unacknowledged obstruction of ureter	0	0	22,562	1	1.0 *
Urinary retention	14,471	9	17,644	7	0.8 *

Other	41,080	61	15,101	49	0.06 *
Recurrences	**94,285**	**49**	**27,558**	**18**	**0.0001 ***
Urinary Incontinence ₸	**25,072**	**50**	**20,440**	**51**	**0.8 ***
Uterus-dependent	**0**	**0**	**16,677**	**51**	**<0.0001 ***
Pathological tests	0	0	3,853	49	<0.0001 *
Contacts + procedures	0	0	12,824	13	0.0002 *
Total costs	**1,036,648**	**295**	**683,874**	**295**	**<0.0001 ¤**
Mean costs per patient	**3,514**		**2,318**		

*Wilcoxon signed rank sum. ¤ t-test. *VH* Vaginal hysterectomy. *MP* Manchester-Fothergill procedure. *PACU* post-anesthesia care unit. *₸* De novo or persistent urinary incontinence.

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Table 7 Time at operation theatre, duration of surgery, time in PACU and nights of hospitalization

	VH-group	**MP-group**	**P-value***
Time at operation theatre (min.), median (range), [quartiles 5%; 95%]	165 (95-331), [110; 245] n = 285	120 (70-254), [84; 185] n = 202	<0.0001
Duration of surgery (min.), median (range), [quartiles 5%; 95%]	95 (36-236), [49; 163] n = 285	65 (18-162), [34; 140] n = 202	<0.0001
Time in PACU (min.), median (range), [quartiles 5%; 95%]	110 (0-415), [55; 245] n = 279	81 (1-310), [25; 177] n = 182	<0.0001
Nights of hospitalization, median (range), [quartiles 5%; 95%]	1 (0 – 7), [1; 3] n = 295	0 (0 – 8), [0; 2] n = 295	<0.0001

*Mann Whitney (Wilcoxon) 2-sided, all durations are in minutes. *VH* Vaginal hysterectomy. *MP* Manchester-Fothergill procedure. *PACU* post-anesthesia care unit.

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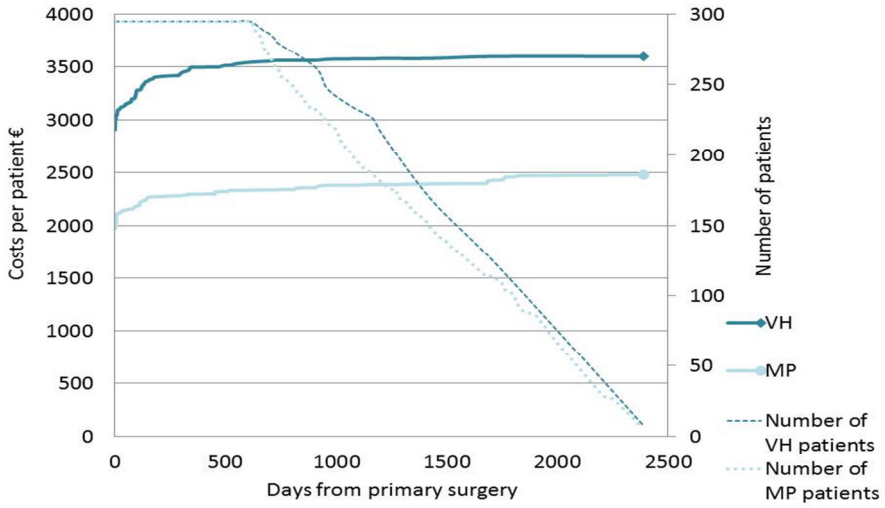

Fig. 13 Costs per patient and number of patients over time

Unbroken lines show the mean costs per patient at different times. *Dotted lines* show the number of patients remaining in the cohort at different times. Costs are weighted by the number of patients remaining at follow-up.

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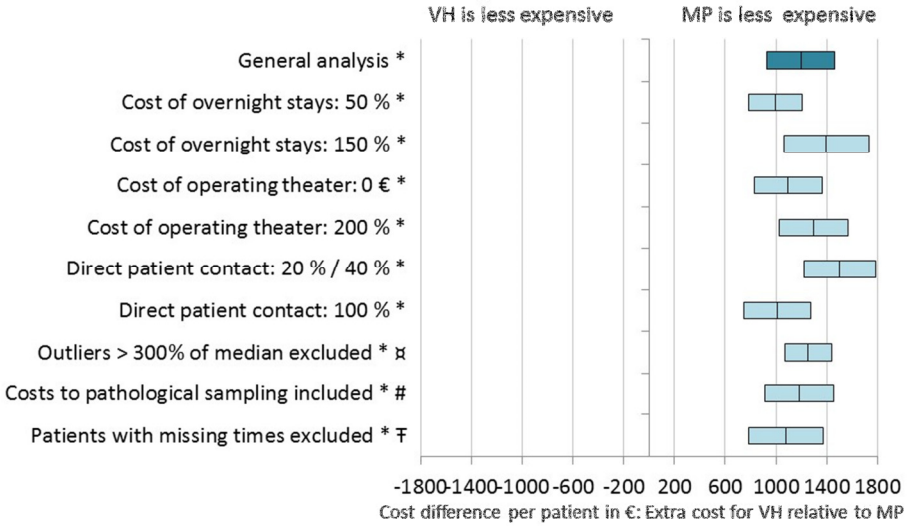

Fig.14 Sensitivity analysis (T-test)

Center line in each box is the mean. *The outer lines* indicate 95% CI. *p <0.0001. ¤Five VHs were >300% of the median costs of VH and six MPs were >300% of the median costs of the MP. These patients and their matches were excluded from the sensitivity analysis on outliers. #57 smears/tissue samples were done within 20 months of surgery in the MP-group, and the costs are included in the analysis. ₸129 patients had missing information on duration and inclusive matches 250 patients were excluded, leaving 340 patients for analysis.

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Conclusion

Study II

The MP is more durable than VH for all compartments, and fewer perioperative complications were related to MP compared to VH. Intra-abdominal bleeding only occurred after VH, and postoperative uterine malignancy was very rare after the MP.

Study III

The MP is significantly less costly than VH in the treatment of apical prolapse, hence substantial economic resources can be saved by choosing the MP over VH.

Discussion

Evidence and variation in strategy for surgical repair of vaginal apical prolapse

The choice of surgical technique for treatment of apical prolapse varies highly internationally. Due to the lack of evidence surgical decisions most likely rely on the surgeon's personal training and experience level, local tradition and perhaps the patient's preference. Generally, surgeons are familiar with the technique of hysterectomy, whereas not all have any experience regarding the MP and other procedures.

The variety in surgical strategy is reflected in study II, as a notable difference was seen between the hospitals. Two of the departments mainly performed VHs whereas the other two preferred the MP. This is interesting since it is found within a very small geographical area, hence is seems reasonable to assume education and surgical training of doctors to be equal. Also, no difference in the surgeon's experience level between the two procedures was found indicating that none of the procedures were primarily done by less experienced surgeons. Accordingly, surgical decisions must rely on other parameters. In general, it seems there is a tendency for some surgeons to prefer uterine-preserving procedures in case of low degrees of apical prolapse (POP-Q stage I or II), and it might seem obvious to choose the MP over VH when cervical elongation is present. Contrary, no specific procedure is generally preferred among surgeons when it comes to higher stages of apical prolapse (POP-Q stage III or IV)(3). Our study showed that the MP is durable for all stages of apical prolapse (28% had a stage III or IV), which is supported by other studies (92)(88). We did not have information regarding all POP-Q points but only POP-Q stage, thus a potential difference in cervical length between the groups can be hidden. However, the difference in cervical elongation degree was assumed to be negligible in our study. Therefore, the MP should not be restricted to cases of lower degrees of apical prolapse with cervical elongation, which is further supported by the fact that the amputation of the cervical piece is not the crucial step when performing a MP.

Another aspect when considering choice of surgical method is the patients' preference. Two recent studies have shown a great demand for uterus-preserving procedures among patients (111) (112). It was found that 60% (111) would prefer another surgical option to hysterectomy in case the alternative option was equally efficient, and only 20% preferred hysterectomy when outcomes of the procedures were considered equal (112).

Some surgeons prefer VH to uterine-preserving procedures to eliminate the risk of future uterine pathology including endometrial cancer. The risk of endometrial cancer is known to be 0.24-0.35% (113)(114)(68), and a recent decision analysis (68) did not show any benefits from concomitant hysterectomy in case of colpocleisis. In other words, one in 300-400 women with an intact uterus will be diagnosed with an endometrial cancer at some point. This is in accordance with our study where one case (0.3%) of endometrial cancer was discovered. There is no evident reason to presume that patients who have undergone uterine-preserving surgery have an elevated risk of endometrial cancer or pathology compared to the general female population. Still, there is a theoretical risk of delayed diagnostics in case of cervical stenosis, yet a higher rate of uterine malignancy after uterine-preserving procedures has not been proven. Based on this it does not seem reasonable to choose hysterectomy over uterine-preserving procedures to avoid future malignancy.

Clinical outcomes

Recurrence and de novo POP

In study II we found that the MP is more durable for all compartments than VH. After VH the relative risk of recurrence in the apical compartment was 10 (1.3-78.1) compared to after the MP. This equals a recurrence rate of 5.1% after VH, corresponding to the rate of 4-7% shown in the literature (49)(78)(82). Contrary, the recurrence rate after the MP was low (0.3%) which is in agreement with our findings in study I and other previous studies (82)(115). It is well-known that recurrences in the anterior compartment are generally frequent after POP surgery (82)(115), though it was encouraging to find that only 4.1% had recurrence in the anterior compartment after MP in study II. This rate was doubled after VH (8.3 %). Similar findings were done for the posterior compartment, as recurrences were infrequent (1.4%) after MP compared to after VH (8.5%). For patients not undergoing a concomitant anterior colporrhaphy at the time of primary surgery, only patients in the VH-group were in high risk of de-novo POP in the anterior compartment (35.5%), whereas the risk was low (3.4 %) in the MP-group. The risk was higher too for the posterior compartment after VH (15.3% vs. 5.9%). The single existing RCT (116) comparing the two procedures did not find any difference in the postoperative POP-Q C-point or quality of life scores between the procedures, though the study is small. A significant shorter time to re-surgery due to recurrence after VH was shown in a matched cohort study (81), nevertheless the sample size was smaller but follow-up longer compared to our study.

It is becoming commonly accepted that uterine prolapse is not a problem of the uterus alone but of its ligamental attachments. In line with this, the increased rate after VH indicates that removal of the uterus deteriorate the vaginal suspension including the vaginal support level I (117). The differences in recurrences and de novo POP between the two procedures is of clinical importance as the high rates after VH are accompanied by a high rate of re-surgery. When comparing the rate of re-surgery due to recurrence in the apical compartment specifically, no other procedure was found to have a re-surgery rate as low as the MP in our study. Re-surgery rates equal to the rate after VH (2.7%) was seen for laparoscopic sacrohysteropexy (2% at 2.1 years follow-up) (33), open sacrocolpopexy and laparoscopic sacrocolpopexy analyzed as a single group (2.3% at a follow-up of up to 27 months)(40), for laparoscopic sacrocolpopexy specifically (3.5% at 60 months postoperatively) (39), and for transvaginal mesh repair pooled as a single group (2.9% at two years or more after surgery)(65). Only laparoscopic suture hysteropexy had a substantially higher re-operation rate of 16% at a follow-up of less than 20 months (47).

Complications

Perioperative complications only occurred after VH in study II, however the rate was low (2.7%). Far more serious were the potentially life-threatening intra-abdominal bleedings associated with 2% of the VHs. In agreement with this, a higher rate of severe complications after VH (1.9% vs. 0.2%) was shown in a recent study (92). In study I we also found more complications after VH, supported by a register study in which an increased risk of further surgery due to complications within 30 days of surgery was seen after VH (118). Similarly, an intra-abdominal bleeding requiring laparotomy occurred in 2.3% after laparoscopic suture hysteropexy (47), and for sacrocolpopexy an intra-abdominal bleeding was found in 4.4% (45). A slightly lower risk of intra-abdominal bleeding was seen after posterior intravaginal slingplasty where 1.6% needed blood transfusion (66). Contrary, the risk of perioperative rectal injury was higher for posterior intravaginal slingplasty 2.4% (64) compared to the MP and VH in our study, where no cases were seen. Due to cervical stenosis haematometra/pyometra occurred three times (1%) in the MP-group in our study, which is in agreement with previous studies (90)(91).

Economic outcomes

In study III we found a substantial difference in economic costs between VH and the MP, since a MP accounts for two-thirds of the mean cost of a VH, despite of the continuing costs related to preserving the uterus. This correlates well with the fact that VH is a more extensive surgery than the MP. Similarly, vaginal procedures for apical prolapse repair in general seem cheaper than abdominal procedures. One can think that costs related to uterus preservation might increase over time but we found that these costs were significantly higher for premenopausal than for postmenopausal women due to the decrease in procedures related to menstruation and cervix smears in the postmenopausal group. Besides, the costs related to uterus preservation were limited as they only constituted 2.4% of the total cost for a MP.

Economic analyses of POP surgeries are few, and differences in methodology make comparison difficult. In our study we conducted a simple activity-based costing analysis which is different from the standard cost-benefit, cost-effectiveness, and cost-utility analyses.

In a cost-benefit analysis the approach is whether an intervention leaves society as a whole better off by weighing up benefits (advantages) and disadvantages (costs). This assessment requires a full list of all benefits and costs for society, which is furthermore complicated by the obligation to measure all effects in monetary value, as some benefits (e.g. quality of life) and costs (e.g. dead) are hardly valued or quantified. For that reason, cost-benefit analyses can be controversial and are better avoided in health care economics in general. The cost-effectiveness analysis calculates the costs of a defined effect, and interventions compared are only allowed to have a single common output and no concurrent (side) effects. A cost-utility analysis is a specific kind of cost-effectiveness analysis in which the single common output is health benefits measured in Quality Adjusted Living Years (QALYs) (119). This would have been the ideal analysis in our study but unfortunately it was not possible due to our study design, as we did not have data on prolapse related quality of life for the cohort.

The costing analysis in our study was constructed to evince the actual hospital costs related to each procedure, as costs of treatment due to complications or other related conditions after hospital discharge were included. Since the Danish DRG-fees are based on average costs of treatment in a group of different interventions, they do not necessarily reflect the actual average costs for a specific intervention - or the costs associated with a specific patient within this group.

In 2017 the DRG-fee was 41.411 DKK for a VH and 12.521 DKK for a MP, respectively (120). In comparison the mean cost estimated in our study was 26.355 DKK (3,514 €) for a VH and 17.385 DKK (2,318 €) for a MP. In other words, a VH is 3.3 times as expensive as a MP based on DRG-

fees, whereas it is 1.5 as expensive according to our costing analysis. From a clinical perspective, the large difference in the reimbursement received by the surgical departments is inappropriate, as disproportionately greater economic resources are allocated to departments which perform VHs rather than MPs, thereby providing a *perverse incentive* to treat patients by performing VHs instead of MPs, because the surgical departments produce more DRGs that way. In general the Danish model of activity based financing tended to encourage a focus on activity rather than quality in health care (121). In line with this, a phenomenon known as *DRG-creep* emerged, as more comorbidity may have been reported by the hospital departments to increase the reimbursement (122). Furthermore, activity based financing may have encouraged more hospital admissions, out-patient visits and procedures. This increased the risk that physicians may perform interventions not strongly indicated (123). Some of the issues related to the Danish model of activity based financing mainly apply to countries with a similar financial model. Differences in financial models internationally can potentially lead to different clinical recommendations on choice of POP surgery, as more costly procedures might predominantly be performed in non-public health care systems financed by private insurance companies.

At last, all health care systems face the same economic challenges for the future, as the costs related to POP surgery, among others, will increase substantially within a few years. Accordingly, the resource use in health care needs to be optimized to gain more health benefits at the same cost, alternatively the same benefit at a lower cost. Thus, the need for surgeons to balance benefits from prolapse surgery against possibly differences in costs is growing.

Strengths and limitations

Study I

The systematic review followed the MOOSE guidelines to secure transparency and reduce the risk of bias. To ensure a throughout and reliable systematic literature search, our search was assisted by a professional scientific librarian. No studies were excluded due to language, study design, methodology, sample size, follow-up, or year of publication. All publications in languages other than English were translated and screened. As a consequence of our broad inclusion criteria and the very scarce literature, a large inter-study variation was seen. The studies were highly heterogeneous concerning study design, sample size, outcomes and follow-up time. Of the included studies only one was a randomized controlled trial (RCT) which furthermore had a small sample size. The included studies were small in general, and almost half

of them were 20 years old or more, making comparison difficult due to changes in hospital routines and technological development over time. The divergence in outcomes assessed was remarkable. Only a third of the studies examined the re-operation and conservative re-intervention rate, whereas the main part evaluated operative outcomes such as operating time and duration of hospital stay. Variations in the surgical procedures were seen too, including the frequency of concomitant anterior and posterior colporrhaphy, and in some studies no information was available on the specific technique used in in the two procedures. Furthermore, the great inter-study variations made conduction of a meta-analysis impossible. Hence, the review cannot serve as a basis for any clinical recommendations.

Study II and III

So far, study II is the largest comparing VH to the MP in apical prolapse repair, and to our knowledge study III is the only to compare the economic costs of the two procedures. The study cohort included a very large number of unselected patients operated within only five years, and the matching on age and preoperative prolapse stage in the apical compartment eliminated confounding by the matching factors and ensured comparability between the groups. It is well-known that the incidence of POP grows with increasing age (11)(124), and in general age is in itself a strong confounder of disease. When assessing outcomes of POP surgery, matching on preoperative POP-Q stage is crucial. Differences in preoperative prolapse stage could possibly affect the surgical indication and hence, choice of surgical procedure. Our study design was suitable for examining outcomes which are not particularly frequent, as was the case for our outcomes. Contrary, RCTs are not realistic or cost-effective in examining infrequent outcomes, and inappropriate for economic analyses. Only women operated at one of the four hospitals in the Capital Region were included in our cohort. These hospitals were selected because they were considered comparable as they all had a specialized urogynecological unit and were located within a small geographical area, thus demographics were assumed to be equal. Moreover, data from the electronic patient records were easily accessible as a single electronic health information system was used throughout the Capital Region. The data completeness and validity was high for all used registries, and thorough review of all patient records provided data on events concerning the surgeries as well as subsequent events. It has been shown that objective anatomical results alone do not correlate well with patients' evaluation of overall improvement (125). Consequently, we defined recurrence and de novo POP as POP treated with pessary or surgery and/or POP-Q stage II with POP symptoms as both imply symptomatic POP which has made the patient encounter for examination. Our third definition,

POP-Q stage ≥ III independent of POP symptoms rely on the fact that most patients experience POP symptoms when the prolapse reaches the hymen or beyond. Since the most distal point of the prolapse does not reach the hymen in all POP-Q stage II prolapses, we defined recurrence or de novo POP as POP-Q stage ≥ III to ensure that the prolapse reached the hymen or below, which is in agreement with international recommendations (125). We analyzed high and low uterosacral ligament suspension as a single group, which is a potential limitation, however, equal outcomes for these two suspension types was found in a large study from 2017 (51).A trained urogynecologist attended nearly all operations, indicating a high and uniform degree of expertise in the groups. Around 80% of recurrences in both groups occurred within 20 months from the primary surgery, and the cost difference seemed to continue constantly until 80 months after the primary surgery, suggesting a sufficient follow-up period. The costing analysis was based on actual costs and not estimated of predicted costs as is the case for DRG-fees. Furthermore, the sensitivity analysis underlined the validity and robustness of the cost difference between the two procedures.

Due to use of different electronic health information systems we did not have access to data from private practitioners or gynecologists, hence the rate of recurrent or de novo POP might be higher than shown in this study. This affected the costing analysis too, as costs of POP examinations and treatments performed outside hospitals were not included, why the actual costs were probably higher than demonstrated. Though, we find it unlikely that the share of patients cared for elsewhere differed between the groups. Costs related to sick leave was also not included in the costing analysis. Thirty-six percent of patients were older than age of retirement. We assumed that reporting of major complications was equal between the departments but information bias cannot be ruled out. Durations were calculated for those patients with missing information on the duration of surgery, time at the operation theatre and in PACU. The main part of surgeries with missing information was out-patient surgery, in general associated with shorter durations than for surgery in the central operating theatre. Hence, calculations might be overestimated resulting in an underestimation of the cost difference between the two procedures. Finally, the selection of hospitals assures comparability between the included patients but it might slightly affect the external validity.

Conclusions

The literature comparing VH to the MP in the treatment of apical prolapse is very scarce but in general in favor of the MP, though evidence is lacking.

Our study showed that the MP is more durable than VH for all compartments, as recurrence or de novo POP was significantly more frequent after VH both in any and each compartment individually. Also, the MP showed to be efficient and durable for all stages of apical prolapse. The MP was found to be safer than VH since perioperative complications were more frequent after VH, and intra-abdominal bleeding only occurred in this group.
Moreover, the incidence of postoperative uterine malignancy was shown to be very low. Pathological evaluation of the tissue removed by surgery indicated no difference in the preoperative cervical length between the groups. Thus, MP is not an operation addressing women with cervical elongation only. Variation in surgical preference was seen between the included hospitals, affirming that no consensus on a surgical strategy exists, not even within a very small geographical area. We found that VH is significantly more expensive than the MP in treatment of apical prolapse, and the cost difference seemed to be reasonably constant when looking at the entire follow-up of 80 months. Thus, considerable economic resources can be saved in health care budgets if the MP is chosen over VH.
Taken together, our results suggest that the MP should be preferred to VH with uterosacral ligament suspension in apical prolapse repair for medical and economic reasons.

Perspectives

Surgeons are obliged to ensure the quality of surgical treatment by making evidence based decisions and reducing personal interests and preferences. This thesis emphasizes the general lack of consensus regarding a surgical strategy for apical prolapse repair, and especially the very scarce literature comparing VH to the MP. It contributes decently to the literature as study II is the largest to date comparing the clinical outcomes of the two procedures, and study III the only to evaluate the related economic costs. The knowledge provided is vital to come closer to a clinical recommendation for surgical repair of apical prolapse ensuring all affected women the best possible postoperative outcome with the least risk of recurrence, need for re-intervention, and complications.

Study III highlights the potential difference in economic costs between surgical procedures, and underlines the need to balance the advantages of a surgical treatment not only against the risks of complications, recurrence and need for re-intervention but also against the economic costs when making surgical decisions in the future.

Future research

As the RCT is the highest ranking in the evidence hierarchy, it is tempting to conduct a RCT comparing the outcomes of VH and the MP. Conducting RCTs comparing surgical procedures is a very controversial topic, though. A great share of patients might not be willing to participate, and a significant number of patients often drop out if they are not randomized for the operation they hope for, which can lead to selection bias. Based on our results we do not find it ethically acceptable to randomize between VH and the MP, and hence a well-designed RCT comparing the two procedures will probably never be conducted.

Aside from this, our studies have identified the following areas which need further research:

- Large long-term prospective follow-up studies comparing VH with the MP to confirm our results and strengthen evidence.
- A study assessing the frequency of different surgical procedures for apical prolapse repair internationally to identify which procedures are most frequently used worldwide.
- Studies comparing the MP with the most frequently performed uterine-preserving procedures including hysteropexy and mesh suspension kits.

- Studies comparing the MP with the most frequently performed non-uterine-preserving procedures including colpopexies.

In general future studies should include economic evaluation as an outcome when comparing surgical treatments for POP.

Summary

This PhD thesis is based on three original papers. The studies were conducted in 2015 – 2018 during my employment as a research fellow at the Department of Obstetrics and Gynecology at Herlev and Gentofte University Hospital, Denmark.

Pelvic organ prolapse (POP) affects millions of women worldwide. In apical prolapse there is a descent of the cervix, uterus, or vaginal vault in previously hysterectomised women. It is a benign condition but it is able to reduce the quality of life substantially. In many women surgical treatment is required to cure POP symptoms, and in Denmark the lifetime risk of POP surgery is 19% for women aged 80 years. The aim of POP surgery is to restore the normal vaginal anatomy and thereby reduce symptoms.

Due to lack of evidence, the surgical strategy for repair of apical prolapse varies highly internationally, and vaginal hysterectomy (VH) has been the most common surgical treatment for years. Together with the Manchester-Fothergill Procedure (MP) it is among the most frequently performed surgeries for apical prolapse in Denmark.

It has been forecasted that the annual costs associated with POP surgery will grow at twice the rate of population growth in the US and Europe during the next decades, amongst others due to the aging population.

The overall aim of this thesis was to compare VH to the MP as a treatment of apical prolapse. Moreover, we estimated the hospital costs related to the two procedures.

In **study I** we conducted a systematic review of the literature comparing VH to the MP as a treatment of apical prolapse. We found the existing literature to be very scarce and studies highly heterogenous, though in general in favour of the MP. More anatomic recurrences in the apical compartment were seen after VH, and the re-operation and conservative re-intervention rate were higher too. Furthermore, the operating time was longer and the postoperative blood loss larger for VH.

Study II and III were based on the same matched historical cohort including women with apical prolapse who had a VH or MP done in one of four public hospitals in the Capital region of Denmark in 2010-2014. All participants were followed from the date of surgery till recurrence, de novo POP or hysterectomy (for the MP-group only), alternatively to August 31st 2016,

whichever came first. In total 295 participant pairs were matched on preoperative POP-Q stage in the apical compartment and age. Follow-up ranged from 20 to 80 months. The study cohort was identified through the Danish Urogynecological Database (DugaBase). The Danish Hysterectomy and Hysteroscopy Database was used to identify and exclude patients registered with concurrent indications to VH. Data was obtained from the DugaBase, the Danish Anaesthesia Database, the Danish National Pathology Registry and Data Bank, and the corresponding electronic medical records.

Study II was a matched historical cohort study. We found recurrence or de novo POP to be significantly more frequent after VH both in any and in each compartment individually. In any compartment recurrence or de novo POP was seen in 18.3% after VH compared to 7.8% after MP (P=0.0002) (HR=2.5, 95% CI: 1.3-4.8). The relative risk of recurrence in the apical compartment specifically was 10 after VH (95% CI: 1.3-78.1), as recurrence occurred in 5.1% after VH and 0.3% after the MP (P=0.0004).
Perioperative complications were also more frequent after VH (2.7%) than the MP (0%) (P=0.007), and so was postoperative intra-abdominal bleeding (2.0% vs. 0%, P=0.03).
A small lymfocytic lymphoma was found in the removed uterus in one patient (0.3%) from the VH-group, and during follow-up one patient (0.3%) from the MP-group was diagnosed with a stadium IA endometrial adenocarcinoma.
In **study III** we conducted an activity-based costing analysis in which we found that the total average costs at 20 months follow-up were 3,514 € for a VH compared to 2,318 € for a MP, corresponding to a difference of 1,196 € (95% CI: 927-1465 €) (P<0.0001). When the primary surgery only was analyzed, the cost difference was 898 € (95% CI: 818-982) (P<0.0001).
The cost difference seemed to be reasonably constant in the long run when looking at the entire follow-up of 80 months.
For VH the time in the operating theatre, duration of surgery, stay in PACU, and hospital stay were all significantly longer than for the MP.

In conclusion, we found that the MP is more durable than VH for all compartments. It is also associated with fewer perioperative complications than VH, and no cases of intra-abdominal bleeding were seen after the MP. Furthermore, the incidence of postoperative uterine malignancy was very low. VH is significantly more expensive than the MP in treatment of apical prolapse, thus considerable economic resources can be saved if the MP is chosen over VH in the treatment

of apical prolapse. The outcomes of this thesis suggest that the MP should be preferred to VH with uterosacral ligament suspension in apical prolapse repair.

Resumé

Denne ph.d.-afhandling er baseret på tre artikler. Studierne blev udført i 2015 – 2018 under min ansættelse som klinisk assistent ved Gynækologisk Obstetrisk Afdeling på Herlev og Gentofte Universitetshospital i Danmark.

Millioner af kvinder verden over har genitalt prolaps (POP). Apikalt prolaps er en nedsynkning af cervix, uterus eller vaginaltoppen hos tidligere hysterektomerede kvinder. Det er en benign tilstand, som dog kan reducere livskvaliteten betydeligt. For mange kvinder er kirurgisk behandling nødvendig for at kurere prolapssymptomerne, og i Danmark er risikoen for prolapskirurgi 19 % for 80-årige. Formålet med prolapskirurgi er at genskabe den normale vaginale anatomi og derved reducere symptomerne.
På grund af manglende evidens er der internationalt stor variation i den kirurgiske strategi til behandling af apikalt prolaps, og vaginal hysterektomi (VH) har i årevis været den mest anvendte kirurgiske behandling. I Danmark er VH sammen med Manchester-Fothergill-operationen (MP) blandt de hyppigst udførte operationer. Det er estimeret, at de årlige udgifter forbundet med prolapskirurgi vil stige dobbelt så hurtigt som befolkningstilvæksten i USA og Europa i løbet af de næste årtier, bl.a. på grund af den aldrende befolkning.
Det overordnede formål med afhandlingen var at sammenligne VH med MP i behandlingen af apikalt prolaps. Derudover undersøgte vi hospitalsudgifterne forbundet med hver af de to operationer.

I **studie I** lavede vi et systematisk review af den litteratur, der sammenligner VH med MP i behandlingen af apikalt prolaps. Den eksisterende litteratur var meget begrænset, og studierne meget heterogene, men dog i MPs favør. Der var flere anatomiske recidiver i det apikale kompartment efter VH, og både re-operationsraten og den konservative re-interventionsrate var højere. Ydermere var operationstiden længere, og det postoperative blodtab større efter VH.

Studie II og III var baseret på den samme matchede historiske kohorte, som inkluderer kvinder, der har fået foretaget en VH eller MP på et af fire offentlige hospitaler i Region Hovedstaden i Danmark i 2010-2014 pga. apikalt prolaps. Alle deltagere blev fulgt fra operationsdatoen og frem til eventuelt recidiv, de novo prolaps eller hysterektomi (kun for MP-gruppen), alternativt til den 31. august 2016. I alt blev 295 deltagerpar matchet svarende til den præoperative

prolapsgrad i det apikale kompartment og alder. Follow-up svingede fra 20 til 80 måneder. Studiekohorten blev identificeret via Dansk Urogynækologisk database (DugaBasen). Dansk Hysterektomi og Hysteroskopi Database blev brugt til at identificere og ekskludere patienter, som var registreret med en anden samtidig indikation for hysterektomi. Data stammede fra DugaBasen, Dansk Anæstesi Database, Patobank og patienternes elektroniske journaler.

Studie II var et matchet historisk kohortestudie. Recidiv og de novo prolaps var signifikant hyppigere efter VH for både et hvilket som helst kompartment (any compartment) og for hvert kompartment isoleret set. I et hvilket som helst kompartment (any compartment) havde 18,3 % recidiv eller de novo prolaps efter VH sammenlignet med 7,8 % efter MP (P=0,0002) (HR=2,5, 95 % CI: 1,3-4,8). Den relative risiko for recidiv specifikt i det apikale kompartment var 10 efter VH (95% CI: 1,3-78,1), eftersom recidiv forekom hos 5,1 % efter VH og 0,3 % efter MP (P=0.0004). Perioperative komplikationer var også hyppigere efter VH (2,7 %) end efter MP (0 %) (P=0.007), hvilket også gjaldt for postoperativ intraabdominal blødning (2,0 % vs. 0 %, P=0,03). I den fjernede uterus fra en patient (0,3 %) i VH-gruppen blev der fundet et lille lymfocytisk lymfom, og i løbet af follow-up perioden blev en patient (0,3 %) fra MP-gruppen diagnosticeret med et stadium IA endometrielt adenokarcinom.
I **studie III** lavede vi en aktivitetsbaseret omkostningsanalyse, hvor vi fandt, at den totale gennemsnitsudgift ved 20 måneders follow-up var 3514 € for en VH sammenlignet med 2318 € for en MP svarende til en forskel på 1196 € (95 % CI: 927-1465 €) (P<0,0001). For operationen alene var forskellen 898 € (95 % CI: 818-982) (P<0,0001). Når udgifterne til de to operationer blev gjort op for hele follow-up perioden på 80 måneder, så det ud til, at udgiftsforskellen var nogenlunde konstant på længere sigt.
Varigheden af opholdet på operationsstuen, det kirurgiske indgreb, opholdet på opvågningen og selve hospitalsopholdet var alle signifikant længere for VH.

Sammenfattende fandt vi, at MP giver bedre resultater i alle kompartments end VH. MP er desuden forbundet med færre perioperative komplikationer, ligesom der ikke sås nogle tilfælde af intraabdominal blødning. Forekomsten af postoperativ malignitet i uterus var meget lav. VH var signifikant dyrere end MP, hvorfor betydelige økonomiske ressourcer kan spares, hvis MP udføres frem for VH i behandlingen af apikalt prolaps. Resultaterne af denne afhandling taler dermed for at vælge MP frem for VH med uterosakral ligament suspension i behandlingen af apikalt prolaps.

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Appendix

Papers I-III

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REVIEW ARTICLE

The Manchester procedure versus vaginal hysterectomy in the treatment of uterine prolapse: a review

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Abstract
Introduction and hypothesis Uterine prolapse is a common health problem and the number of surgical procedures is increasing. No consensus regarding the surgical strategy for repair of uterine prolapse exists. Vaginal hysterectomy (VH) is the preferred surgical procedure worldwide, but uterus-preserving alternatives including the Manchester procedure (MP) are available. The objective was to evaluate if VH and the MP are equally efficient treatments for uterine prolapse with regard to anatomical and symptomatic outcome, quality of life score, functional outcome, re-operation and conservative re-intervention rate, complications and operative outcomes.
Methods We systematically searched Embase, PubMed, the Cochrane databases, Clinicaltrials and Clinical trials register using the MeSh terms "uterine prolapse", "uterus prolapse", "vaginal prolapse" "pelvic organ prolapse", "prolapsed uterus", "Manchester procedure" and "vaginal hysterectomy". No limitations regarding language, study design or methodology were applied. In total, nine studies published from 1966 to 2014 comparing the MP to VH were included.
Results The anatomical recurrence rate for the middle compartment was 4–7 % after VH, whereas recurrence was very rare after the MP. The re-operation rate because of symptomatic recurrence was higher after VH (9–13.1 %) compared with MP (3.3–9.5 %) and more patients needed conservative re-intervention (14–15 %) than after MP (10–11 %). After VH, postoperative bleeding and blood loss tended to be greater, bladder lesions and infections more frequent and the operating time longer.
Conclusions This review is in favour of the MP, which seems to be an efficient and safe treatment for uterine prolapse. We suggest that the MP might be considered a durable alternative to VH in uterine prolapse repair.

Keywords Uterine prolapse · Surgery · Vaginal hysterectomy · Manchester procedure · Efficacy · Safety

Introduction

The prevalence of anatomical uterine prolapse is 14.2 % in postmenopausal women in a large population-based study [1]. The lifetime risk of undergoing at least one operation for pelvic organ prolapse or urinary incontinence is 11–20 % [2, 3], and, owing to the aging population in most western countries, the number of operations performed has been increasing over the last decade [4]. In the USA around 350,000 prolapse surgeries are performed annually, of which around 50 % include repair of prolapse in the middle compartment [5].

Despite great activity, no consensus regarding the surgical strategy for repair of uterine prolapse exists internationally, and the topic remains controversial. The surgical procedures vary greatly worldwide. However, vaginal hysterectomy (VH) tends to be the preferred surgical procedure for uterine prolapse repair in the world today [6, 7]. The Manchester procedure (MP) is a uterus-preserving method that has proven durable and safe [8], and may be considered a reasonable alternative to hysterectomy as a treatment of uterine prolapse. Most MPs performed today are modified versions of the original MP first performed in 1888. The original MP consisted of

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an amputation of the cervix combined with an anterior and posterior colporrhaphy. Later, the technique was modified by de-attachment of the cardinal ligaments, which, after cervix amputation, are sutured to the corpus–cervical zone to keep the uterus elevated. An anterior colporrhaphy is routinely performed and, when indicated, a posterior colporrhaphy too. In cases of pronounced cervical elongation, cervix amputation can be undertaken as an isolated procedure without concomitant colporrhaphy.

The objective of this review is to compare VH with the MP in the treatment of uterine prolapse regarding postoperative outcome, risk of complications, durability, recurrence of symptoms and need for re-surgery.

Materials and methods

We carried out a systematic review based on the following clinical questionnaire:

1. Population: women with uterine prolapse requiring surgical treatment
2. Intervention: surgical repair of uterine prolapse by either VH or the MP
3. Comparison: surgical repair by VH compared with repair using the MP
4. Outcomes: anatomical and symptomatic outcome in the same or another compartment, quality of life score, functional outcome, re-operation and conservative re-intervention rate, complications and operative outcomes

Search strategy

An extensive systematic search was carried out in PubMed, Embase and the Cochrane databases using the terms "uterine prolapse", "uterus prolapse", "vaginal prolapse", "pelvic organ prolapse", "prolapsed uterus", "Manchester operation/repair/procedure/method", "Manchester–Fothergill", "uterine prolapse and Manchester operation", "uterine prolapse and vaginal hysterectomy", and "Manchester operation and vaginal hysterectomy". The systematic search was assisted by a professional scientific librarian.

Further manual searches of the reference lists in relevant articles, books and reviews were carried out. No ongoing clinical trials comparing VH with the MP as a treatment of uterine prolapse were identified through the clinical registers, www.clinicaltrials.gov and www.clinicaltrialsregister.eu.

No limitations regarding language, study design, methodology, sample size number, follow-up or year of publication were applied. All non-English publications were translated and screened as described. Our search strategy was adapted to suit each database. The last search was undertaken on 10 June 2016.

Study selection

All the studies identified underwent abstract screening and those eligible were full-text screened. Studies were selected for the review if they met the eligibility criteria of comparing VH with the MP as a treatment for uterine prolapse. Studies were also considered eligible if they provided a comparison of more surgical procedures for the treatment of uterine prolapse, but only if VH and the MP were included, and if data for each procedure were available for individual analysis (Fig. 1).

Data extraction

Data were extracted from the studies included according to availability. Not all of the selected outcomes were examined or described in all the papers included. We extracted data on method, patient characteristics and outcomes (Table 1).

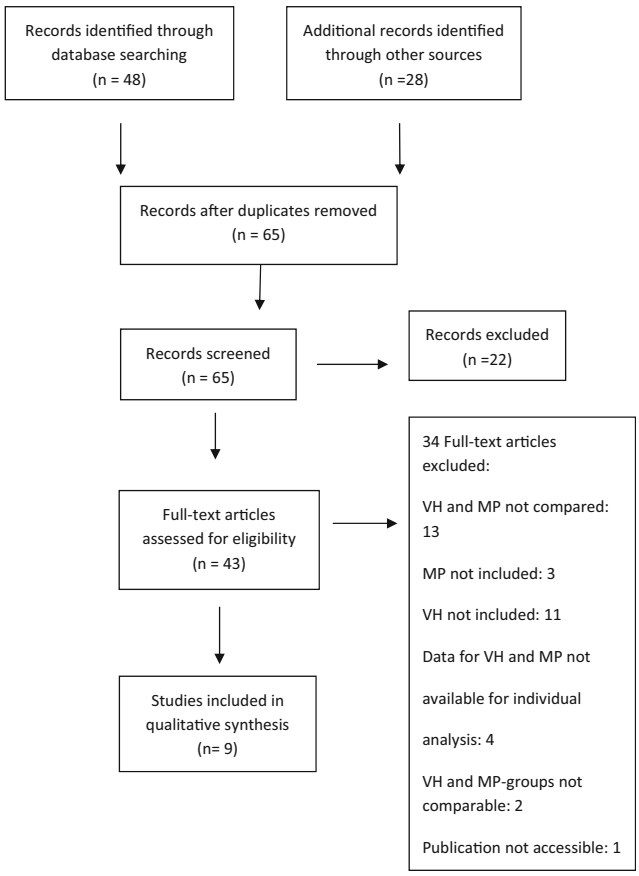

Fig. 1 Flow diagram following Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines showing the selection of studies comparing vaginal hysterectomy (VH) with the Manchester procedure (MP) as a treatment for uterine prolapse

Table 1 The studies included

References	Type of study	Number	Outcomes	Follow-up
Rubin [16]	Retrospective observational study, not matched	MP: 248 VH: 385 OP: 341 *N* (total): 974	Duration of hospital stay, blood loss, peroperative complications, postoperative complications	NS
Kalogirou et al. [19]	Retrospective, not matched	MP: 190 VH: 231 (+ anterior± positive repair) *N* (total): 421	Operating time, blood loss, blood transfusions, duration of hospital stay	Mean 3 years
Thomas et al. [18]	Retrospective observational study, matched by the year of surgery	MP: 88 VH: 105 (+ anterior ± positive repair) *N* (total): 201	Operating time, blood loss, blood transfusions, antibiotic treatment, duration of hospital stay, suprapubic catheter	No follow-up
Ottesen et al. [17]	Database Register study	MP: 1,813 VH: 2,663 *N* total =10,555	Duration of hospital stay, re-operation rate	No follow-up
Miedel et al. [10]	Prospective observational follow-up study	MP: 74 VH: 36 OP: 75 *N* (total): 185	Anatomical recurrence, operated compartment, new compartment occurrence, symptomatic at last visit, proceeded to further surgery	6–8 weeks, 1, 3 and 5 years
De Boer et al. [11]	Retrospective observational multicentre study, not matched	MP: 81 (modified MP) VH: 75 (+ anterior ± positive repair) *N* (total): 156	POP-Q, DDI, IIQ, UDI, operating time, blood loss, duration of hospital stay, urinary retention, catheterisation	1 year
Thys et. al. [15]	Retrospective matched cohort study, matched for prolapse grade, age, parity	MP: 98 VH: 98 *N* (total): 196	Morbidity, recurrence of POP, UDI, POP requiring re-intervention, DSQOL, sexual function	Median 6 years
Ünlübilgin et al. [9]	Randomised controlled trial	MP: 49 VH: 45 *N* (total): 94	Operating time, duration of hospital stay, QoL, recurrence of POP	6 weeks, 6 months, 1, 2, 3, 4, 5 years
Iliev [12]	Retrospective matched cohort study, matched for prolapse grade, age, parity	MP: 33 VH: 33 *N* (total): 66	Recurrence of POP, re-intervention, blood loss, operating time, complications, duration of hospital stay	1 year

MP Manchester procedure, *VH* vaginal hysterectomy, *OP* other procedures, *NS* not specified, *POP-Q* Pelvic Organ Prolapse Quantification System, *DDI* Defecatory Distress Inventory, *IIQ* Incontinence Impact Questionnaire, *UDI* Urogenital Distress Inventory, *DSQOL* disease-specific quality of life, *QoL* quality of life

Results

The Embase search identified 37 publications, and the search in PubMed resulted in 10 publications, all of them duplicates from the Embase search. Another duplicate publication was identified through a search in the Cochrane databases. Four of the identified studies were not in the English language, 1 of which was in Russian, 1 in Dutch, 1 in German and 1 in Danish.

Through other sources, an additional 28 records were found, leading to a total of 65 records for screening. After screening by abstract, 22 records were excluded. Full-text screening of 43 records was carried out, and 34 of these were excluded for the reasons listed in Fig. 1. Two studies were excluded because of a systematic difference between the VH and the MP groups, as patients in the VH group were consistently older than patients in the MP group. The records comparing more surgical procedures for the treatment of uterus prolapse, including VH and the MP, were excluded in case the data were pooled and not available for each procedure for individual analysis. Nine studies met the eligibility criteria and were included in the review (Table 1).

Of the studies included only 1 study was a randomised controlled trial, whereas 6 were retrospective cohort studies, 3 of which were matched. One study was a database register study

and another was a prospective observational follow-up study. The randomised controlled trial included has some limitations, as the sample size is small and only total vaginal length (TVL) and the POP-Q C-point were measured.

The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines were followed (Fig. 1).

The studies are highly heterogeneous in terms of study design, outcome measures, follow-up time and number of participating patients. Some only compared the VH with the MP and others compared a number of different surgical techniques with the VH and the MP being just two among more techniques. Some focused only on outcomes related directly to the surgical procedure, such as operating time, blood loss etc., whereas others had anatomical or symptomatic POP recurrence, need for re-intervention and patient satisfaction as their main outcomes. Regarding the MP, a number of variations of this procedure were performed, most of them modified from the original MP. In some of the studies, not all patients underwent an anterior colporrhaphy. In general, the performance of a posterior colporrhaphy varies as it is performed only on indication in some and consistently as a prophylactic procedure in others. Information on the MP method is missing in 3 studies, whereas an unmodified version of the MP was only performed in 2. Information on the exact VH method is lacking in 3 studies, but in general the vaginal vault was fixated to the uterosacral ligaments. In some studies, the VH was combined with either an anterior or a posterior colporrhaphy if indicated, and in others the VH was consistently combined with a prophylactic posterior colporrhaphy or a combined prophylactic anterior and posterior colporrhaphy.

Outcome measures

Anatomical outcome

A randomised controlled trial found a significantly shorter vaginal length after VH compared with MP (6.0 cm vs 8.3 cm, $p = 0.02$) [9], whereas a non-significant difference in the POP-Q point C was found (−6.0 vs −6.3, $p = 0.1$).

Surgical failure was defined as a POP-Q stage ≥ 2 at 5 years' follow-up by Miedel et al. [10]. The frequency of the anatomical recurrence of POP in any compartment was high, at 50 % after VH and 44.6 % after MP. The distribution of POP after VH was 73 % in the anterior compartment, 7 % vaginal vault prolapses and no isolated POP in the posterior compartment. In 20 %, POP was found in more than one compartment. After MP, the distribution showed 60 % in the anterior compartment, no isolated POP in the middle compartment, 15 % in the posterior compartment and 24 % in more than one compartment. The presence of anatomical recurrence was accompanied by symptoms in 33.3 % after VH and 57.6 % after MP.

In another study, recurrence was also defined as POP-Q stage 2 or more, independent of the compartment in which the prolapse appeared [11]. A high recurrence rate was observed for the anterior compartment, at 47.9 % in the VH group vs 46 % in the MP group. The recurrence rate in the middle compartment was 4 % in the VH group and no recurrence was seen in the MP group at the 1-year follow-up.

A third study found that 39 % of all recurrences were symptomatic, but that recurrence was not well-defined in this study [12].

Symptomatic outcome

Postoperative symptoms were assessed using the Urogenital Distress Inventory (UDI) [13, 14] by two studies.

An improvement in all domains of the UDI was shown for both operations by De Boer [11] when the preoperative score was compared with the score 1 year postoperatively. For POP symptoms, the decrease in score after surgical treatment was 41.9 (80 %) after VH vs 43.1 (84.7 %) for the MP. The postoperative score was 10.5 after VH and 7.8 after MP. However, the difference between the groups was not significant.

After a median follow-up of 6 years, Thys et al. [15] compared the UDI after the two procedures (11.6 after VH vs 11.0 after the MP), and in accordance with De Boer, did not show any significant differences between the groups.

Quality of life

Quality of life was only assessed in 2 studies, 1 of which found a significant improvement in prolapse-related quality of life scores after surgery in both groups (from 40 to 16 after both VH and the MP), but there were no significant differences between the groups [9]. The other study only assessed the quality of life postoperatively and did not show a significant difference between the groups either [15].

Functional outcome

Two studies examined the changes in urinary incontinence in relation to VH and the MP and both found an improvement in urinary incontinence from preoperatively to postoperatively in both groups [11, 15]. One of the studies showed a decrease in urinary incontinence from 48 % in both groups to 13 % after VH and 20 % after MP [15], whereas the other found a decrease in the UDI incontinence score of 6.4 after VH and 12.6 after the MP [11]. However, none of these differences were significant. No information was available on the proportion of cured or de novo incontinence in any of the studies.

Two studies examined sexual function and found no difference after either of the two procedures [9, 15].

Re-operation rate and conservative re-intervention rate

As a measure of procedure efficacy three studies evaluated the need for re-intervention consisting of the re-operation rate and the need for conservative re-intervention.

At a mean follow-up of 53.2 months, one study found a re-operation rate of 13.3 % after VH vs 9.5 % after MP. Most of the symptomatic anatomical recurrences were prolapse in another compartment and as such the re-operation was a primary prolapse surgery at a different site. It is not possible to distinguish between this type of surgery and repeat surgery at the same site for each procedure as data are pooled [10].

In another study, POP recurrence was defined as any stage of POP that required re-intervention. The median follow-up in the VH group was 75 months and 68 months in the MP group. The conservative re-intervention rate was 14 % after VH and 11 % after the MP ($p = 0.52$) and the surgical re-intervention rate was 9 % after VH vs 4 % after the MP ($p = 0.15$). After VH, 77.8 % of the re-operations were primary prolapse surgeries at a different site (anterior or posterior colporrhaphies without mesh) and 22.2 % repeat surgeries at the same site (sacral colpopexy). For the MP, the numbers were 75 % primary prolapse surgeries at a different site (anterior or posterior colporrhaphies without mesh) and 25 % repeat surgery at the same site (Amreich–Richter). The time to re-surgery was significantly shorter (8 months) after VH ($p = 0.03$), and the hazard ratio for POP recurrence was 2.5 (confidence interval: 0.8–8.0) in favour of the MP [15].

Symptomatic recurrence requiring treatment occurred in 15 % after VH and 10 % after the MP ($p = 0.28$) at 1-year follow-up, and conservative re-intervention was needed in 15 % after VH vs 10 % after the MP ($p = 0.28$). Re-operation was performed in 9.1 % after VH and 3.3 % after the MP. All re-operations were primary prolapse surgeries at a different site, with 1 anterior colporrhaphy and 2 posterior colporrhaphies after VH and 1 posterior colporrhaphy after the MP. Notably, the number of patients in this study was very low. The hazard ratio for POP recurrence in this study was identical to the hazard ratio in Thys et al., 2.5 (confidence interval: 0.8–8) in favour of the MP [12].

Complications

Perioperative complications

Injuries to the bladder occurred in 1–3 % after VH vs 0–0.4 % after the MP, whereas bowel lesions were seen in 0–0.5 % after VH compared with 0.4–1 % after the MP [16, 17].

Postoperative complications

Postoperative haemorrhage

Four studies determined postoperative haemorrhage (e.g. manifested as a haematoma), which occurred in 1–6 % after VH vs 0–3 % after the MP [10, 12, 15, 16]. These findings are in accordance with those of another study that found a significantly increased risk of further surgery after VH (6 % vs 3 %, $p = 0.0002$), because of postoperative bleeding, bladder injury and infection [17].

Infection

Oral antibiotic treatment for vaginal infection, abscess, urinary tract infection, renal infection or for unstated reasons was needed in 21.1 % in the VH group and 14.8 % in the MP group. A difference was seen for vaginal infection and abscess, as antibiotic treatment was given to 4.8 % after VH and none after the MP. However, this difference was not significant [18]. Another study explored postoperative urinary tract infection and showed a high rate of infections, with 30 % (10 patients) after VH vs 15 % (5 patients) after MP, with no significant difference between the groups [12].

Urinary retention

In one study the tendency towards delayed hospital discharge due to urinary retention was found to be lower after VH (8.6 % vs 17.1 %), but the difference was not significant [18]. In a recent study, urinary retention was seen in 19 % after VH compared with 25 % after the MP [12]. These numbers were slightly lower in another study, as 12 % in the VH group and 9 % in the MP group experienced urinary retention ($p = 0.3$) [11]. Notably, urinary retention was not defined in any of the studies.

Operative outcomes

Operating time

Five studies compared the operating time of VH with that of the MP and a significantly shorter operating time for the MP was found in all studies [9, 11, 12, 18, 19]. Some studies provided the mean operating time, whereas others provided the median time. The range for the mean/median operating time for the VH was 77.8 to 130 min vs 62.4 to 110 min for the MP. In general, the operating time was shorter for both procedures in the more recent studies.

Blood loss and blood transfusions

The mean perioperative blood loss was measured in five studies [11, 12, 16, 18, 19]. The range of the mean perioperative blood loss was 180–623 mL for VH vs 191–408 mL for the MP [14–16]. Four studies found greater blood loss for VH [11, 12, 16, 18], whereas one [19] found greater blood loss for the MP. In general, the blood loss for both procedures was lower in the more recent studies. Two studies appraised the need for blood transfusions after the surgical procedures, and more patients in the VH

group (11 %) needed blood transfusions compared with the MP group (4 %) [18, 19].

Duration of hospital stay

Duration of the hospital stay was assessed by 7 studies [9, 11, 16–19]. In 6, the patients had a longer hospital stay after VH compared with the MP. Only 1 study found a significantly shorter hospital stay after VH (a mean of 5.2 days vs 6.1 days respectively; $p = 0.018$) [11]. In general, the duration of the hospital stay was considerably shorter in the more recent studies.

Discussion

The literature comparing the MP with VH for the treatment of uterine prolapse is limited, and nearly half of the studies included in this review are 20 years old or more. The large timespan between the studies makes comparison difficult, as the surgical settings and routines have changed considerably over the years. In general, the studies are heterogeneous, which also contributes to difficulties with comparisons.

During our search, we identified two reviews on the surgical repair of uterine prolapse in which the MP and the VH were examined. One was published in 2009 [20] and none of the studies included compared VH with the MP. The other review from 2011 [21] was narrative and included studies both comparing and not comparing VH with the MP. All of the comparative studies from this review are included in the present review. Subsequently, three studies have been published including the only randomised controlled trial.

The studies focus on a number of different outcomes, and regarding durability, most studies focus on the anatomical outcome, symptomatic outcome and the surgical and conservative re-intervention rate.

Anatomical recurrence in any compartment was very frequent after both procedures, with a clear excess in the anterior compartment. This tendency towards recurrence in this compartment is well known, but is often asymptomatic [22]. An anatomical recurrence rate of 4–7 % for vaginal vault prolapse after VH was seen [10, 11], which is in accordance with the literature, as vaginal vault prolapse requires surgical repair in 6–8 % of all patients after VH [23]. Anatomical recurrences in the middle compartment were very rare after the MP. In one study, a shorter vaginal length after VH was seen, which can affect the functionality of the vagina.

Many studies did not examine postoperative symptoms, even though the absence of a vaginal bulge should be considered the most important measure of treatment success. In the two studies examining symptomatic outcome no difference in the postoperative UDI prolapse score was found between the two procedures.

It is known that POP surgery can aggravate urinary incontinence or cause de novo incontinence owing to existing masked incontinence. However, improvements can be obtained as well. The two studies that assessed changes in urinary incontinence found an improvement in both groups, with nether procedure being superior to the other in this matter.

Within 5 years' follow-up significantly more patients had proceeded to re-operation after VH because of symptomatic recurrence. One study showed a significantly shorter time interval to re-intervention after VH [15]. This is in accordance with Oversand et al. [8], who showed excellent results of the MP when carried out in a dedicated urogynecological unit. In this study, 95 % of the patients reported subjective satisfaction at follow-up 1 year postoperatively, concomitant with 86.7 % having POP-Q stage 0–1. At follow-up after 5 years, the re-operation rate was 2.6 %.

The re-operation rate was higher after VH (9–13.1 %) compared with MP (3.3–9.5 %) [10, 12, 15]. As expected, the lowest rate (9.1 % for VH and 3.3 % after the MP) was seen in the study with the shortest follow-up (12 months) [12]. This trend was recovered regarding conservative re-intervention, where more patients needed conservative re-intervention after VH (14–15 %) than after the MP (10–11 %) [12, 15]. The conservative re-intervention rate did not seem to change substantially with the longer follow-up, as it was almost identical in the two studies, despite one having six times longer follow-up (68–75 months) [15] than the other (12 months) [12].

With reference to complications, there is a trend towards greater postoperative bleeding, more bladder lesions and more infections after VH compared with post-MP. In line with that, Ottesen et al. [17] showed a significantly increased risk of further surgery due to postoperative haemorrhage, bladder injury and infection after VH in a large register study.

Two studies examined urinary retention and no significant difference between the two procedures was seen. However, no definition of urinary retention was stated in any of the studies.

The results of this review underline that VH is a more invasive procedure than the MP. The need for re-surgery because of postoperative bleeding, bladder injury and infection is more frequent after VH than after the MP. In addition, the operating time tends to be longer, the blood loss larger and transfusions needed more frequently. None of the studies assessed any socioeconomic outcomes, but from an economic point of view the MP appears advantageous too. The MP is often undertaken as out-patient surgery, contrary to VH, which can be performed as such, but most often requires hospitalisation.

Critics of the MP may state that uterus-preserving surgical methods carry an inherent risk of future uterine pathological conditions. In some cases, cervical stenosis may develop after the MP, eventually leading to haematometra and an absence of symptoms of uterine pathological conditions. The risk of development of endometrial cancer after uterus-preserving POP surgery has been shown to be only 0.24 to 0.35 % [24, 25], which was confirmed in a recent study evaluating the utility of vaginal hysterectomy when colpocleisis is performed to avoid future

cases of endometrial cancer [26]. In a decision analysis model, it was found that the expected utility for colpocleisis alone was higher than for colpocleisis combined with a vaginal hysterectomy for women aged 40–90 years. That said, VH is definitely eligible to be a treatment of uterine prolapse in cases of an identified uterine pathological condition before surgery.

The MP is the only uterine-sparing procedure that is compared with VH in this review. Some critics may proclaim that the MP is an old and outdated operation that has been replaced by more advanced uterine-preserving procedures, of which sacrospinous hysteropexy (SH) is one of the best studied techniques. In a randomised controlled trial [27] SH was compared with VH, and the time from surgery to return to work was significantly shorter after SH (43 vs 66 days, $p = 0.02$), but no differences in quality of life or functional outcomes were found between the two groups. In contrast to the shorter recovery time after SH, POP recurrence in the middle compartment (stage 2 or more) at the 1-year follow-up was notably more frequent after SH, with a 17 % higher risk after SH (21 % after SH vs 3 % after VH, $p = 0.03$). However, Lin [28] found that when SH was combined with a cervical amputation, as performed during the MP, no recurrence was seen.

A number of mesh-based operations for the repair of uterine prolapse are available, but should be strictly limited to selected cases of uterine prolapse, as the rate of mesh-related complications is up to 15–25 % after transvaginal mesh insertion for POP repair, with mesh erosions in up to 10 % of patients [29, 30]. In 2008, these findings led to the FDA public health notification on mesh use, with an update in 2011 [31, 32]. In accordance with that, a scientific committee (SCENIHR) under the European Commission in 2015 stated that the use of meshes for POP repair should usually be considered as a second choice after failed primary surgery [33]. In many countries, these notifications have caused a decrease in the use of mesh and many mesh kits have been withdrawn from the market. New types of mesh have been introduced, but so far little is known about their safety as long-term follow-up is lacking.

Another aspect when considering the choice of surgical method is the patients' preference. Two studies from 2013 [34, 35] surveyed patient preference for uterine preservation vs hysterectomy in women with uterovaginal prolapse. One study [34] found that 60 % would prefer another surgical option to hysterectomy if the alternative option was equally as efficient. Hysterectomy was only preferable if its benefit substantially exceeded the benefit of an alternative uterine-preserving procedure. The other study [35] supports these findings, as 36 % preferred uterine-preserving surgery and only 20 % preferred hysterectomy when the outcomes of the procedures were considered equal. The preference for uterine-preserving surgery was so strong that 21 % of the patients persistently preferred it to VH, even if hysterectomy was proven to be superior. Sufficient evidence-based information for patients is required if they are to provide informed consent on the choice of surgery based not on beliefs or trust in the doctor's personal opinion. Doctors' current preference for VH in the treatment of uterus prolapse is striking as it does not sufficiently rely on evidence. In general, there is an ongoing trend in surgery leading to an increasing number of minimally invasive procedures in many fields, including gynaecology. In the light of this, the sustained preference for VH stimulates a great deal of thought. An explanation could be that in many clinics VH has been performed as a routine treatment of uterine prolapse for decades and hence experience with other surgical procedures, including the MP, is lacking.

This review is in favour of the MP, but the benefits cannot necessarily be transferred to other uterine-preserving methods, whether based on native tissue repair or not. Comparisons of uterine-preserving surgical methods in general are scarce, and studies on the MP vs other uterine-preserving methods are lacking, as uterine-preserving surgical methods in general are compared with VH, even though they represent two distinctly different surgical approaches.

We regard our broad inclusion criteria, according to which no studies were excluded because of language, method, sample size, follow-up or year of publication, as strengths of this review, although it also causes some limitations owing to the heterogeneity of the studies. Some studies included patients who had undergone previous surgery because of POP or UI [10, 11], and in one study concomitant surgery for UI was performed in some patients [10].

Conclusion

This review challenges the position of VH as the preferred surgical treatment of uterine prolapse. The durability of the MP appears to be superior, as prolapse recurrence is more frequent after VH and both the re-operation rate and the rate of conservative re-intervention due to symptomatic recurrence is higher after VH. In addition, there is a trend towards greater postoperative bleeding, more bladder lesions and more infections after VH. The operating time is longer, blood loss tends to be higher and transfusions are also needed more frequently. Based on the findings in this review, we suggest that the MP should be considered a durable alternative to VH for treatment of uterine prolapse, but randomised controlled trials and larger long-term prospective studies on this topic are required.

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Compliance with ethical standards

Conflicts of interest CK Tolstrup received travel expenses and conference fees for the EUGA Annual Congress Leading Lights 2015 from by Astellas Pharma; Gunnar Lose received research grants from Astellas Pharma and consultant fees from Contura; Niels Klarskov received

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Authors' contributions CK Tolstrup: protocol development, data collection, data analysis, manuscript writing/editing.

G Lose: protocol development, manuscript editing.

N Klarskov: protocol development, data analysis, manuscript editing.

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ORIGINAL ARTICLE

The Manchester-Fothergill procedure versus vaginal hysterectomy with uterosacral ligament suspension: a matched historical cohort study

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Abstract

Introduction and hypothesis This study compares vaginal hysterectomy with uterosacral ligament suspension (VH) with the Manchester-Fothergill procedure (MP) for treating pelvic organ prolapse (POP) in the apical compartment.

Methods Our matched historical cohort study is based on data from four Danish databases and the corresponding electronic medical records. Patients with POP surgically treated with VH ($n = 295$) or the MP ($n = 295$) in between 2010 and 2014 were matched for age and preoperative POP stage in the apical compartment. The main outcome was recurrent or de novo POP in any compartment. Secondary outcomes were recurrent or de novo POP in each compartment and complications.

Results The risk of recurrent or de novo POP in any compartment was higher after VH (18.3%) compared with the MP (7.8%) (Hazard ratio, HR = 2.5, 95% confidence interval (CI): 1.3–4.8). Recurrence in the apical compartment occurred in 5.1% after VH vs. 0.3% after the MP (hazard ratio (HR) = 10.0, 95% confidence interval (CI) 1.3–78.1). In the anterior compartment, rates of recurrent or de novo POP were 11.2% after VH vs. 4.1% after the MP (HR = 3.5, 95% CI 1.4–8.7) and in the posterior compartment 12.9% vs. 4.7% (HR = 2.6, 95% CI 1.3–5.4), respectively. There were more perioperative complications (2.7 vs. 0%, $p = 0.007$) and postoperative intra-abdominal bleeding (2 vs. 0%, $p = 0.03$) after VH.

Conclusions This study shows that the MP is superior to VH; if there is no other indication for hysterectomy, the MP should be preferred to VH for surgical treatment of POP in the apical compartment.

Keywords Manchester-Fothergill procedure · Pelvic organ prolapse · Recurrence · Vaginal hysterectomy

Introduction

Uterine prolapse is a common condition for which no current standard for surgical repair exists. Anatomical uterine prolapse affects 14.2% of postmenopausal women [1], and ~175,000 apical-compartment prolapse surgeries are performed annually in the USA [2]. The aging population in many developed countries has caused an increase in this rate [3], which may increase further. Due to an absence of evidence, the surgical strategy for uterine prolapse repair varies greatly. Vaginal hysterectomy (VH) has been the most common surgical method for years and remains the preferred procedure worldwide [4–6]. New surgical procedures for treating prolapse in the apical compartment have been developed in recent years, and in some countries, mesh-based procedures and robotic surgery have gained popularity. Currently, many patients demand uterus-preserving procedures [7, 8], and recent studies have shown less morbidity and shorter hospitalization associated to uterus-preserving procedures compared with VH [9, 10]. The Manchester-Fothergill procedure (MP)—a uterus-preserving technique performed for more than a century—has proven safe and durable [11]. Even so, studies comparing other surgical procedures to the MP are scarce, and only one small, randomized controlled trial (RCT) comparing VH to the MP exists [12]. In general, the existing literature is in favor of the MP [10].

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Materials and methods

Data sources

In Denmark, reporting to all databases is mandatory, which ensures data completeness of >90% [14, 15], except for DAD, for which data completeness is >70% [16]. Data was collected from four national databases and corresponding medical records. The Danish personal identification number was used to link data from four national databases and corresponding medical records:

The Danish Urogynecological Database (DugaBase) comprises data on pelvic organ prolapse (POP) surgery performed in all public or private hospitals in Denmark. From it, we obtained body mass index (BMI), age at surgery, smoking status, weekly alcohol consumption, American Society of Anesthesiologists(ASA) score, preoperative Pelvic Organ Prolapse Quantification (POP-Q) staging for all compartments (estimated by the simplified technique from Swift et al. [13]), surgeon experience level with each procedure, hospital referral, and preoperative short-form questionnaire on objective examination and patient characteristics completed by the gynecologist. In Denmark, no formal recommendation for a routine preoperative screening of prolapse patients exists, and the preoperative examination varies between hospitals. However, all patients undergo a gynecological examination preoperatively, but ultrasound scans, endometrial biopsies, etc., are done at the individual doctor's discretion.

The Danish Hysterectomy and Hysteroscopy Database (DHHD) contains data on all hysterectomies performed in public or private hospitals in Denmark. This enabled us to exclude patients hysterectomized due to indications other than POP in the apical compartment.

The Danish Anesthesia Database (DAD) holds data on all surgeries in Denmark requiring anesthesia. Data on BMI and ASA score was primarily obtained from the DugaBase, but for patients with missing data or unlikely values (BMI <15 or >50 and ASA > 4), data was replaced with that from DAD.

The Danish National Pathology Registry (DNPR) and the Danish National Data Bank (DNDB) comprise information on all pathological evaluations in Denmark covering all public and private hospitals and clinics. From there, information on pathological evaluation of tissue removed by VH or the MP was obtained. For the MP group, data on any tissue excised from the uterus/cervix during follow-up was collected. From the corresponding electronic medical records, data regarding patient characteristics, the surgical procedure, concomitant surgery, perioperative complications, and postoperative complications were extracted. Minor complications were defined as requiring either no treatment, pharmacological treatment (e.g., over-the-counter analgesics), or other kinds of treatment not requiring anesthesia (cutting of vaginal sutures in the outpatient clinic, etc.).Data from follow-up was compiled for any compartment regarding recurrence, surgical, or pessary treatment due to recurrent/de novo POP, and regarding pelvic floor muscle training. Patients had either an outpatient workup or a phone interview 3 months postoperatively. In case of symptom relapse, new symptoms, or any problem related to surgery, the patient was invited for an examination. Review of the medical records was done by two of the authors (CKT and KRH).

This study contains information on public hospital contacts, admissions, and outpatient visits in the Capital region only, because different electronic health information systems exist nationwide and between public hospitals, private clinics, and general practitioners.

Study population

We included women with prolapse in the apical compartment who had either VH or the MP done at one of four public university hospitals in the Capital region of Denmark. All operations were performed from 2010 to 2014, and all hospitals had a specialized urogynecological unit. Distribution of operations between hospitals is shown in Table 1. Surgeries performed after 2010 only were included, as data completeness in DugaBase was <90% before 2010 [14]. Patients were followed from the date of VH/MP until recurrence/de novo POP, hysterectomy (for the MP group only), or until 31 August 2016, whichever came first. All patients were followed until 31 August 2016 for postoperative complications.

Exclusion criteria were previous POP surgery in the apical compartment, connective tissue disease, concurrent indication for VH, the MP plus hysteropexy, and concomitant surgical procedures at the time of the VH/MP (e.g., transvaginal tape).

Matching was according to age and preoperative POP-Q stage. An age difference up to 5 years between patients was accepted, whereas the preoperative POP-Q stage in the apical compartment was equal for all pairs. Matching was done by an independent statistician, and the process is displayed in Fig. 1. Due to exclusions after the first matching, a second matching was necessary to include as many patients as possible. The nonexcluded partner in an excluded pair re-entered the pool of patients available for matching.

Table 1 Distribution of surgeries

Hospital	Surgeries, *n* (%)	MP, *n* (%)	VHs, *n* (%)
1	17 (2.9)	17 (5.8)	0 (0)
2	244 (41.3)	182 (61.7)	62 (21)
3	190 (32.2)	49 (16.6)	141 (47.8)
4	139 (23.6)	47 (15.9)	92 (31.2)
Total	590 (100)	295 (100)	295 (100)

MPs Manchester-Fothergill procedures, *VHs* vaginal hysterectomies

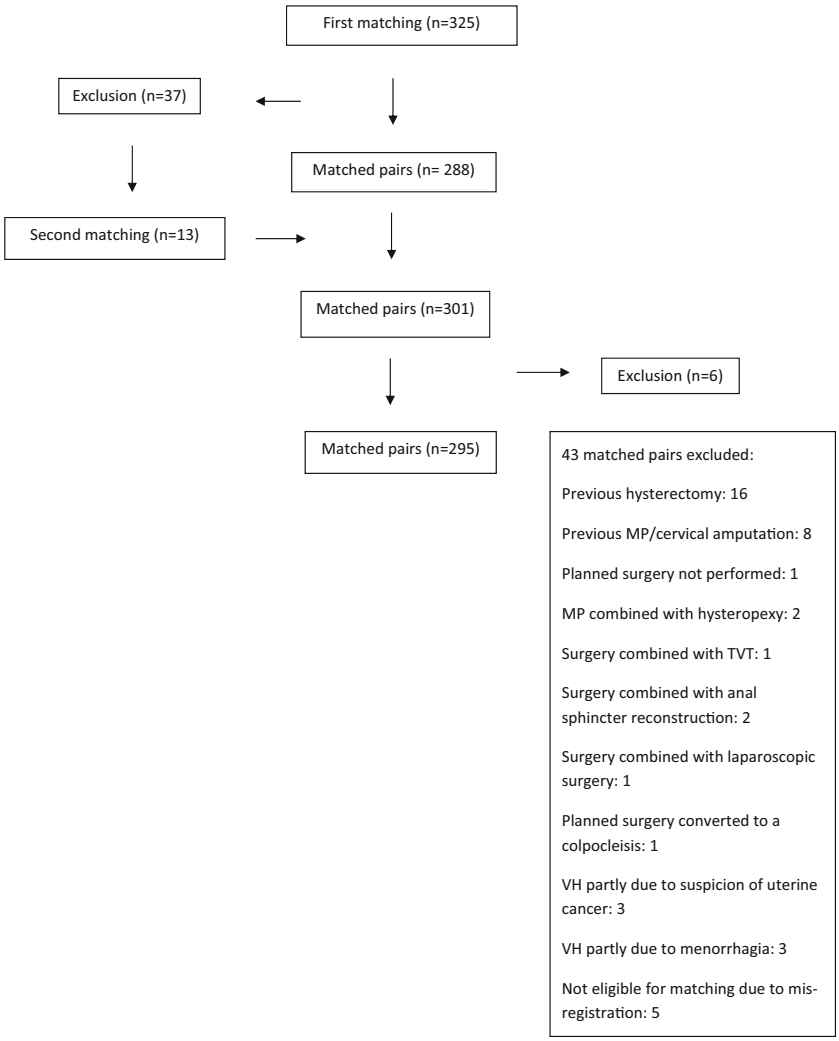

Fig. 1 Participant matching process

Description of surgical procedures

For vaginal hysterectomy, the vaginal wall is circumcised around the cervix, the bladder is isolated, and the peritoneum is opened, making access to the pouch of Douglas. The uterosacral and cardinal ligaments are cut and the uterus removed. The vaginal vault is suspended by high or low uterosacral ligament (USL) suspension. High suspension consists of attaching sutures to the USL bilaterally followed by a fixation of the anterior and posterior arm of each suture to the pubocervical and rectovaginal fascia [17]. In low suspension, sutures are attached to the left USL, followed by plication of the peritoneum of the cul-de-sac, succeeded by placement of sutures through the right USL. Before internal sutures are tied, additional sutures are potentially placed through the posterior vaginal wall, through the USLs, back through the vaginal wall, and tied in the vagina [18]. Finally, the mucosa is closed in both suspension procedures. High and low suspension was analyzed as a single group.The first step in the MP [19] is circumcision and isolation of the cervix. The cardinal ligaments are cut and the cervix amputated. The distal part of the cardinal ligaments is then sutured to the front side of the remaining cervical stump, and a new portio is created using Sturmdorff sutures. VH and the MP can be accompanied by anterior and/or posterior colporrhaphy and/or perineorrhaphy.

Outcome measures

Primary outcome was recurrent or de novo POP in any compartment. Recurrence was defined as POP in a previously operated compartment, and de novo POP as new occurrence in a previously unoperated compartment. Both where defined as one or more of the following:

- POP treated with pessary or surgery
- POP-Q stage II with POP symptoms
- POP-Q stage ≥ III independent of POP symptoms

Secondary outcomes were recurrence and de novo POP in each compartment, perioperative and postoperative

complications, pathological evaluation of the surgically removed uterus/cervix, and—for the MP group—uterine/cervical samples taken during follow-up.

Statistical analysis

The sample size for this study is based on a calculation using McNemar's *Z*-test with two-sided equality, where a difference was considered clinically important if 15% of patients had recurrence/de novo POP in any compartment after one procedure while 25% had recurrence or de novo POP after the other. Power (1-p) was set to 0.8 and α to 5%. This equals a total sample size of 253 pairs.

A Cox proportional hazard model was used to examine the association between surgical procedure and recurrence/de novo POP. Because of competing risk (i.e., hysterectomy for the MP group), the hazard ratio (HR) is interpreted as cause specific. Due to the matched design, baseline intensity is estimated for every combination of matched variables. The time axis shows time from date of operation until censoring. Two-sided 95% confidence intervals (CI) and *p* values for the HR were calculated on the basis of Wald's test of the Cox regression parameter. The risk of having an event at any given time was illustrated in cumulative hazard plots. Logistic regression was used to analyze the association between postoperative complications and surgical procedure. Age and POP-Q stage were incorporated in the model due to the matched design. A *p* value <0.05 was considered significant for all tests. Statistical analyses were conducted using SAS Enterprise Guide 7.11 (SAS, NC, USA).

Approval

The Danish Health and Medicines Authority has approved acquisition of data from patient records for the study (3–3013-1397/1 and 3–3013-1397/2), and the data collection was also approved by the Danish Data Protection Agency (2012–58-0004).

Results

Study population

We matched 338 pairs. Initially, 325 pairs were matched, and due to exclusion of 37 pairs, a second matching was done yielding another 13 pairs. After the second matching, six patients were excluded, resulting in 295 matched pairs. Reasons for exclusion of the 43 matched pairs are listed in Fig. 1, and baseline characteristics are shown in Table 2.

No significant differences in baseline characteristics were found, except for use of local estrogen treatment, which was more frequent in the VH group, as hospital four—which mainly performed VH—was the only hospital routinely prescribing local estrogen treatment preoperatively. The two procedures were also unevenly distributed among hospitals, with hospital three and four mainly doing VH while hospitals one and two preferred the MP.

All patients in the VH group had an apical support procedure: 246 (83.34%) were low suspensions and 49 (16.6%) high. Follow-up ranged from 20 to 80 (mean 51) months for the VH group and 48 months for the MP group ($p = 0.02$).

Outcome measures

Recurrence or de novo POP

Recurrence or de novo POP in any compartment and in each compartment individually was significantly more frequent after VH. Table 3 summarizes recurrences and de novo POP, while Fig. 2 shows cumulative hazard plots for compartments combined and each compartment specifically. Within 20 months of the primary POP surgery, 83.3% of all recurrences in any compartment occurred after VH and 78.2% after the MP, indicating a sufficient follow-up period to disclose a meaningful recurrence rate.

Complications

Table 4 shows perioperative and postoperative complications.

Perioperative complications more often occurred in the VH group. Only 36 patients ($n = 237$) in the VH group and 23 ($n = 257$) in the MP group had blood loss >100 ml ($p = 0.03$). Postoperative complications were also more frequent after VH, though the difference was not significant. Altogether, 80 postoperative complications were seen after VH and 68 after the MP ($p = 0.3$). The subgroup of minor complications accounted for most postoperative complications. Frequent minor complications were hematomas (12 patients after VH vs. four after the MP) and pain (13 patients after VH vs eight after the MP). Remarkably, dyspareunia was only recorded in six patients after VH and none after the MP; however, patients were not routinely asked about dyspareunia pre- and postoperatively. Intraabdominal bleeding occurred only after VH: six patients experienced blood loss ≥1000 ml. Median blood loss was 1700 ml (range 1000–3700 ml). All patients underwent surgical treatment within 24 h, and in three patients, open surgery was necessary. Blood transfusion was administered in all cases (median 3.5 U, range 2–6 U), whereas fresh–frozen plasma was administered in two patients. Superficial vaginal bleeding requiring surgical treatment was found in two patients in each group. Antibiotic treatment in hospital was equally frequent in both groups. Only infections diagnosed <30 days postoperatively were included. Urinary tract infections were excluded, as we had no access to data from general

Table 2 Baseline characteristics

Characteristic	MP	VH	*P* value
Age at surgery (years), mean ± SD [total patients]	59.6 ± 13.0 [295]	61.1 ± 11.4 [295]	0.2*
Body Mass Index (kg/cm^2), mean ± SD [total patients]	25.7 ± 4.0 [287]	25.4 ± 3.8 [295]	0.4*
Current smoker, n (%) [total patients]	40 (13.6) [277]	33 (11.2) [271]	0.5**
Weekly alcohol consumption, median units (range) [total patients]	[194]	[221]	
	3.0 (0–21)	3.0 (0–16)	0.2***
ASA classification,[total patients]	[294]	[295]	0.6**
I n (%)	151 (51.3)	142 (48.2)	
II n (%)	124 (42.2)	137 (46.4)	
III n (%)	19 (6.5)	16 (5.4)	
IV n (%)	0 (0)	0 (0)	
Local estrogen treatment, n (%) total patients]	121 (41.01) [285]	157 (53.22) [291]	0.006**
Cesarean sections, median (range) [total patients]	0 (0–4) [269]	0 (0–2) [284]	0.4**
Vaginal deliveries, median (range) [total patients]	2 (0–5) [269]	2 (0–9) [284]	0.1**
Mean (±SD)	2.0 ± 0.9	2.2 ± 1.1	
Preoperative POP-Q stage apical compartment [total patients]	[295]	[295]	1.0**
I n (%)	4 (1.3)	4 (1.3)	
II n (%)	208 (70.5)	208 (70.5)	
III n (%)	76 (25.8)	76 (25.8)	
IV n (%)	7 (2.4)	7 (2.4)	
Preoperative POP-Q stage anterior compartment [total patients]	[293]	[294]	0.3**
0 n (%)	35 (11.9)	23 (7.8)	
I n (%)	35 (11.9)	37 (12.6)	
II n (%)	89 (30.1)	78 (26.5)	
III n (%)	125 (42.4)	145 (49.3)	
IV n (%)	9 (3.0)	11 (3.8)	
Preoperative POP-Q stage posterior compartment[total patients]	*[288]*	*[293]*	*0.1***
0 n (%)	*97 (33.7)*	*107 (36.5)*	
I n (%)	*124 (43.0)*	*97 (33.1)*	
II n (%)	*50 (17.4)*	*70 (23.9)*	
III *n* (%)	*16 (5.6)*	*17 (5.8)*	
IV n (%)	*1 (0.3)*	*2 (0.7)*	
Previous colporrhaphy [total patients]	[295]	[295]	
No n (%)	261 (90.3)	268 (90.8)	0.4**
Anterior colporrhaphy n (%)	21 (7.3)	22 (7.5)	1.0**
Posterior colporrhaphy n (%)	13 (4.5)	10 (3.4)	0.7**
Previous surgery in the genital pelvis, n (%) [total patients]	46 (15.6) [295]	38 (12.9) [295]	0.4**
Antithrombotic treatment [total patients]	[271]	[271]	0.2**
No n (%)	23 (85.2)	242 (89.3)	
Yes n (%)	40 (14.8)	29 (10.7)	
Surgeon experience level with each procedure [total patients]	[289]	[294]	0.6**
≤ 25 surgeries n (%)	47 (16.2)	54 (18.3)	
26–100 surgeries n (%)	32 (11.0)	38 (12.8)	
>100 surgeries n (%)	210 (72.6)	202 (68.6)	
Concomitant surgery [total patients]	[295]	[295]	
Anterior colporrhaphy n (%)	245 (83.1)	242 (82.0)	0.8**
Posterior colporrhaphy/enterocele n (%)	60 (20.3)	96 (32.5)	0.001**
Perineorrhaphy n (%)	27 (9.2)	43 (14.6)	0.06**

MP Manchester-Fothergill procedure, *VH* vaginal hysterectomy, *SD* standard deviation

**T*-test. **Fisher's exact test. ***Wilcoxon rank-sum test

Table 3 Recurrence or de novo pelvic organ prolapse (POP)

	MP	VH	*P* value*
Any compartment, n (%) [total patients]	*23 (7.8) [295]*	*54 (18.3) [295]*	*0.0002*
Risk of recurrence/de novo POP, HR (95% CI)	1.0 (ref.)	2.5 (1.3–4.8)	
Apical compartment, n (%) [total patients]	*1* (0.3) *[295]*	*15* (5.1) *[295]*	*0.0004*
Risk of recurrence, HR (95% CI)	1.0 (ref.)	10.0 (1.3–78.1)	
Surgical treatment, n (%) [total patients]	0 (0) [295]	8 (2.7) [295]	0.007
Pessary treatment, n (%) [total patients]	1 (0.3) [295]	9 (3.1) [295]	0.02
PMFT, n (%) [total patients]	0 (0) [295]	2 (0.7) [295]	0.5
No treatment, n (%) [total patients]	0 (0) [295]	2 (0.7) [295]	1.0
Anterior compartment, n (%) [total patients]	*12 (4.1) [295]*	*33 (11.2) [295]*	*0.002*
Risk of recurrence/de novo POP, HR (95% CI)	1.0 (ref.)	3.5 (1.4–8.7)	
Recurrence (previously operated), n (%) [total patients]	11 (4.1) [266]	22 (8.3) [264]	0.05
De novo POP, n (%)	1 (3.4) [29]	11 (35.5) [31]	0.002
Surgical treatment, n (%) [total patients]	6 (2.0) [295]	19 (6.4) [295]	0.01
Pessary treatment, n (%)	5 (1.7) [295]	13 (4.4) [295]	0.09
PMFT**, n (%) [total patients]	7 (2.4) [295]	10 (3.4) [295]	0.6
No treatment, n (%) [total patients]	2 (0.7) [295]	3 (1.0) [295]	0.7
Posterior compartment, n (%) [total patients]	*14 (4.7) [295]*	*38 (12.9) [295]*	*0.0007*
Risk of recurrence/de novo POP, HR (95% CI)	1.0 (ref.)	2.6 (1.3–5.4)	
Recurrence (previously operated), n (%) [total patients]	1 (1.4) [73]	9 (8.5) [106]	0.05
De novo POP, n (%) [total patients]	13 (5.9) [222]	29 (15.3) [189]	0.02
Surgical treatment, n (%) [total patients]	6 (2.0) [295]	25 (8.5) [295]	0.0006
Pessary treatment, n (%) [total patients]	1 (0.3) [295]	10 (3.4) [295]	0.01
PMFT**, n (%) [total patients]	9 (3.1) [295]	11 (3.7) [295]	0.8
No treatment, n (%) [total patients]	5 (1.7) [295]	2 (0.7) [295]	0.5

MP Manchester-Fothergill procedure, *VH* vaginal hysterectomy, *PFMT* pelvic floor muscle training, *HR* hazard ratio, *CI* confidence interval

* Fisher's exact test

practitioners or private clinics. In the VH group, one patient acquired pneumonia, another was treated for a vaginal infection, and in a third, it was not possible to determine the cause of infection. Three patients in the MP group were treated for vaginal or cervical infection: one patient had an infected vaginal mucosal defect and another an infection of unknown origin.

No difference in urinary retention was found, and the median duration for both groups was 14 days. An unacknowledged obstruction of the left ureter at bladder level was discovered 33 days postoperatively in a patient from the MP group. At diagnosis, the patient had developed urosepsis and hydronephrosis requiring an acute nephrostomy. Two-and-a half months postoperatively, the patient suffered from pyelonephritis, which recurred 1 month later. Later again, the ureter ostium was resected, and a JJ-catheter was incorporated. This was removed 6 months postoperatively, and the patient regained normal renal function. Three other complications requiring surgery occurred in the VH group; one was a suture removal using local anesthesia 73 days postoperatively, another suture loosening under general anesthesia after 14 days, and a third underwent gastroscopy 2 days postoperatively because of hematemesis.

Pathological evaluation

For the MPs ($n = 270$), mean length of the amputated cervix was 24.9 mm (range 4–60 mm) compared with a mean length of 34.3 mm (range 15–80 mm) for the cervix attached to the removed uterus in the VH group ($n = 136$). A small lymfocytic lymphoma was found in the uterus removed from one patient who had previously been examined because of an increased M-component. A concurrent lymphoma was found in bone marrow samples. The uterine lymphoma did not lead to any further treatment. In one patient from the MP group, a mild cervical dysplasia was revealed. No treatment was given, and dysplasia was not seen in later cervical smears.

One case of asymptomatic hematometra was seen 1 year postoperatively in a patient suspicious of having a uterine polyp on ultrasound scan. No polyp was found, but a hematometra was removed hysteroscopically. Endometrial biopsies revealed no malignancy. The same patient subsequently had a

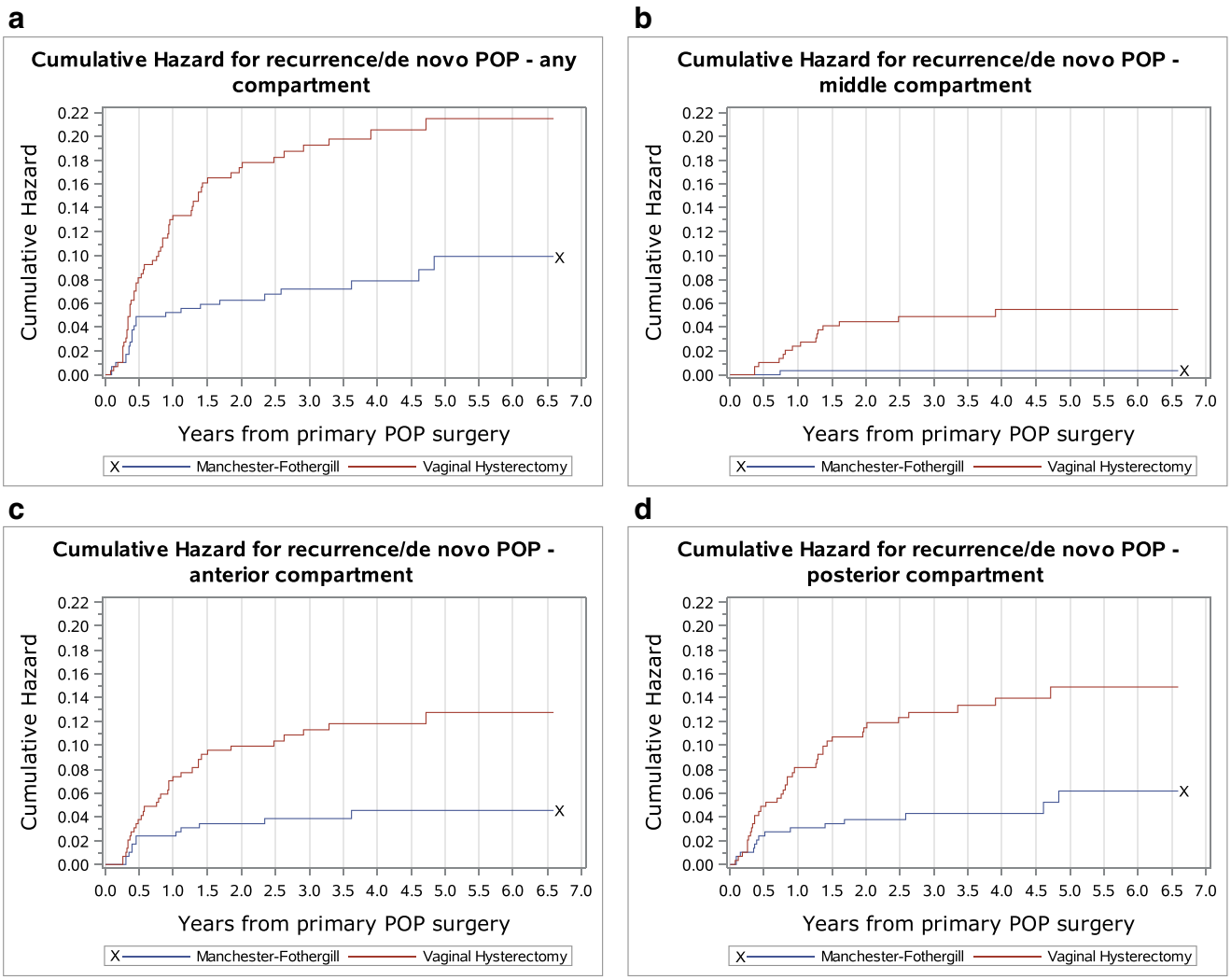

Fig. 2 Cumulative hazard plots showing cumulative hazard of recurrence/de novo pelvic organ prolapse (POP) as a function of time from surgery in any compartment (**a**), the apical (**b**), the anterior (**c**), and the posterior (**d**) compartment

nonmalignant pyometra. Another patient had a pyometra evacuated 82 days postoperatively, as an ultrasound scan had revealed a broadened endometrium; no malignancy was found.

During follow-up, one case of stadium IA endometrial adenocarcinoma was identified 15 months postoperatively. Endometrial samples were taken because of prolonged menstrual bleeding in a premenopausal patient. A laparoscopic total hysterectomy with concomitant bilateral salpingo-oophorectomy was done, and no further treatment was needed. Another patient had a complex endometrial hyperplasia with atypia. At the end of follow-up, the patient had undergone no treatment. Three more patients underwent hysterectomy: one at 36 months for suspicion of endometrial carcinoma and another 31 months postoperatively due to symptomatic fibromas. The third patient had a prophylactic hysterectomy concurrently with bilateral salpingo-oophorectomy for suspicion of ovarian cancer 60 months postoperatively. No uterine malignancy was detected in any of the cases.

Discussion

We found that the MP is more durable than VH for all compartments. The relative risk of recurrence in the apical compartment was 10 after VH (1.3–78.1) and recurrence rate was in agreement with the literature (4–7%) [17, 20, 21]. Conversely, low recurrence rates after MP the MP were demonstrated in previous studies [10, 21]. Frequent recurrences in the anterior compartment is an important issue in POP surgery [21, 22]. It is therefore encouraging that only 4.1% had recurrence in this compartment after the MP vs a recurrence rate twice as high after VH (8.3%). Recurrence in the posterior compartment was infrequent after the MP and 8.5% in the posterior compartment after VH. VH patients without anterior colporrhaphy at the index procedure were at high risk of de novo POP in the anterior compartment (35.5%); the same was not true for the MP patients (3.4%). However, the risk was higher in the posterior compartment after VH. The increased

Table 4 Complications

Complication	MP n = 295	VH n = 295	*P* value*
Perioperative complications, n (%)	*0 (0)*	*8 (2.7)*	*0.007*
Obstruction of ureter detected perioperatively and suture cut/loosened	0 (0)	4 (1.4)	
Organ lesion**	0 (0)	1 (0.3)	
Other***	0 (0)	1 (0.3)	
Bleeding > 500 ml	0 (0)	2 (0.7)	
Postoperative complications, n (%)	*50 (16.9)*	*63 (21.4)*	*0.2*
Risk of postoperative complication, OR (95% CI)	1.0 (ref.)	1.3 (0.9–1.9)	
Unaknowledged obstruction of ureter requiring surgery n (%)	1 (0.3)	0 (0)	
Urinary retention n (%) §	7 (2.4)	9 (3.0)	0.8
Hematometra/pyometra n (%)	3 (1.0)	0 (0)	
Antibiotic treatment in hospital n (%)	5 (1.7)	3 (1.0)	0.7
Bleeding n (%)	2 (0.7)	8 (2.7)	0.1
Superficial n (%)	2 (0.7)	2 (0.7)	
Intra-abdominal n (%)	0 (0)	6 (2.0)	0.03
Other complication requiring surgery n (%)	0 (0)	3 (1.0)	
Minor complications n (%)	50 (16.9)	57 (19.3)	0.5

MP Manchester-Fothergill procedure. *VH* vaginal hysterectomy, *OR* odds ratio, *CI* confidence interval

* Fisher's exact test. ** Bladder lesion. *** Missed surgical napkin removed laparoscopically during ongoing anesthesia. *CI* Confidence interval. § Urinary retention: Retention requiring treatment with intermittent catheterization/indwelling catheter

recurrence and de novo POP indicate that removing the uterus causes deterioration of vaginal suspension, including vaginal support level I [23]. Only one small RCT [12] comparing the two procedures exists, and it reported no difference between groups regarding quality of life scores. Vaginal length was longer after the MP, while there was no significant difference in POP-Q C-point. A matched cohort study showed significant shorter time to reoperation due to recurrence for the VH group [24]. Matching criteria were similar to the study reported here; however, although the sample size was smaller, follow-up was longer.

More perioperative complications and intra-abdominal bleeding were related to VH. This corroborates results from a recent study that showed a higher rate of severe complications after VH (1.9% vs. 0.2%) [25]. More complications after VH were also confirmed in another review [10], and a register study found an increased risk of further surgery due to complications [26].

In contrast to uterus-preserving procedures, VH eliminates the risk of future uterine pathology. The risk of endometrial cancer is known to be 0.24–0.35% [27–29], and a decision analysis [29] showed no benefits from concomitant hysterectomy in case of colpocleisis. In our study, one case (0.3%) of endometrial cancer was seen.

Our study reflects the variety in surgical strategy for repairing uterine prolapse, as a large difference in choice of surgical procedure was seen between hospitals. There was no difference in surgeon experience level, indicating that none of the procedures were primarily performed by less experienced surgeons. The study is also the largest to date comparing VH to the MP for treating prolapse in the apical compartment. Strengths include patient matching according to age and preoperative prolapse stage in the apical compartment. Since reporting to the databases is mandatory, data completeness is high for all included databases, and data validity is high for the DugaBase [14], the main database used in this study. Reporting data to The Danish National Pathology Registry and Data Bank is automatic by all hospitals and clinics in Denmark. In this study, we had no information regarding all POP-Q points—only POP-Q stage, which can hide a potential difference in cervical length between groups. However, pathological evaluation showed that amputated cervices from the MP group were 24.9 mm and cervices attached to the removed uteri were 34.3 mm. Hence, a potential difference in cervical elongation degree is expected to be negligible. A weakness of this study is the lack of access to data from private practitioners and clinics, as the recurrence rate might be higher than shown in this study. We do not know whether the reporting of complications is comparable between departments, and information bias cannot be ruled out, though it seems reasonable to assume that reporting of major complications is equal between departments. Except for participant matching on a few selected criteria, no other attempts were made to adjust for further confounding, making residual confounding a potential issue. Low and high USL suspension was analyzed as a single group, which might be a limitation; however, a large study

from 2017 showed equal outcomes for these two suspension types [30]. The the MP is a less invasive procedure with shorter operating time and hospitalization [10]. Considered this, as well as the higher rate of recurrence, de novo POP, and complications, VH appears less attractive in from an economic aspect also. The project group is currently conducting an economic analysis comparing the two procedures.

Based on our results and the existing literature, the MP should be preferred to VH with USL suspension for surgical treatment of POP in the apical compartment when no specific indication for hysterectomy is present. In the future, uterine-preserving procedures should be compared with the MP rather than with VH.

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Compliance with ethical standards

Conflicts of interest C.K. Tolstrup has, in relation to the study, received a research grant from the Nordic Urogynaecological Association (NUGA) and a travel grant from the Oticon Foundation, and has, outside the study, a conference fee and travel expenses paid by Astellas Pharma.

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G. Lose has received consultation fees from Astellas and Contura.

T.I. Kopp, P.H. Viborg, and U.S. Kesmodel have nothing to disclose.

N. Klarskov has, outside the study, received personal fees from Astellas Pharma.

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ORIGINAL ARTICLE

Manchester–Fothergill procedure versus vaginal hysterectomy with uterosacral ligament suspension: an activity-based costing analysis

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Abstract

Introduction and hypothesis Pelvic organ prolapse (POP) is a common diagnosis that imposes high and ever-growing costs to the healthcare economy. Numerous surgical techniques for the treatment of POP exist, but there is no consensus about which is the ideal technique for treating apical prolapse. The aim of this study was to estimate hospital costs for the most frequently performed operation, vaginal hysterectomy with uterosacral ligament suspension (VH) and the uterus-preserving Manchester–Fothergill procedure (MP), when including costs of postoperative activities.

Methods The study was based on a historical matched cohort including 590 patients (295 pairs) who underwent VH or MP during 2010–2014 owing to apical prolapse. The patients were matched according to age and preoperative prolapse stage and followed for a minimum of 20 months. Data were collected from four national registries and electronic medical records. Unit costs were obtained from relevant departments, hospital administration, calculated, or estimated by experts. The hospital perspective was applied for costing the resource use.

Results Total costs for the first 20 months after operation were 3,514 € per VH patient versus 2,318 € per MP patient. The cost difference between the techniques was 898 € (95% confidence interval [CI]: 818–982) per patient when analyzing the primary operation only and 1,196 € (CI: 927–1,465) when including subsequent activities within 20 months ($p < 0.0001$).

Conclusions The MP is substantially less expensive than the commonly used VH from a 20-month time perspective. Healthcare costs can be reduced by one third if MP is preferred over VH in the treatment of apical prolapse.

Keywords Activity-based costing analysis · Apical prolapse · Economic analysis · Manchester–Fothergill procedure · Pelvic organ prolapse · Vaginal hysterectomy

Abbreviations

ASA	American Society of Anesthesiologists
BMI	Body mass index
DAD	Danish Anesthesia Database
DHHD	Danish Hysterectomy Database
DugaBase	Danish Urogynecological Database
DKK	Danish kroner
EUR	Euro
PACU	Post-anesthesia care unit
POP	Pelvic organ prolapse

Introduction

Pelvic organ prolapse (POP) is a common diagnosis affecting women worldwide. Symptoms of POP are experienced by 2.9% to 11.4% of women [1, 2]. When conservative treatment is insufficient, surgical treatment is considered, to maintain the quality of life. For Danish women, the lifetime risk for prolapse surgery is 18.7% [3] and the number of operations is rapidly growing [4]. The economic costs of prolapse surgeries are substantial and will grow significantly [4, 5]. With limited healthcare resources, it is relevant to apply procedures that offer good quality at reasonable costs.

The study was presented at: Nordic Urogynecological Association (NUGA) 30 bi-annual Meeting, Reykjavik, Iceland, April 2017 and the International Urogynecological Association (IUGA) 42nd annual Meeting, Vancouver, Canada, June 2017

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There is a range of surgical techniques to treat apical prolapse [6], but currently there is no consensus regarding which technique is the ideal one. The procedures can be divided into uterus-preserving techniques, such as the Manchester–Fothergill procedure (MP) and non-preserving techniques such as vaginal hysterectomy with uterosacral ligament suspension (VH). VH is the most frequently used operation for treating uterine descent worldwide [7, 8]. MP is a minor procedure with less blood loss, shorter operating time, shorter hospitalization, and less severe complications [9, 10]. However, VH prevents subsequent uterus cancer and other uterus disorders, although the rate of uterine pathological conditions is low (0.8%) [11].

The aim of this study was to estimate the hospital costs of VH and MP when the costs of postoperative activities including complications, recurrences, urinary incontinence, and uterus-dependent issues within a 20-month period were included.

Materials and methods

This study is secondary to a study on POP recurrence and clinical outcomes after MP and VH reported by Tolstrup et al. [12]. The same historical matched cohort was used for this study. In a historical cohort study, the data are collected after the event has taken place from records and registries where the information has been recorded prospectively. Patients in the two groups were matched according to preoperative prolapse stage in the apical compartment and age. The patients were eligible for both types of operation; thus, the women in the MP group and the VH group were carefully assessed to be fully comparable. We assessed the resource and cost aspects of the two procedures, including related costs in the first 20 months after the primary operation.

Data sources

Data were collected from the Danish Urogynecological Database (DugaBase), the Danish Anesthesia Database (DAD), the Danish Hysterectomy Database (DHHD), and the Danish National Pathology Registry, and Data Bank. The data from the different databases were merged using the personal identification number in the Danish Civil Registration System. Furthermore, the electronic medical records for all patients were reviewed.

The DugaBase includes data on all surgeries for urinary incontinence and POP operations performed in public or private hospitals in Denmark. Reporting to the DugaBase is compulsory by law, entailing very high coverage of the database (>90%) and high validity [13]. The study population was identified as patients registered in the DugaBase. Patients registered with hysterectomies with concurrent indications other than prolapse were excluded from the analysis using DHHD. The DugaBase registry includes information about the POP state in the three compartments, body mass index (BMI), the American Society of Anesthesiologist (ASA) score, smoking habits, and alcohol consumption. From DAD operative time, time of anesthesia, and time in the post-anesthesia care unit (PACU) were obtained. Further, for patients with missing or unlikely values in DugaBase (BMI < 15, BMI > 50, and ASA > 4) replacement data were obtained from DAD.

The Danish National Pathology Registry and Data Bank include data on all analyzed tissue samples from public and private hospitals and the primary sector in Denmark. Information on pathological evaluations of tissues removed during a POP operation and tissues taken from the uterus during the follow-up for the MP group were obtained.

From reviews of electronic medical records, complications, recurrences, and uterus-related activities were obtained. Information about procedures, evaluations, and number of contacts were registered, even for minor complications. All uterus-related activities were included, regardless of severity. Also, information on parity, previous cesarean sections, and previous prolapse surgery in the anterior and posterior compartments was obtained from electronic medical records.

The Danish Health and Medicines Authority approved the data collection from patient records (3–3013-1397/1 and 3–3013-1397/2). The storage of data was approved by the Danish Data Protection Agency (2012–58-0004).

Study population

The study population consisted of women who had a VH or MP performed during 2010–2014 (both inclusive) at specialized urogynecological units in the Capital Region (Gentofte Hospital, Herlev Hospital, Hillerød Hospital, and Hvidovre Hospital).

Women with a previous POP procedure in the apical compartment were excluded. Exclusion criteria also included indications other than POP for VH, known connective tissue disease, MP accompanied by hysteropexy, and other concomitant surgical procedures at the time of the primary POP surgery (e.g., midurethral slings, rectal surgery, or laparoscopy).

In total, 590 patients (295 patient pairs) were matched. The patients treated with MP and VH were comparable on age at surgery, body mass index, smoker status, weekly alcohol consumption, ASA classification, cesarean sections, vaginal deliveries, previous colporrhaphy, antithrombotic treatment, surgeons' experience, concomitant surgery, and stage of prolapse in the anterior and posterior compartments. The two groups had, because of the matching, exactly the same distribution of

prolapse stage in the apical compartment (stage I: 4 patient pairs, stage II: 208 patient pairs, stage III: 76 patient pairs, stage IV: 7 patient pairs). The only significant difference identified was in preoperative local estrogen treatment, which could be explained by different instructions at the participating units. The mean age was 59.6 (standard deviation [SD] ± 13.0) for MP patients vs 61.1 (SD ± 11.4) for VH patients Tolstrup et al. [12].

All data collection was limited to 31 August 2016, meaning that the observed follow-up time ranged from 20 to 80 months. The primary cost analysis was based on 20-month follow-up observations, which all patients had. A secondary analysis used the entire registered observation period up to 80 months (see Fig. 2). In this analysis, the costs were weighted by the number of observed patients at the time of the cost occurrence.

Surgical techniques

In the Manchester–Fothergill procedures, the cervix was isolated and amputated, whereupon the remaining uterus was suspended by re-attaching the cardinal ligaments to the anterior part of the uterus. For all vaginal hysterectomies, the vaginal vault was suspended by low or high uterosacral ligament suspension. The VH and MP could be accompanied by anterior and/or posterior colporrhaphy and/or perineorrhaphy, but never by a continence operation Tolstrup et al. [12].

A urogynecological specialist was defined as a consultant working more than 50% of his/her work time in urogynecology.

Costs

The cost analysis was designed with the hospitals as the analytical perspective, which means that the analysis reports on hospital resource use and assumes identical resource use in the primary sector and elsewhere for the two groups of patients. Costs of pathological analyses of remaining uteruses and cervices were included, and when the tissue samples were taken in the primary sector and at private gynecologists.

Unit costs were obtained from relevant departments or hospital administration, calculated mainly based on salary expenses, or estimated by local experts. A list of all unit costs is accessible in Appendix 1. All costs were obtained in DKK (year 2016) and converted to Euros (1 € = 7.5 DKK).

The cost of the primary operations was estimated based on the duration of the procedure, wages to personnel, utensils (sterilization of operating instruments, sutures, band aid, gloves and smocks for the operating personnel, and covers for the operating table), pathological tests, use of the operating theater, and nights of hospitalization. For both types of operations, it was assumed that two operating nurses and one nurse anesthetist were present during the time of operation and anesthesia. During the operation one senior gynecologist and one junior gynecologist were assumed to attend. A senior anesthetist was assumed to be in charge of two operating theaters at a time; thus, costs of his/her attendance was assumed to be half the wage for the time of anesthesia. We added half an hour's work for the two gynecologists to read the medical record, do the surgical wash, and see the patient before and after the operation. In the PACU, one nurse was assumed to care for two patients at a time; thus, costs of his/her attendance were assumed to be half the wage of the time in the PACU.

Annual salaries to healthcare professionals were obtained from the hospital administration (122,000 €/year for a hospital physician senior, 77,333 €/year for a hospital physician junior, 60,667 €/year for a nurse anesthetist, 56,267 €/year for a nurse in an operating theater or PACU, and 56,000 €/year for a physiotherapist). A full year was assumed to consist of 1,650 h and the proportion of the work time related to direct patient contact was assumed to be 40% for physicians and 60% for nurses and physiotherapists. Based on information from the hospital administration, one night of hospitalization was expected to cost 545 € including the costs of 24-h staff, running costs, hospital porter, etc. The hourly cost of the operating theater was assumed at 133 € per hour. Unit costs of utensils for operations, radiological procedures, blood products, pathological tests, and ring pessaries were obtained from relevant departments. Unit costs for subsequent contacts were based on wages and assumed the following duration of standard contacts: 30 min for an outpatient visit and 10 min for a telephone call.

Operations following complications were divided into three groups: minor, including cystoscopies, gastroscopies, and hysteroscopies, removal of sutures, and JJ-catheters; medium, including vaginal surgery; and major, including intra-abdominal surgery. Based on consensus among six urogynecological experts, costs were assumed to be proportional to the primary operation: minor complications were equivalent to 25% of MP (500 €), medium complications equivalent to 50% of MP (1,000 €), and major complications equivalent to VH with high uterosacral ligament suspension (3,500 €).

Also, unit costs of recurrence operations were assumed to be proportional to those of primary operations. Uterosacral ligament suspension corresponded a VH with a high uterosacral ligament suspension (3,500 €). A colpocleisis/colpectomy corresponded to an MP (2,000

€). Anterior colporrhaphy, posterior colporrhaphy, and enterocele repair corresponded to 80% of an MP if performed solely (1,600 €) and corresponded to an MP if performed mutually combined or combined with a perineorrhaphy (2,000 €).

Operations for urinary incontinence were estimated to cost 1,600 € for midurethral slings and urethral injection therapy, and 1,000 € for Botox injection into the bladder.

In the sensitivity analysis, costs of pathological sampling were included, even if performed in the primary sector. For patients who underwent smear tests, the costs were set to the rate of a consultation plus smear and for other patients the costs were set to a consultation plus a tissue sampling. Fees paid to private gynecologists by the regional health authorities were used as unit costs.

Costs associated with recurrences were included when patients approached with symptoms.

Duration of surgery, anesthesia, and PACU

The durations of surgery, anesthesia, and recovery were obtained from DAD. For 3–5% of VH patients and 32–38% of MP patients, the information was missing. For these patients, a median time was assigned based on stratification into surgical technique (VH or MP), suspension for VH operations (low uterosacral ligament suspension or high uterosacral ligament suspension), ASA score, and experience with the current operation of the surgeon.

Sensitivity analysis

A sensitivity analysis was performed for six parameters:

1. Costs to hospitalization overnight
2. Costs of the operating theater

Table 1 Total costs within 20 months of the primary operation

	Total costs (EUR) VH	*n*	Total costs (EUR) MP	*n*	*p* value
Primary operation	825,630	295	560,680	295	<0.0001*
Surgeons (time of surgery +30 min before/after surgery)	191,159	295	143,203	295	<0.0001**
Surgical nurses (time at operating theater)	94,799	295	69,670	295	<0.0001**
Anesthetic nurse + ½ doctor (time at operating theater)	128,176	295	94,199	295	<0.0001**
PACU nurse ½ (time at PACU)	17,361	295	12,084	295	<0.0001**
Operating theater	111,188	295	81,714	295	<0.0001**
Overnight stays	177,648	259	71,386	117	<0.0001**
Utensils	22,795	295	19,719	295	<0.0001**
Pathological evaluations	66,867	295	50,976	295	<0.0001**
Contacts (control visits)	14,941	252	17,729	260	0.04**
CT urography related to primary operation	698	3	0	0	0.25**
Complications	91,661	74	58,518	56	0.02**
Postoperative bleeding (superficial or deep)	36,110	8	3,211	2	0.02**
Unacknowledged obstruction of ureter	0	0	22,562	1	1.0**
Urinary retention	14,471	9	17,644	7	0.8**
Other	41,080	61	15,101	49	0.06**
Recurrences	94,285	49	27,558	18	0.0001**
Urinary incontinence[a]	25,072	50	20,440	51	0.8**
Uterus-dependent	0	0	16,677	51	<0.0001**
Pathological tests	0	0	3,853	49	<0.0001**
Contacts and procedures	0	0	12,824	13	0.0002**
Total costs	1,036,648	295	683,874	295	<0.0001*
Mean costs per patient	3,514		2,318		

VH vaginal hysterectomy, *MP* Manchester–Fothergill procedure, *PACU* post-anesthesia care unit

**t* test

**Wilcoxon signed rank sum

[a] De novo or persistent urinary incontinence

3. The percentage of a health care professional's working time involved in direct patient contact
4. Patients costing more than 300% of the median costs of MP and VH respectively were excluded (also, patient matches from the opposite operation group were excluded
5. The costs of sampling the pathological specimen were added regardless of whether performed in the primary sector or at private gynecologists
6. Patients with missing information about duration of surgery and/or anesthesia and/or PACU were excluded (also, patient matches from the operation group were excluded)

Statistical analysis

Paired *t* tests were applied to the analysis of costs of the primary operation and the total 20-month costs, whereas the Wilcoxon signed rank sum was used on the remaining categories. Paired *t* tests were used as sensitivity analysis. Mann–Whitney test was applied to the analysis of durations.

For all tests, a p value of ≤ 0.05 was considered significant. The statistical analyses were performed using SAS 9.4 (SAS, Cary, NC, USA).

Results

The total costs including the primary operation and subsequent events during the 20-month period were on average 3,514 € vs 2,318 € per patient operated on with VH and MP respectively.

The total cost difference between the two surgical techniques was 1,196 € (95% confidence interval (CI): 927–1,465 €) when including the 20 months after primary operation thereof 898 € (CI: 818–982 €) were related specifically to the primary operation.

The costs of the primary operation, complications, recurrences, and total costs were statistically significantly lower for MP than for VH. Costs related to uterus-dependent activities occurred for MP patients only. For costs related to urinary incontinence, de novo or persistent, there was no significant differences between the two surgery techniques.

The total costs and the different cost items are shown in Table 1. It appears that the primary operation represented 80% and 82% of the total cost for VH and MP respectively. Complications accounted for 8.8% and 8.6%; recurrences 9.0% and 4.0%; urinary incontinence 2.4% and 3.0%; and uterus-dependent activities 0% and 2.4% for VH and MP respectively.

Costs of the primary operation mainly consisted of wages of health care professionals (52.3% for VH and 56.9% for MP), costs of nights of hospitalization (21.5% for VH and 12.7% for MP), and costs of the operating theater (13.5% for VH and 14.6% for MP).

Time of operation, time in the operating theater, time in the recovery room, and hospitalization were all significantly longer for VH than for MP (Table 2).

The average cost of operations performed on patients with POP-Q stages 1 and 2 in the apical compartment was 2,207 € for MP and 3,502 € for VH ($p < 0.0001$) and for POP-Q stages 3 and 4, it was 2,603 € and 3,545 € for MP and VH respectively ($p = 0.0075$).

The costs per patient were distributed with a large middle group and few very expensive patients (Fig. 1). The few expensive patients are excluded in the sensitivity analysis.

Figure 2 shows the total costs per patient over time. The entire follow-up time is included, varying from 20 months to 80 months. The cost difference between the two surgical techniques seems to be constant over time.

Two hundred and ninety-three of the MPs and 294 of the VHs were performed by at least one urogynecological

Table 2 Time in the operating theater, time of operation, time in the recovery room, and nights of hospitalization

	VH	MP	*p* value
Time in the operating theater (min), median (range), [quartiles 5%; 95%]	165 (95–331), [110; 245] *n* = 285	120 (70–254), [84; 185] *n* = 202	<0.0001
Time of operation (minutes), median (range), [quartiles 5%; 95%]	95 (36–236), [49; 163] *n* = 285	65 (18–162), [34; 140] *n* = 202	<0.0001
Time at recovery room (min), median (range), [quartiles 5%; 95%]	110 (0–415), [55; 245] *n* = 279	81 (1–310), [25; 177] *n* = 182	<0.0001
Nights of hospitalization, median (range), [quartiles 5%; 95%]	1 (0–7), [1; 3] *n* = 295	0 (0–8), [0; 2] *n* = 295	<0.0001

Mann–Whitney (Wilcoxon) two-sided, all durations are in min

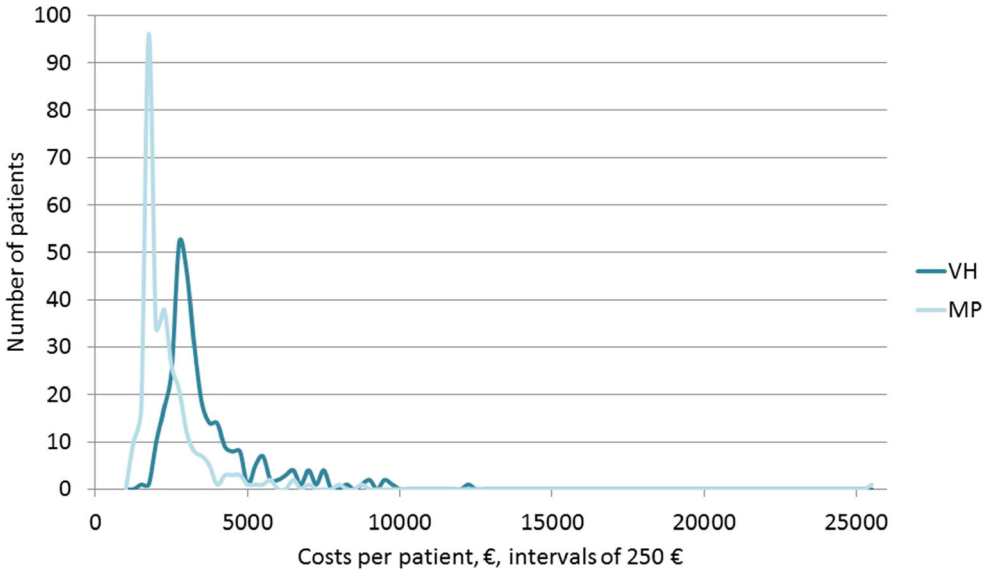

Fig. 1 Distribution of costs per patient. *VH* vaginal hysterectomy, *MP* Manchester–Fothergill procedure

specialist; 63 and 66 of these respectively were performed by two specialists.

Sensitivity analysis

The sensitivity analysis (Fig. 3) emphasizes the conclusion that the MP is less expensive than VH. The conclusion is not affected by adjusting the percentage of direct patient contact, costs of nights of hospitalization, costs of the operating theater, excluding outliers >300% of mean, including costs of pathological sampling, or exclusion of patients with missing times. In all analyses, the cost difference between the operations is highly significant ($p < 0.0001$).

Discussion

This large 20-month cost analysis shows that the MP is significantly less expensive than VH in the treatment of women

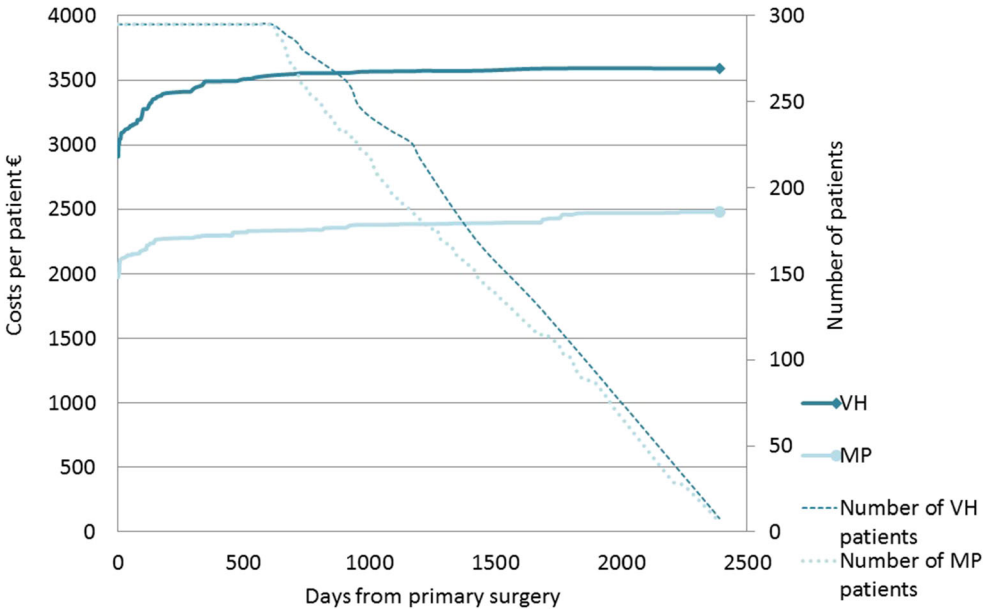

Fig. 2 Costs per patient and number of patients over time. The *unbroken* lines show the mean costs per patient at different times whereas the *dotted lines* show the number of patients remaining in the cohort. Costs are weighted by the number of patients remaining at follow-up

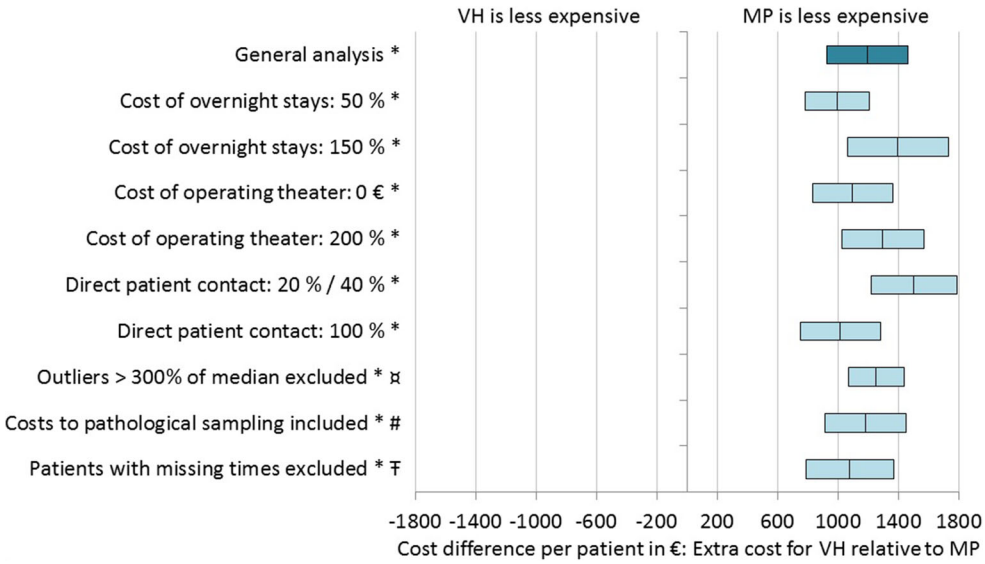

Fig. 3 Sensitivity analysis. *T* test. The *center line* in each box is the mean and the outer lines are 95% confidence intervals. *$p < 0.0001$. ¤Five VH patients were more expensive than 300% of the median costs for VH and 6 MP patients were more expensive than 300% of the median costs of the MP. These 11 patients and their matches were excluded from the sensitivity analysis on outliers. #In the MP group, 39 smears and 18 tissue samples were performed within 20 months of the primary operation. Costs of the sampling of these 57 samples were included in the analysis. ₮In total, 129 patients had missing information on duration and inclusive patient matches 250 patients were excluded, leaving 340 patients to be analyzed

with uterine prolapse, even those with POP-Q stages 3 and 4. The primary operation accounts for the largest cost difference, which reflects that VH is a more extensive operation than the MP. However, the cost difference is larger 20 months after the primary operation, as there are more reoperations after the VH. It seems like the cost difference between the two operations continues constantly throughout the first 80 months after the primary operation. Thus, significant amounts of financial resources can be saved by choosing the MP instead of VH. The basic data are supported by previous studies [9, 10, 14]. Another economics study demonstrated that uterus-preserving vaginal sacrospinous fixation yielded significantly lower costs than the laparoscopic and abdominal approach to vaginal prolapse [15].

Sensitivity analysis

Three main factors were crucial to the costs of the two operations: wages of healthcare professionals, the costs of overnight hospitalization, and the costs of time in the operating theater. Sensitivity analysis for these was performed to ensure certainty of the cost difference. Additionally, three analyses were performed: outliers were excluded, costs of pathological sampling—even those performed in the primary sector—were included, and patients with missing information on anesthesia, operation, and PACU times were excluded.

None of the factors affects the results. Thereby, the sensitivity analysis clearly illustrates that the substantial cost difference between VH and the MP is a robust finding.

Uterus-related costs

It can be argued that uterus-related costs of the MP group may increase over a longer time frame. However, we found that premenopausal women were associated with significantly higher costs than postmenopausal women, corresponding to a decrease in routine cervical smears and activities related to menstruation.

Costs of pathological sampling for MP women were included in the sensitivity analysis. The costs were artificially high because of the double registration for the women treated at hospitals; the double registration of consultation for the samples performed simultaneously; and a higher cost of the routine cervical smears, which are typically performed by a general practitioner and not by the more expensive private gynecologists. Despite artificially high costs for MP patients, this surgical technique was still significantly less expensive than the VH ($p < 0.0001$).

We looked up pathological tests for MP patients only. VH patients undergo tests, for instance, smears from the vaginal vault, despite the fact that they have no uterus.

Strengths and limitations

Strengths

Unique study design This collection of a very large number of unselected patients operated within only 5 years is unique. The data collection was made possible by the thorough registration in Danish databases and could not have been performed with a randomized controlled trial. The two patient groups were highly comparable owing to matching and the data completeness was very high owing to compulsory registration in DugaBase. Furthermore, all events concerning the operations and subsequently events could be included in the analysis because of the thorough reading of medical journals.

Robust findings The sensitivity analysis emphasizes the validity and robustness of the cost difference between the two surgical techniques.

Actual costs Information on specific events for all 590 patients was obtained from electronic patient records, and data on resource use were obtained from administrative registers. Thus, economic costs reflect the actual costs and not estimated or predicted costs.

Duration of follow-up All patients were followed for at least 20 months, which is sufficient to disclose most recurrences [12]. Moreover, the cost difference seems to continue constantly until 80 months after the primary operation (Fig. 2).

Urogynecological specialists A urogynecological specialist was present during nearly all operations, which indicates a high and uniform degree of expertise in both groups.

Limitations

Durations—missing information Because of missing information on the exact duration of surgery, time in the operating theater and PACU was calculated for some patients. Most of the missing data were for operations performed as outpatient surgery, where the duration is typically shorter than in the central operating theater.

Quality-adjusted life years Owing to a lack of data, it was not possible to quantify procedures in quality-adjusted life years (QALY). However, assuming that patients with fewer complications and recurrences have a better quality of life, the best quality of life is achieved by the less expensive operation, which is why QALY might not be relevant.

Primary sector and sick leave Some patients may have their POP handled by private gynecologists and general practitioners, which is why the actual costs are expected to be higher than demonstrated in this study. Also, costs related to sick leave were not included. However, 36% of the cohort were older than the age of retirement.

The Danish healthcare system The Danish public healthcare system is free of charge for the patients and doctors are paid a fixed salary; thus, the choice between operation types has been influenced by economic interest by neither the patient nor the doctor. However, the hospitals get different reimbursement for the MP and VH. The reimbursement for VH is higher and for MP it is lower than the actual costs for the two surgical techniques found in this analysis. This discrepancy may encourage VH to be performed.

Despite the above-mentioned limitations, this large study has shown MP to be a considerably less expensive technique than VH for treating women with apical prolapse. Substantial economic resources can be saved on health budgets if MP is preferred to VH.

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Compliance with ethical standards

Conflicts of interest KR Husby has, in relation to the study, received funding for conference participation from Tove Birthe Jensens Mindelegat and the Fund of the Danish Urogynaecological Society.

CK Tolstrup has, in relation to the study, received a research grant from the Nordic Urogynaecological Association (NUGA) and a travel grant from the Oticon Foundation, and has, outside the study, had conference fees and travel expenses paid by Astellas Pharma.

G Lose has received consultation fees from Astellas Pharma and Contura.

N Klarskov has, outside the study, received personal fees from Astellas Pharma.

Appendix 1: Unit costs and salaries

Table 3 Unit costs

	DKK	EUR	Source
Costs of supplies			
Utensils used during the primary operation			
MP	500	66.67	Department of Anesthesiology, Herlev & Gentofte Hospital, Helle Kia
VH	550	73.33	Department of Anesthesiology, Herlev & Gentofte Hospital, Helle Kia
Cystoscopy	130	17.33	Department of Anesthesiology, Herlev & Gentofte Hospital, Helle Kia
Blood products used and blood testing performed because of deep bleeding			
SAGM	861	114.80	Department of Clinical Immunology, The Blood Bank, Herlev & Gentofte hospital, Hans Åge Vollert
Fresh frozen plasma	506	67.47	Department of Clinical Immunology, The Blood Bank, Herlev & Gentofte hospital, Hans Åge Vollert
BAC test	288	38.40	Department of Clinical Immunology, The Blood Bank, Herlev & Gentofte hospital, Hans Åge Vollert
Urogynecological items			
Vaginal ring pessary	250	33.33	Department of Urogynecology, Herlev og Gentofte Hospital (from shopping portal Relex), Marianne Iversen
Catheter (permanent)	33	4.40	Department of Urogynecology, Herlev og Gentofte Hospital (from shopping portal Relex) Marianne Iversen
Catheter (single use)	0.2	0.03	Department of Urogynecology, Herlev og Gentofte Hospital (from the shopping portal Relex) Marianne Iversen
Costs of personnel, examinations, etc.			
Contacts—calculated based on salaries (for further information on salaries, see below)			
Doctor OPD	906.31	120.84	Salary of one nurse and one senior doctor for half an hour
Nurse OPD	213.13	28.42	Salary of one nurse for half an hour
No show OPD	0		–
Doctor phone call	231.06	30.81	Salary of one senior doctor for 10 min
Nurse phone call	71.04	9.47	Salary of one nurse for 10 min
Unanswered phone call	0		–
Pelvic floor muscle training	1,272.73	169.70	Salary of one physiotherapist: 4 × 45 min
Rate for operating theater and overnight stays			
Operating theater per hour	1,000	133.33	Estimated by experts
Nights of hospitalization	4,087	544.93	Herlev & Gentofte Hospital administration, Christian Bering Haarup (including 24-h staff, operating costs, hospital porter, etc.)
Pathological evaluation (costs of pathological evaluation after the primary operation [MP and VH] and due to uterus-related activities. The cervical smear is part of the national screening program for all women between the ages of 23 to 65 years. The HPV test is done in addition to the cervical smear under particular circumstances. Evaluations due to suspected cancer are much more complex/comprehensive, reflecting the higher costs)			
MP (collum)	1,296	172.80	Department of Pathology, Herlev & Gentofte Hospital, Dorte Linnemann & Birgitte Winberg
VH (uterus uncomplicated)	1,700	226.67	Department of Pathology, Herlev & Gentofte Hospital, Dorte Linnemann & Birgitte Winberg
Cervical smear	123	16.40	Department of Pathology, Amager & Hvidovre Hospital, Frank Lindhard Mabit
HPV test	276	36.80	Department of Pathology, Amager & Hvidovre Hospital, Frank Lindhard Mabit
Uterus—complicated (suspicion for cancer or fibroids)	5,000	666.67	Department of Pathology, Herlev & Gentofte Hospital, Dorte Linnemann & Birgitte Winberg

Table 3 (continued)

	DKK	EUR	Source
Other pathological evaluations (such as polyps and abrasions)	1,000	133.33	Department of Pathology, Herlev & Gentofte Hospital, Dorte Linnemann & Birgitte Winberg
Pathological sampling (costs of pathological sampling, used in the sensitivity analysis. The rate of consultation is added to the relevant pathological sampling)			
Consultation	351.49	46.87	Regional health authorities, rates for private gynecologists
Smear	60.53	8.07	Regional health authorities, rates for private gynecologists
Samples other than smear (such as Vabra)	528.13	70.42	Regional health authorities, rates for private gynecologists
Radiological evaluations			
Ultrasound (uncomplicated)	544	72.53	Department of Radiology, Herlev & Gentofte Hospital, Lone Friis
CT (uncomplicated)	906	120.80	Department of Radiology, Herlev & Gentofte Hospital, Lone Friis
MRI (uncomplicated)	2,175	290.00	Department of Radiology, Herlev & Gentofte Hospital, Lone Friis
CT urography (with contrast medium)	1,746	232.80	Department of Radiology, Herlev & Gentofte Hospital, Lone Friis
Pyelography	1,001	133.47	Department of Radiology, Herlev & Gentofte Hospital, Lone Friis
Renography	1,693	225.73	Department of Clinical Physiology and Nuclear Medicine, Herlev & Gentofte Hospital, Christina Rachel Mortensen-Mouyal
Costs of operations subsequent to the primary operation—costs set proportional to the primary operation			
Recurrence operations			
Colpocleisis	15,000	2,000	As MP
High uterosacral ligament suspension	26,250	3,500	As VH with high uterosacral ligament suspension
Anterior colporrhaphy/posterior colporrhaphy/enterocele: single compartment	12,000	1,600	As 80% MP
Anterior colporrhaphy/posterior colporrhaphy/enterocele: combined or combined with perineorrhaphy	15,000	2,000	As MP
Vaginal lateral colpopexy	26,250	3,500	As VH with high uterosacral ligament suspension
Operations due to complications (costs were set proportional to the primary operation)			
Minor	3,750	500	Scopies (cystoscopy, gastroscopy, hysteroscopy), removal of sutures, and JJ catheter
Medium	7,500	1,000	Vaginal surgery
Major	26,250	3,500	Intra-abdominal surgery
Urinary incontinence operations			
Midurethral slings/urethral injection therapy	12,000	1,600	Estimated by experts
Botox injection into the bladder for overactive bladder function	7,500	1,000	Estimated by experts

DKK Danish kroner, *EUR* Euros, *SAGM* erythrocytes stored in a fluid of saline, adenine, guanine, mannitol, *BAC* blood alcohol content, *OPD* outpatient department,*HPV* human papilloma virus,*CT* computed tomography, *MRI* magnetic resonance imaging

Table 4 Salary costs

	Salary per year (DKK)	Estimated working time involving direct clinical patient contact (%)	Salary per hour (direct patient contact)	
			DKK	EUR
Hospital physician senior (gynecologist/anesthesia)	915,000	40	1,386.36	184.85
Hospital physician junior (anesthetist/gynecologist)	580,000	40	878.79	117.17
Nurse anesthetist	455,000	60	459.60	61.28
Nurses (in the operating theater or other)	422,000	60	426.26	56.84
PACU nurses	422,000	60	426.26	56.84
Physiotherapist	420,000	60	424.24	56.57

1,650 clinical work hours per year

224 working days a year, 37 h a week, in total 1,657.6 h/year

Herlev & Gentofte Hospital administration, Christian Bering Haarup

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