Best practices in minimally invasive gynecology: making sense of the evidence

Sandberg, E.M.

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Making sense of the evidence

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Voor mijn ouders, voor hun onvoorwaardelijke steun

Voor Oma, die haar passie voor wetenschap aan haar kleinkinderen heeft doorgegeven

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Chapter 1

Introduction and thesis outline

Compared with open surgery, minimally invasive surgery (MIS) is associated with significant advantages such as decreased postoperative pain, shorter hospital stay and lower risk of (wound) infections.[1] Because of these advantages, the laparoscopic approach is nowadays often considered as the self-evident technique of many surgical procedures. Although MIS is still evolving due to the introduction of even less invasive techniques such as single port (LESS) or natural orifice surgery (NOTES), its introduction in its present form three decades ago has definitely changed daily surgical practice. MIS has even been described as the most important revolution in surgery of the last century.[2]

However, MIS was initially heavily criticized by surgeons who did not believe in the advantages of laparoscopy and were worried about the consequences of this complex technique. Still in 1997, in a paper published in the Lancet, laparoscopic surgery was defined as 'an expensive luxury, rather than a surgical revolution'.[3] Despite the criticism, MIS further developed and new instruments specifically designed for this technique were introduced (e.g. coagulation). In the twenty-first century, the implementation of advanced laparoscopic procedures drastically accelerated in all fields, including gynecology. In the Netherlands, for gynecology, this was particularly observed for laparoscopic hysterectomy (LH). In 2002, only 3% of the hysterectomies was performed laparoscopically, whereas ten years later it was 36%.[4]

With this rapid and broad introduction of MIS, external parties such as the Health Care Inspectorate (*Inspectie Gezondheidszorg*) in the Netherlands expressed in 2007 their concerns regarding patient safety during MIS. They urged for the development of a more formal quality system for surgical innovation. Yet, the introduction of new (surgical) techniques is a complex clinical dilemma in health care because of the fine line between innovation and safety. In general, the true impact of new surgical techniques can only be appreciated after a certain period of time, once the learning curve has been completed and experience has been gained. Nevertheless, it goes without saying that patient safety should be assured at all time, regardless of the surgical experience. In contrast to the introduction of new medication, techniques and devices are often introduced without extensive evaluation of efficacy and safety. In Europe, a *Conformité Européenne (CE) Marking* is sufficient to place a product on the market. Yet, this CE approval does not guarantee sufficient clinical evidence. Finally, doctors, but also patients, often presume that a new technique is per definition better than the previous one. This enthusiasm for new technology has in the past regularly outstripped evidence.[6]

Because of the above-mentioned challenges faced in the field of surgery, many guidelines have been written over the years describing how to properly implement and assess new techniques and devices. In 2009, a British research group published in the Lancet the IDEAL recommendations (Idea, Development, Exploration, Assessment, Long-term follow-

up).[7] This framework was the first one specifically established for surgical innovations. The authors of the IDEAL group described five stages through which every surgical innovation should go, from the proof of concept up to the long-term evaluation. This framework emphasizes firstly, that surgical innovations should be prospectively evaluated, secondly, that the outcome measures should be predefined and include the learning curves of the surgeons and finally, that the efficacy of the innovation should be by preference assessed through randomized controlled trials. Similarly, in 2012 in the Netherlands, a report was published on how to assure patient safety in the hospital.[8] The report recommended hospitals to perform a *Prospective Risk Inventory* (PRI) using for example the Health Care Failure Mode and Effect Analysis (HFMEA) method for high risk health care processes such as a surgery.[9] Rather than focusing on adverse events that have already occurred, the HFMEA method aims to identify potential risks by evaluating a health care process in a systematic way and most importantly before its implementation.[9]

Looking specifically at the introduction of MIS in gynecology, it can be assumed that in general this technique has not been introduced in every hospital according to the guidelines as described in previous paragraph. Although it is unrealistic that methods or tools such as IDEAL or HFMEA would foresee every risk, it seems that for certain instruments or techniques within MIS the introduction could have been better. In addition, as advanced procedures in MIS have been introduced so rapidly, it is also probable that surgeons have developed policies based on their own expert-opinion. Although it is questionable if (small) clinical variations between hospitals always negatively influence patient outcomes, it feels conflicting that in an era of evidence-based medicine, patient's care depends to a certain extent on the hospital where the patient is treated. To discard unwanted practice variations, the development of a best practice guideline is a first step. Govaerts et al. already demonstrated that for colorectal surgery standardization of care at a national level resulted in better outcomes and simultaneously in a decrease in costs.[10] Particularly for MIS, it is interesting to formulate national recommendations that are specifically tailored to this technique. Indeed, in many hospitals, protocols from open surgery are also applied to MIS procedures, and this potentially counteracts with the advantages associated with this less invasive approach.

Aim of the thesis

MIS is still a relatively young surgical specialty that has rapidly been adopted over the past decades. As such, we hypothesized that many aspects of this surgical technique are based on limited scientific support. In an era of evidence-based medicine, these *expert-*

based medical practices should be addressed. The aim of this thesis is to identify clinically relevant topics within the field of MIS and to formulate best practices for them.

Firstly, we focused on the most performed advanced procedures in MIS in gynecology: the LH. The ultimate goal was to cover all (technical) aspects of LH to allow for a uniform implementation of this procedure in the field of gynecology. As such, an evidence-based guideline providing insight into the best practice for LH was developed in collaboration with the Dutch Society of Endoscopic Surgery (WGE), a working group of the Dutch Society of Obstetrics and Gynecology (NVOG). In addition, various clinical topics related to LH that were found to be based on limited evidence were further studied. With this research, we aim to close specific knowledge gaps of LH encountered in daily practice.

Secondly, we concentrated in this thesis on the laparoscopic myomectomy (LM). Although LM has been recognized to be safe and effective, this procedure remains technical challenging. We specifically aim to get insight into the limits of this new technique and to evaluate its relative efficacy compared to other uterine-sparing treatment options for fibroids. To determine the benefits of the different approaches, we primarily evaluated outcomes that were directly relevant for patients.

In healthcare, it has been broadly recognized that the opinion and experiences of patients are of added value when evaluating the provided care. Over the past decade, tools such as patient reported outcome measures (PROMs) have being introduced in most medical fields. In this light, in the finale part of the thesis, we evaluated aspects of MIS from patient's perspectives.

Thesis outline

In the first part of this thesis, clinically relevant topics related to laparoscopic hysterectomy (LH) are discussed. To start, a guideline for LH was developed to standardize daily practice of this procedure. In **chapter 2** the clinical recommendations of this guideline are summarized. In **chapter 3** to **chapter 7**, specific issues related to LH and based on limited evidence are further studied.

In **chapter 3**, the surgical outcomes of LH are compared to vaginal hysterectomy (VH). VH has been demonstrated to be the technique of first choice for surgical removal of the uterus. Yet, looking at the increasing numbers of LHs performed at the expense of VH, re-evaluation of the two techniques based on recent literature is necessary. Similarly, in an effort to extend the benefits of minimally invasive surgery, an enthusiasm for the laparoendoscopic single site surgery (LESS) has emerged. In **chapter 4**, the literature is reviewed to determine if LESS for hysterectomy has added value over the conventional laparoscopic approach from a safety and efficacy point of view.

The utility of routine cystoscopy after hysterectomy is another controversial topic studied in this thesis. Standard cystoscopy has been recommended after hysterectomy to detect intra-operative ureter injuries. In **chapter 5** the additional value of this policy is being evaluated based on a large retrospective cohort.

The best timing to remove the indwelling urinary catheter after uncomplicated LH also remains unclear and not well-studied. To define the best moment to remove the catheter, nurses were asked to give their opinion on catheter management after LH. Also, we evaluated the standard indwelling catheter policy after LH in all Dutch hospitals. The data of both topics are presented in **chapter 6**. In addition, a randomized controlled trial was performed to evaluate if direct catheter removal is associated with similar (or better) outcomes compared to delayed removal. The results are given in **chapter 7**.

In the second part of this thesis, the laparoscopic myomectomy (LM) procedure is assessed. Myomectomy has typically been the first choice for surgical treatment of fibroids and with the advances of MIS, more procedures are being performed laparoscopically. In **chapter 9**, the limits of LM are explored by evaluating the risk of conversion. To extract uterine fibroids during LM, (power) morcellation was introduced in the field of MIS. Since the use of power morcellation was discouraged in 2014, contained morcellation has been proposed as the solution and this technique has been widely adopted. However, from an oncological point of view, the safety of this in-bag morcellation technique during myomectomy can be questioned. To assess the presence of spill after myomectomy, peritoneal washings were performed. In **chapter 8**, the results of these peritoneal washings were described.

For women requiring surgical treatment but desiring uterine conservation, a wide range of MIS options are available besides myomectomy. However, limited information exists on relative efficacy of these uterine-sparing treatment options. In **chapter 10**, different minimally invasive treatment options for fibroids are compared in terms of re-intervention risk and quality of life.

In the final part of this thesis, aspects from patient's perspectives are assessed. Patient's perspectives are being increasingly considered when determining the best care. In this light, data on medical liability are an interesting complementary source for that purpose as it gives a unique insight into care judged by patients as being substandard. In **chapter 12**, the medical claims of laparoscopic procedures in gynecology are analyzed and specifically trends and/or risk factors associated with these claims are identified. In **chapter 11**, the postoperative period at home was evaluated for patients undergoing laparoscopic surgery. As these patients tend to have a short hospital stay and recovery mostly at home, the postoperative period at home needs to be well-organized. In **chapter 11**, suggestions are made to facilitate a quick recovery and avoid unnecessary delay when complications occur.

Finally, **chapter 13** and **chapter 14** provide the general discussion including future research perspectives as well as a summary of this thesis (in Dutch and English).

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Chapter 2

Laparoscopic hysterectomy for benign indications: clinical practice guideline

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Abstract

Purpose: Since the introduction of minimally invasive gynecologic surgery, the percentage of advanced laparoscopic procedures has greatly increased worldwide. It seems therefore, timely to standardize laparoscopic gynecologic care according to the principles of evidence-based medicine. With this goal in mind, the Dutch Society of Gynecological Endoscopic Surgery initiated in The Netherlands the development of a national guideline for laparoscopic hysterectomy (LH). This present article provides a summary of the main recommendations of the guideline.

Methods: This guideline was developed following the Dutch guideline of medical specialists and in accordance with the AGREE II tool. Clinically important issues were firstly defined and translated into research questions. A literature search per topic was then conducted to identify relevant articles. The quality of the evidence of these articles was rated following the GRADE systematic. An expert panel consisting of 18 selected gynecologists was consulted to formulate best practice recommendations for each topic.

Results: Ten topics were considered in this guideline, including amongst others, the different approaches for hysterectomy, advice regarding tissue extraction, pre-operative medical treatment and prevention of ureter injury. This work resulted in the development of a clinical practical guideline of LH with evidence- and expert-based recommendations. The guideline is currently being implemented in The Netherlands.

Conclusion: A guideline for LH was developed. It gives an overview of best clinical practice recommendations. It serves to standardize care, provides guidance for daily practice and aims to guarantee the quality of LH at an (inter)national level.

Introduction

Since the introduction of laparoscopic hysterectomy (LH) more than 2 decades ago, a rapid implementation of this procedure has been observed in many countries.[1-3] For the Netherlands, the percentage of hysterectomies performed laparoscopically has increased from 3% in 2002 to 36% in 2012[2] and similar increases have been observed in other parts of the world.[1;3] Such rapid implementation can potentially result in unwarranted practice variations in health care delivery.[4] Unexplained differences in health care delivery should be addressed as they are usually the consequence of a lack of consensus and/or available evidence.[5;6] Without a convenient standard of care, doctors are more prone to adopt medical practices that are based on personal experience.[5;6] Furthermore, studies have shown that standardizing care on best practices is associated with better outcomes and reduced costs.[7] As a result, it seems timely to define a standard of care for LH, according to the principles of evidence-based medicine.

With this goal in mind, the Dutch Society of Gynecological Endoscopic Surgery (WGE) initiated the development of a guideline for LH. This guideline aims to provide gynecologists with an overview of best practices, directly applicable for daily practice. The guideline should also ensure a minimum quality of care and enhance patient safety. This article provides a summary of the main recommendations of the guideline.

Materials and methods

Development of the guideline

The WGE, a working group of the Dutch Society of Obstetrics and Gynecology (NVOG), initiated the development of the guideline. A guideline working group was assembled and consisted of three gynecologists and one resident (WJKH, PMG, ART and EMS). The guideline was developed in accordance with the Dutch guideline of medical specialists.[8] This document, recognized by all Dutch medical societies, provides a detailed overview of the process of developing an evidence-based guideline using the GRADE method.[9] The Appraisal of Guidelines for Research and Evaluation instrument (AGREE II), an internationally recognized assessment tool, was used in a second stage to evaluate the methodological rigor, transparency and quality of the developed guideline.[10] In the next subsections, the different steps undertaken to create this guideline will be briefly described.

Step 1: Key topic analysis

A brainstorming session was organized by the WGE with 40 gynecologists, all performing advanced laparoscopic procedures. During that meeting, key topics for this guideline were determined and transformed into appropriate clinical research questions.

Step 2 and 3: Literature selection, data extraction and assessment of risk of bias

For each research question, a literature search was set up in collaboration with a clinical librarian. PubMed, Medline and Cochrane databases were searched up to 1st of March 2016. Each research question had its own inclusion and exclusion criteria. Overall, we first searched for systematic reviews. If none were available, we focused on randomized controlled trials (RCTs) and, if necessary, added cohort studies as well. Studies from the eligible systematic reviews were reviewed to avoid duplicate inclusions. Only LH for benign indications and/or low-grade malignancy were considered and will hereinafter be referred to as 'laparoscopic hysterectomy' (LH). Studies focusing on endometriosis sanitation with concomitant LH as well as high-grade malignancy were not included. Study reports, letters, non-published manuscripts and articles that were not published in English were also excluded. After selecting the eligible studies, these studies were summarized in evidence tables and when possible, extracted for meta-analysis using Review Manager (version 5.2 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). The quality of evidence was rated for the different outcomes following the GRADE method.[9] The online GRADE program was used for this purpose (GRADEpro Guideline Development Tool [Software], McMaster University, Hamilton, ON, Canada, 2015, developed by Evidence Prime, Inc., available from gradepro.org).

Step 4: Concept guideline

From the initial group of 40 gynecologists who participated in the brainstorm session, an expert panel of 18 members was selected. The expert panel and the members of the guideline met a few times to discuss the research questions according to a standard template. The final recommendations were graded according to the classification used by the American Association of Gynecologic Laparoscopists (AAGL) which was adapted from the US Preventive Services Task Force:[11] Level A: Recommendations are based on good and consistent scientific evidence; Level B: Recommendations are based on limited or inconsistent scientific evidence; Level C: Recommendations are based primarily on consensus and expert opinion.

The experts wrote the first draft, after which the working guideline group merged the different topics into one document and finalized the guideline. All experts involved in the development of this document approved the guideline in its present form.

Step 5: Validation of the guideline

Two independent reviewers, different committees within the NVOG as well as the independent Knowledge Institute of Medical Specialists (KIMS) reviewed the guideline.[12] After approval, our guideline was published on the website of the NVOG to allow all Dutch gynecologists to give feedback. The guideline will be soon adopted in The Netherlands and is valid for 5 years, after which it will be updated. If necessary, it will be (partially) updated earlier.

Findings

Overall

For each of the ten main topics raised during the first brainstorm session, a literature search was performed. In total 5233 articles were reviewed and 119 unique articles were included in the guideline. In the following section, each topic and its best practice recommendations are briefly summarized. More detailed information regarding the selected literature, the quality of evidence according to the GRADE method, the search strings of the different topics and the forest plots of the main outcomes, will be published in the fall of 2017 on the website of the NVOG (http://www.nvog.nl).

Topic 1: A comparison of surgical approaches for hysterectomy

According to the Cochrane review on this topic, vaginal hysterectomy (VH) should be, when technically feasible, the approach of first choice, followed by LH and finally abdominal hysterectomy (AH).[13] However, limitations of the Cochrane review are the lack of differentiation between the various subtypes of LH (total laparoscopic hysterectomy (TLH); laparoscopic-assisted vaginal hysterectomy (LAVH) and robotic hysterectomy (RH)), and the inclusion of data from older trials performed in the implementation period. Because of these potential limitations, a new literature search was performed for this guideline, specifically comparing TLH to VH. In topic 2, the different subtypes of LH were also compared to TLH. To limit the bias of a learning curve and reflect current practice, we only focused on studies published in the last 15 years (from 1st of January 2000 up to 1st of March 2016).

TLH versus VH

As can be observed in Table 2.1, VH was associated with a significantly shorter operative time, a lower risk of conversion and a lower risk of vaginal cuff dehiscence. Patients in the TLH group had lower postoperative pain scores and required analgesia for a shorter period. The other outcomes were similar, and notably the risk of ureter and bladder injury did not differ between the groups, in contrast to what was found in previously published studies.[13] Many factors, such as patient and surgeon characteristics, influence the choice of approach. Our results show that since the implementation of LH, the differences in clinical outcomes between VH and TLH have been minimized. However, when both approaches are feasible, VH is still associated with more relevant benefits compared to LH and should therefore be the approach of first choice.

Recommendations

> When both approaches are feasible, VH still offers the most relevant benefits and should be the approach of first choice. (level A–C, Table 2.1)

Table 2.1: Summary of outcomes comparing TLH to VH

	Favors TLH	Similar TLH/VH	Favors VH	Mean difference or Odds ratio (OR)	95% confidence interval
Operative time (RCTs only)			■	+36 min	[5.90, 65.13]
Blood loss (RCTs only)		■		-38 mL	[-96.7, 21.31]
Length of stay (RCTs only)		■		-0.32 days	[-0.85, 0.20]
VAS 24hr postoperatively	■			-1.1 VAS score	[-1.74, -0.42]
Days of analgesia use	■			-0.64 days	[-1.06, -0.22]
Costs			■	3889.9 US dollars	[2120.3, 8900.0]
Major complications		■		OR 1.25	[0.60, 2.61]
Vaginal dehiscence			■	OR 6.75	[2.44, 18.69]
Ureter/bladder injury		■		OR 0.81	[0.31, 2.06]
Minor complications		■		OR 0.79	[0.52, 1.18]
Conversion			■	OR 3.77	[2.14, 6.65]
Conversion (RCTs only)		■		OR 1.00	[0.10, 9.89]
Sexual dysfunction		■		--	--
Patient satisfaction		■		--	--
Detection of intra-operative pathology	■			--	--
Cutaneous scars			■	--	--

TLH: total laparoscopic hysterectomy; VH: vaginal hysterectomy; RCT: randomized controlled trial.

Topic 2: A comparison of the different subtypes of LH

TLH versus LAVH

The percentage of hysterectomies performed using the LAVH technique is decreasing. Currently, LAVHs account for 3% of the LHs in The Netherlands.[14] Based on current literature, no clinically relevant differences were observed between the two approaches. From the meta-analysis performed on this topic, we concluded that the mean differences of 19.7 min (13.08, 26.37) for operative time and 82 ml (-151.95, -12.07) for intra-operative blood loss were not deemed to be clinically relevant. Although the risk of vaginal cuff dehiscence was higher after TLH [OR 2.97 (1.43, 6.18)], the incidence of cuff dehiscence is still low. Furthermore, no overall difference was observed for major complications [OR 1.06 (0.66, 1.68)].

Recommendations

> The surgeons should use the technique that they best mastered, as no particular preference for TLH or LAVH was observed. (level B)

TLH versus RH

The results of the meta-analysis showed no clinically relevant differences between TLH and RH for most surgical and patient outcomes. Regarding the costs of the procedure, no meta-analysis could be performed because of incomplete data. Yet, all studies showed that LH was significantly less expensive with mean differences of 1.916 US dollars,[15] 3.049 US dollars[16] and 11.214 US dollars.[17]

Recommendations

> For LH, RH has no advantages and is associated with higher costs. (level B)

TLH versus supra-cervical laparoscopic hysterectomy (SLH)

The results of the meta-analysis for this topic are summarized in Table 2.2. Despite the fact that most included studies were underpowered and nonrandomized, the expert panel concluded that no major differences were observed between the two procedures, except potentially for complications. In addition, it is important to realize that in the SLH group morcellation is always necessary, which could result in more (mini)laparotomies (topic 8). Finally, the pre-operative cervix cytology, the impact of follow-up screening and the increased risk of cyclic bleeding should also be considered when weighing the pros and cons of the two procedures.

Recommendations

No clinically relevant surgical differences were found between TLH and SLH, except potentially for complications. (level B)

It is important to counsel a patient about the pros and cons of both approaches (Table 2.2). (level C)

Shared decision making is recommended. (level C)

Table 2.2: Summary of outcomes comparing TLH to SLH

	Favors TLH	Similar TLH/SLH	Favors SLH	Mean difference or Odds ratio (OR)	95% confidence interval
Operative time		■		+7.56 min	[12.82, 2.31]
Blood loss		■		-14.09 mL	[7.66, -35.84]
Length of stay		■		+0.15 days	[0.20, 0.10]
Return to normal activities		■		3.61 days	[7.72, -0.49]
Major complications			■	OR 2.13	[1.20, 3.79]
Minor complications			■	OR 2.42	[1.42, 4.11]
Ureter injuries		■		OR 1.46	[0.45, 4.78]
Bladder injuries			■	OR 5.00	[1.82, 13.76]
Postoperative hemorrhage			■	OR 5.62	[2.18, 14.52]
Conversion			■	OR 1.67	[1.15, 2.41]
Cyclic bleeding	■			0% versus 14.3%	--
Cervix excision			■	0% versus 0.5%	--
Pelvic prolpas		Unclear*		--	--
Sexual dysfunction		■		--	--
Patient satisfaction		■		--	--

* Lethaby et al. (systematic review): no difference in rate of pelvic prolapse.
Berner et al. (RCT): higher risk of (asymptomatic) prolapse 12 months after TLH (10% versus 32%).
TLH: total laparoscopic hysterectomy; SLH: supra-cervical hysterectomy; RCT: randomized controlled trial.

Topic 3: What is the added value of pre-operative treatment—gonadotropin-releasing hormone agonists (GnRHa) or Ulipristal—prior to LH for uterine fibroids?

This topic evaluated the effect of pre-operative medical treatment (GnRHa and/or Ulipristal) on complication risk, conversion risk, intra-operative blood loss and operative time during LH. The available evidence was limited, especially because many studies did not differentiate between the different approaches of hysterectomy (abdominal, vaginal and

laparoscopic). Based on the selected literature, we concluded that there is currently no need to standard pre-operatively treat patients who desire LH for uterine fibroids as the advantages are marginal. However, substantial volume reduction has been demonstrated in some studies (two weeks in gestational age,[18] including a 47% reduction in the study of Donnez et al.[19]). Therefore, for each patient a well-considered decision should be made, taking into account the expected volume reduction and hence the possibility for a minimally invasive approach, the side effects and the costs of treatment.

Recommendations

Standard pre-operative treatment of patients with fibroids does not seem advisable as the advantages are marginal. (level B)

When uterine volume reduction is desirable, especially to increase the possibility for a minimally invasive approach, pre-operative treatment with GnRHa should be considered. (level B)

If prescribed, GnRHa should be given for at least three months. (level C)

Topic 4.1: Which patient characteristics influence surgical outcomes during laparoscopic hysterectomy?

To answer this research question, one systematic review was selected.[20] In this review, associations between patient characteristics and surgical outcomes of LH were described based on 85 articles (four RCTs, 29 prospective cohort studies, 47 retrospective cohort studies and five case-control studies).

Recommendations

It is necessary to discuss with patients the fact that high BMI, large uterine weight and/or previous surgeries (e.g. intra-abdominal adhesions) influence intraoperative blood loss, operative time and complication and conversion risks (level A)

Topic 4.2: What is the added value of bimanual examination and medical imaging (ultrasound, MRI) prior to hysterectomy?

Pre-operative gynecological examination (speculum and bimanual examination) gives surgeons information on uterine mobility and an appropriate estimation of the uterine

weight. These findings are relevant for determining the operability of the patient (i.e., best surgical approach). Additionally, an ultrasound is useful for detecting potential intra-abdominal pathologies. The expert panel agreed that an MRI is not necessarily superior to ultrasound for hysterectomy with benign indications.

Recommendations

A vaginal examination (speculum and bimanual examination) should always be performed to estimate the operability of a patient and predict the best surgical approach. (level C)

A MRI is not a standard requirement for LH. Ultrasound is sufficient to detect potential additional pathology. (level C)

Topic 5: Which instrument is the most appropriate: bipolar electrothermical energy or ultrasonic energy?

The aim of this topic was to compare bipolar electrothermical energy with ultrasonic energy, particularly with respect to patient safety. Electrothermical energy with monopolar instruments was not included in this topic.

Because of the rapid development of (new) instruments, studies quickly become outdated. The differences observed in surgical outcomes between instruments (bipolar electrothermical energy versus ultrasonic energy) were probably also influenced by surgeon's experience and preference as well as by the surgical task performed. As differences in clinical findings were small, the expert panel concluded that there was no preference of one instrument over the other. The expert panel emphasized that experience with a specific instrument is valuable and essential for a safe procedure.

Recommendations

Surgeons should use the instruments that they have the most experience with. (level C)

Sufficient knowledge of the used technique is essential. (level C)

Topic 6: What are the indications for a uterine manipulator and what is its role in preventing ureter injuries?

Recommendations

> Although there is no evidence that a uterine manipulator prevents ureter injuries, it is recommended during LH, particularly for better overview of the anatomy. (level C)
>
> There is no preference for a specific manipulator. (level B)

Topic 7: Which techniques prevent and/or detect ureter injuries during LH?

Ureter stents

As limited evidence was available for benign LH, the search was extended to articles included oncological and endometriosis/DIE cases. Ureter stents do not seem to prevent ureter injury as no significant difference was observed for ureter injuries between the group with and the group without stents [OR 2.45 (0.28; 21.29)]. Standard stent placement could also result in unnecessary complications. Stents are, however, easy to insert and improve the identification of the ureters. In the Delphi study by Janssen et al., the experts did not reach consensus regarding the additional value of ureter stents during LH.[21]

Recommendations

> Standard insertion of ureter stents during LH is not recommended. (level B)
>
> In case of expected distorted anatomy (e.g., oncology, DIE), stents can be considered. (level C)

Cystoscopy

Cystoscopy appears to be safe and results in limited extension of the operative time (mean additional time 13 min). When the overall risk of bladder and/or ureter injuries is below 2%, a standard cystoscopy is not cost-effective for LH.[22] The American Association of Gynecologic Laparoscopists (AAGL) have recommended the standard use of a cystoscopy after LH.[23] The expert panel, on the other hand, concluded that based on available evidence, including incidence data and data on cost-effectiveness, there is insufficient justification to recommend routine cystoscopy after LH. However, the threshold to perform a cystoscopy should be low. When injuries are suspected intra-operatively, additional diagnostics during surgery is recommended and for this a cystoscopy can be of

additional value. At last, one should be aware that a normal cystoscopy does not exclude the presence of (lateral thermal) injury, especially for ureter injuries.

Recommendations

A standard cystoscopy after LH is not recommended as the additional value of it has not been proven. (level B)

When a urinary tract injury is suspected intra-operatively, a low threshold for additional diagnostics is recommended (cystoscopy and/or consultation of the urologist). (level B)

Intra- and postoperative advice for ureter injuries

Recommendations

It is important to keep in mind that ureter injuries can become manifest even long after initial surgery and that symptoms can be nonspecific. (level A)

A good knowledge of the pelvic anatomy is recommended. (level C)

Topic 8: What are the current views regarding power morcellation?

Based on the available evidence, we concluded that the incidence of unexpected sarcoma varies between 1:350 and 1:2000[24] and increases with age.[25] Other risk factors associated with uterine sarcomas are the following: African race, Tamoxifen use, previous radiotherapy in the pelvic area, HLRCC syndrome and retinoblastoma in the past medical history.[25] The exact impact of malignant spill on overall survival is uncertain, but the risk of upstaging due to morcellation has been estimated to be between 15 and 64%.[24] One of the proposed solutions to minimize spillage of occult malignancy or parasitic myomas is the use of containment bags during morcellation. Although these bags are certainly not optimal yet, they are theoretically able to prevent spread of (malignant) tissue in the abdomen. Gynecologists performing LH should thoroughly counsel their patients and should acquire the skills of in-bag morcellation so that they can offer all the options to their patients. The ESGE developed a flow chart allowing patients to be classified into a low- or high-risk category for sarcomas based on their risk factors and ultrasound results.[25] However, as long as the nature of the uterine mass cannot be diagnosed pre-operatively with certainty, such classifications are not entirely reliable.

Recommendations

Counsel the patient about the risks of morcellation (risk of spill of potential malignant cells and of parasitic fibroids). (level B)

Open morcellation is not recommended when hypervascularisation is observed on ultrasound and/or MRI in combination with necrosis and/or other risk factors for sarcomas. (level C)

When uncontained morcellation is estimated to be unsafe, perform 'contained morcellation' or a (mini)laparotomy to obtain the specimen. (level C)

Topic 9: When is the best moment to remove the urinary catheter after LH?

Using a urinary catheter during LH is recommended[26] but the best moment to remove it is unclear. Although evidence was limited, particularly for LH, it seems safe to remove the urinary catheter immediately after hysterectomy. Insufficient evidence was available to determine if leaving the catheter for 6 hours offers better outcomes than immediate removal. Leaving the catheter longer than 6 hours does not seem to offer any benefits whereas it does increase the risk of urinary tract infection and prolonged hospital stay.

Recommendations

It is recommended to remove the urinary catheter within six hours after LH. (level C)

Topic 10: What advice and/or interventions are helpful to promote postoperative recovery?

Sufficient evidence is available to state that LH is associated with a shorter hospital stay and a quicker recovery than AH.[13] However, research has shown that the time to return to normal activities after LH (i.e., time to return to work) takes overall longer than would be expected.[27] To maximize the benefits of minimally invasive surgery, it is important to adequately guide patients during recovery at home. The complexity of the surgery, the pre-operative expectations of the patient and their pre-operative mental status seem to directly influence the patients' risk of prolonged absence due to sickness. Therefore, it is important to pre-operatively discuss expectations with the patients. In addition, structured and specific advice results in quicker recovery and E-Health programs can be used for that purpose, Finally, specific advice is needed for each type of hysterectomy as advice is not generalizable for all approaches of hysterectomy.[28]

Recommendations

Specific recovery advice is recommended since it will result in quicker recovery. (level B)
E-health programs are promising tools to stimulate patient recovery. (level B)
It is important to discuss preoperatively the expectations of patients regarding the surgery and recovery. (level B)

Discussion and conclusion

This guideline serves as a summary of best practices of LH, and it should provide clinicians with relevant and evidence-based information for daily practice. In other countries such as Germany, guidelines on hysterectomy have been developed as well with similar recommendations.[29] Besides the fact that such guidelines provide surgeons with an overview of the most relevant topics, studies have shown that standardization of care and subsequent guideline compliance is associated with better outcomes and reduced medical liability.[30;31] Regarding the medico-legal consequences of this guideline, it is probable that in the future it may be used for litigation in the Netherlands. Deviating from this standard of care is obviously allowed, provided that the motivation is thoroughly documented.

Regarding the methodology of this guideline, we focused on systematic reviews and RCTs. If insufficient evidence was available from the RCTs, we added cohort studies to our analysis. A limitation of this approach is that it increases the methodological and clinical heterogeneity. For instance, by including cohort studies, differences in baseline characteristics might exist, which could have influenced the outcomes. On the other hand, this method can also be seen as a strength because for rare events RCTs are often not the best study design as they are often underpowered. During the development of this guideline, we realized that, although GRADE is currently a well-established instrument to assess the quality of evidence,[9] it has its limitations as well. The main problem we encountered was that for many topics the available evidence was limited and therefore the quality of the evidence was instantly downgraded to 'low' or 'very low'. This point has been raised previously by other authors[32] and the GRADE working group[33] has stated that on occasion even low available evidence can lead to strong recommendations. The GRADE working group has also emphasized that clinical and cultural settings are of influence and might result in (slightly) different recommendations across countries.[33] Therefore it is essential to choose an expert panel that is well-supported.[33] As the development of our guideline was initiated by the Dutch medical society itself, we believe we had support

from the entire country, especially since the panel was a good representation of all Dutch gynecologists.

Conclusion

The guideline for LH serves as guidance for gynecologists performing LHs. The recommendations in this best practice review should enhance quality of care, minimize (unfavorable) practice variations at the (inter)national level and thereby increase patient safety.

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Chapter 3

Total laparoscopic hysterectomy versus vaginal hysterectomy: a systematic review and meta-analysis

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Abstract

Hysterectomies performed laparoscopically have greatly increased within the last few decades and even exceed the number of vaginal hysterectomies (VH). This systematic review compares surgical outcomes of total laparoscopic hysterectomy (TLH) and VH to evaluate which approach offers the most benefits and was conducted according to the Meta-analysis of Observational Studies in Epidemiology guidelines. A literature search was performed in PubMed, Embase, Web of Science for all relevant publications from January 2000 through February 2016. All randomized controlled trials and cohort studies for benign indication or low-grade malignancy comparing TLH to VH were considered for inclusion. From the literature search, 24 articles were found relevant and included in this review. The results of our meta-analysis showed no difference between the two groups for overall complications (Odds ratio (OR) 1.24 [0.68, 2.28] for major complications, OR 0.83 [0.53, 1.28] for minor complications), risk of ureter and bladder injuries (OR 0.81 [0.34, 1.92]), intraoperative blood loss (MD -30 mL [-67.34, 7.60]), length of hospital stay (-0.61 days [-1.23, -0.01]), VH was associated with a shorter operative time (MD 42 min [29.34, 55.91]), a lower rate of vaginal cuff dehiscence (OR 6.28 [2.38, 16.57]), and conversion to laparotomy (OR 3.89 [2.18, 6.95]). Although not significant, the costs of procedure were lower for VH (MD 3889.9 dollars [2120.3; 89000]). Patients in the TLH group had lower postoperative VAS scores (MD -1.08, [-1.74, -0.42]) and required less analgesia during a shorter period of time (MD -0.64 days, [-1.06, -0.22]). Defining the best surgical approach is a dynamic process that requires frequent re-evaluation as techniques improve. Although TLH and VH result in similar outcomes, our meta-analysis showed that when both procedures are feasible, VH is currently still associated with greater benefits: shorter operative time, lower rate of vaginal dehiscence and conversion to laparotomy, lower costs. Many factors influence choice for surgical approach to hysterectomy and shared-decision making is recommended.

Introduction

Since the first publication on laparoscopic hysterectomy (LH) in 1989, annual hysterectomies performed laparoscopically have greatly increased worldwide.[1] Similar to the United States[2] and Finland,[3] the rapid implementation of LH in the Netherlands[4] (from 3% in 2002 to 36% in 2012) is associated with a decrease of abdominal hysterectomies (AH) (68% in 2002 versus 39% in 2012) as well as vaginal hysterectomies (VH) (29% in 2002 versus 25% in 2012). Surprisingly, in 2012 the rate of performed LH surpassed for the first time the rate of VH 4. The reason for this shift seems multifactorial (development of technology, improved skills of surgeons, surgeons' preference, and increased exposure to minimally invasive techniques during residency).[4] Presently, standard practice guidelines are based on the Cochrane review[5] that states that for hysterectomies performed for benign indications, VH should be performed unless vaginal access is not possible. According to the Cochrane review LH took longer to complete.[5] Further, they reported shorter hospital length of stay and faster return to normal activity. Limitations of the Cochrane review are that the comparison of LH with VH might be influenced by the data of older trials, the low number of events of certain outcomes (which is inherent to RCTs), and the lack of differentiation between the various subtypes of LH (total laparoscopic hysterectomy, laparoscopic assisted vaginal hysterectomy, and robotic hysterectomy).

As the current trend regarding surgical approach to hysterectomy does not agree with available evidence, it should be re-evaluated if the numbers of LHs need to be cut down and if an active counseling in favor of VH should be encouraged. In this light, the aim of this study is to perform a systematic review and meta-analysis comparing surgical outcomes of specifically TLH and VH based on recent studies.

Methods

Eligibility criteria, information sources, search strategy

The systematic review and meta-analysis was conducted according to Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) guidelines.[6] A search of the literature in PubMed, Medline and Web of Science included identifying published original articles from January 1, 2000 through March 1, 2016 comparing TLH and VH. The search was set up in collaboration with a clinical librarian and exact search terms are presented in Appendix 3.1. Randomized controlled trials (RCTs) were included as well as prospective and retrospective cohort studies and comparative case series. Only benign indications for hysterectomy and low-grade (pre)malignancy (cervical intraepithelial neoplasia or endometrial hyperplasia) without lymph node dissection were included. As we aimed to

specifically analyze the TLH procedure, studies were only included if the entire procedure was performed laparoscopically (type IV according to the American Association of Gynecologic laparoscopists[7]). When it was unclear which subtype of LH was performed, studies were excluded. Other exclusion criteria were studies not published in English, non-original articles, animal studies, cohort studies with less than 10 patients per subgroup, published abstracts without a full manuscript, and reports from meetings. Patients with concomitant procedures (e.g. prolapse surgery) other than salpingo-oophorectomy were also excluded as was the supracervical approach owing to not being applicable to the vaginal approach.

Study selection and data extraction

The first two authors (EMS and ART) independently screened titles and abstracts for relevance. Potentially relevant studies were obtained in full text and assessed for inclusion. In case of disagreement, a third author (FWJ) was consulted. The cross-references of the selected articles were checked to identify other potential relevant studies.

To evaluate the two hysterectomy approaches, the following outcomes were primarily assessed and extracted from the included studies: operative time, blood loss, length of stay, complications, postoperative pain, patient satisfaction, sexual function, and costs. We only included postoperative pain expressed on a self-reported scale (e.g. Visual Analogous Scale (VAS), numerical rating scale (NRS)[8]). All complications described in the selected articles were classified into 'major' and 'minor' complications as defined by the Dutch Society of Obstetrics and Gynecology.[9] Major complications included major hemorrhage or hematoma (requiring transfusion); urinary tract, bowel or vascular injury; pulmonary embolism; major anesthesia problems; wound dehiscence (vaginal cuff dehiscence and port site hernia); and conversion to laparotomy. Minor complications were defined as hemorrhage (not requiring transfusion) or hematoma (with spontaneous drainage); infection of the chest, urinary tract, wound, pelvis, other or pyrexia 38 °C on any single occasion; deep vein thrombosis; other minor complication requiring treatment (including voiding dysfunction and ileus).

All data were when possible pooled for meta-analysis. To limit bias additional subanalysis for RCTs only was performed. For each included RCT study, study characteristics were also collected and summarized in tables using the templates of Review Manager v.5.1 software designed for composing Cochrane reviews: methodological details, number of included participants, country where the study was conducted, potential disclosures or funding, and characteristics of the participants (age, body mass index (BMI), previous surgery and uterine weight).

Assessment of risk of bias

The risk of bias of all selected papers was assessed using the checklists adapted from Guyatt et al.[10] (Table 3.1).

Quality of evidence was rated according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach,[11] which judges the quality of evidence for each outcome, not for individual studies. The quality of evidence was classified into one of four categories: high quality, moderate quality, low quality or very low quality. We used the online GRADE program (GRADEpro Guideline Development Tool [Software], McMaster University, Hamilton, ON, Canada 2015, developed by Evidence Prime, Inc., available from gradepro.org). The quality of evidence for a specific outcome was assessed based on five criteria as shown in Table 3.1. The GRADE methodology recommends first considering RCTs. When sufficient evidence could not be found in these studies, cohort studies were added to the analysis.

Table 3.1: Criteria for risk assessment (individual studies and per outcome)

Criteria for risk of bias of selected papers (adapted from Guyatt)	
RCTs	Observational studies
1. Random sequence generation	1. Appropriate eligibility criteria
2. Allocation concealment	2. Adequate measurement of both exposure and outcome
3. Blinding of participants, surgeons and investigators	3. Adequate control of confounding
4. Incomplete accounting of patients and outcome events	4. Loss to follow-up*
5. Loss to follow-up*	
6. Selective reporting bias	
7. Other: e.g. reporting bias or confounders such as co-interventions and/or difference in surgical experience	

Criteria for a specific outcome according to GRADE method
1. Limitations in design (downgraded when >25% of the participants were from studies with a high risk of bias);
2. Inconsistency of results (downgraded when inconsistent findings across studies were observed);
3. Indirectness (downgraded when the target population - patients older than 18 years, undergoing hysterectomy - was not included);
4. Imprecision (downgraded when the 95% confidence was wide and included no effect and/or the patient size was not optimal);
5. Other (e.g. publication bias).

* Loss to follow-up, which was defined as low risk when less than 10% were lost to follow-up and as high risk when more than 20%. The risk of bias was reported as unclear for retrospective studies.

Data synthesis and statistical analysis

Meta-analysis was conducted using the Review Manager v.5.1 software designed and used in Cochrane reviews. Random effects models were used. For dichotomous variables, results were given as odds ratios (ORs). For continuous outcomes, the results were expressed as mean differences (MDs). When summary data were missing, e.g. only the median and range were available, data were transformed when possible according to the definitions of Hozo et al.[12]

Results

Study selection and study characteristics

The search strategy identified 2268 articles, of which 1155 were duplicate records. As can been seen in the flow-diagram (Figure 3.1), 24 of the 1205 screened articles were included in this review.[13-36] Studies were excluded owing to duplication of study cohorts in more than one article, overlapping study periods making it difficult to differentiate data, for meta-analyses only the largest was included. In total 3955 women were included in the TLH group and 4969 women in the VH group. The selection of articles comprised 7 RCTs,[30-36] 6 prospective cohort studies[17;20;23-25;29] and 11 retrospective cohort studies.[13-16;18;19;21;22;26-28] The included studies are summarized in Appendix 3.2 (available online).

Randomized controlled trials

Of the included RCTs, three originated from Italy,[30;32;34] one from Egypt,[35] one from Czech Republic,[33] one from Brasil[31] and one from India.[36] All studies had a single center design. Patients and/or staff were not blinded in any of the RCTs. Each arm included 20 to 41 women. Four studies, included a randomized third arm (abdominal hysterectomy or laparoscopic assisted vaginal hysterectomy).[31;33;35;36] Six studies reported no significant difference in patient characteristics with respect to age, BMI, previous surgery, and uterine weight.[30;32-36] In one study baseline characteristics were unclear.[31]

Cohort studies

Of the included cohort studies, two studies originated from the United States,[13;22] one from Canada,[19] two from France,[25;29] four from Italy,[14;27;28;32] two from Korea,[21;26] one from Turkey[24;37] and five from Germany.[15-18;20] Seventeen studies had a single-center design,[13-24;26-29] one study was multi-center.[25] The LH groups included 35 to 958 patients and the VH groups included 40 to 2534 patients.[13-29] In seven studies, a third or fourth treatment group was

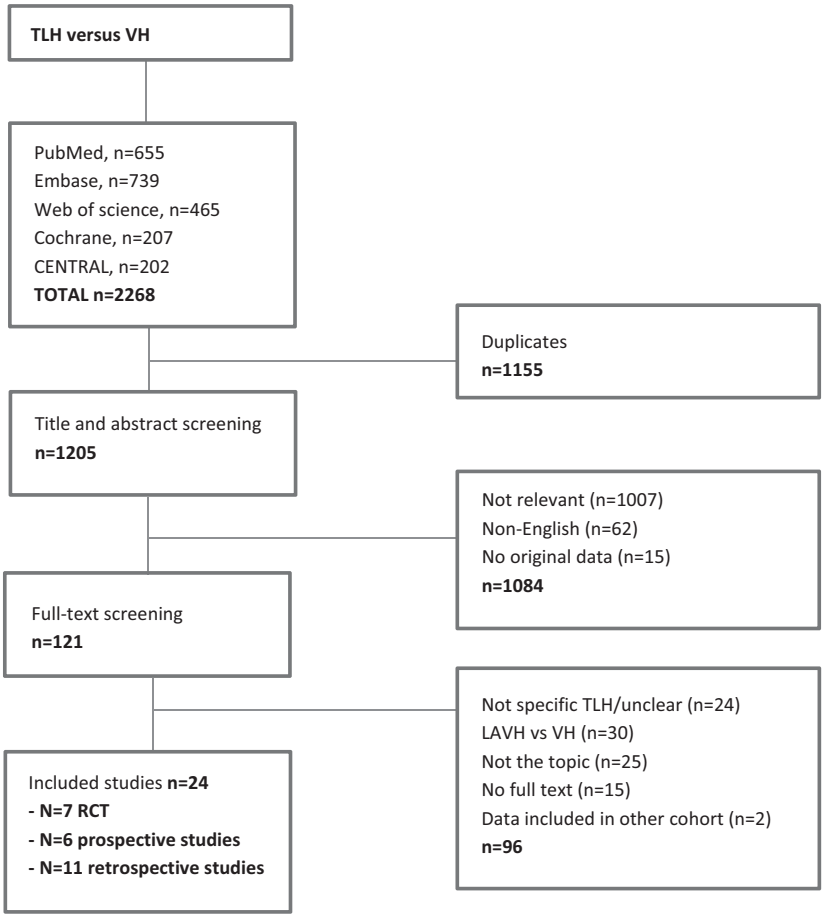

Figure 3.1: Flow diagram of literature search.

included in the comparison (abdominal hysterectomy and laparoscopic assisted vaginal hysterectomy).[14;16;20;22;24;25;29;37] In six studies, at least one of the patient characteristics (age, BMI, previous procedures and uterine weight) differed significantly between the TLH and VH group.[14;16;19;25-27]

In nine studies, it was explicitly mentioned that patients with prolapse as indication for hysterectomy were excluded and/or that no other concomitant surgery, except salpingo-oophorectomy, was performed.[14;17-20;23;26;28;29] With respect to the other indication for surgery, studies did not show major differences or indications were not clearly defined.

Risk of bias

The risk of bias for the individual studies were summarized as noted in Figure 3.2 (RCTs)[29-35] and Figure 3.3 (cohort studies).[16;19;22-24;28;13-16;18;19;21;22;26-28] For the overview of GRADE findings, see Table 3.2.

Operative time, intra-operative blood loss and length of stay

The meta-analysis included 14 studies with operative time data and found a shorter operative time in the VH group, for all included studies (42 min [29.34, 55.91] I^2=98%)[13-

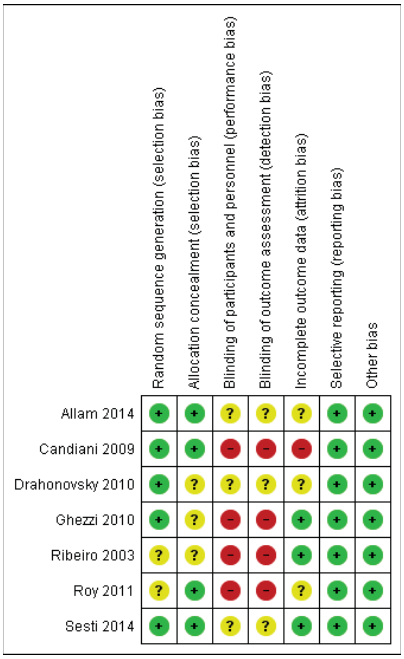

Figure 3.2a: Quality assesment of RCTs. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

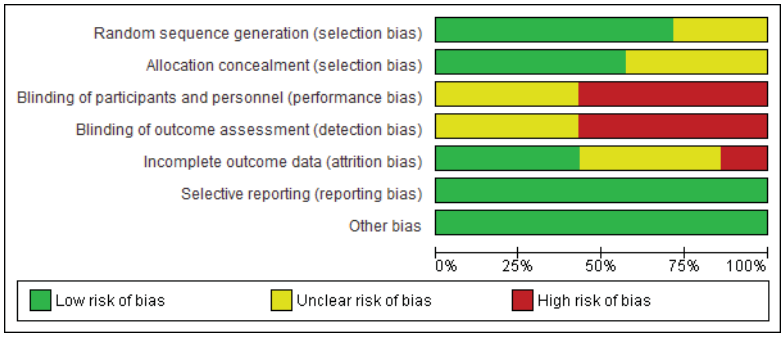

Figure 3.2b: Quality assesment of RCTs. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

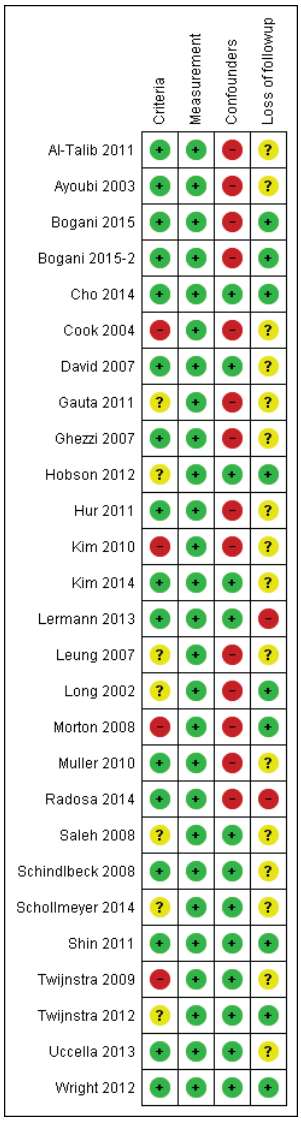

Figure 3.3a: Quality assessment of cohort studies. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

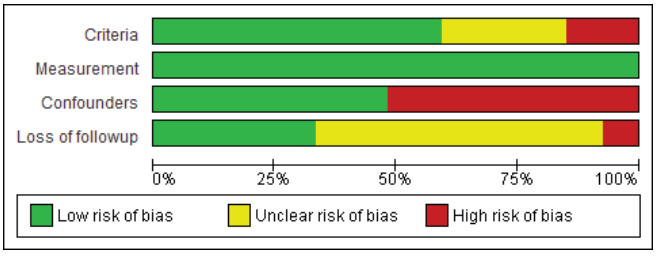

Figure 3.3b: Quality assessment of cohort studies. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Table 3.2: GRADE assessment for TLH compared to VH for hysterectomy

Quality assessment							Summary of findings				
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With VH	With TLH		Risk with VH	Risk difference with TLH
OR time											
415 (7 RCTs)	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	207	208	-		MD 36 min more (5.89 more to 65.14 more)
Blood loss											
415 (7 RCTs)	not serious	serious [2]	not serious	serious [3]	none	⊕⊕◯◯ LOW	207	208	-		MD 38 ml more (96.7 fewer to 21.31 more)
Length of stay											
415 (7 RCTs)	serious [4]	very serious [2]	not serious	not serious	none	⊕◯◯◯ VERY LOW	207	208	-		MD 0.32 days fewer (0.85 fewer to 0.2 more)
Complications - major											
6423 (14 observational studies)	serious [5]	serious [2]	not serious	serious [3]	none	⊕◯◯◯ VERY LOW	89/3855 (2.3%)	104/2568 (4.0%)	OR 1.49 (0.78 to 2.85)	23 per 1,000	11 more per 1,000 (5 fewer to 40 more)
Complications - minor											
2384 (12 observational studies)	very serious [5]	not serious	not serious	serious [3]	none	⊕◯◯◯ VERY LOW	72/1156 (6.2%)	49/1228 (4.0%)	OR 0.83 (0.53 to 1.28)	62 per 1,000	10 fewer per 1,000 (28 fewer to 16 more)

VAS score											
202 (3 RCTs)	serious	not serious	not serious	serious [6]	none	⊕⊕◯◯ LOW	101	101	-	The mean VAS Score was 3.5 VAS	MD 1.1 VAS lower (1.74 lower to 0.42 higher)
Costs											
842 (3 observational studies)	serious [7]	serious [8]	not serious	serious [1]	none	⊕◯◯◯ VERY LOW	337	505	-	The mean costs was 16874.85 dollars (US)	MD 33899 dollars (US) higher (2120.3 higher to 8900.1 higher)
Sexual function											
874 (5 observational studies)	serious [9]	not serious	not serious	not serious	none	⊕◯◯◯ VERY LOW					
Patient satisfaction											
517 (2 observational studies)	serious [9]	not serious	not serious	not serious	none	⊕◯◯◯ VERY LOW					

CI: Confidence interval; MD: Mean difference; OR: Odds ratio.
1. Wide confidence interval
2. Some studies in favor of VH, other in favor of TLH
3. Crossing the line of no effect, wide confidence interval
4. Different local protocols regarding length of stay
5. Different definitions of complications
6. Underpowered
7. Bias according to country
8. Inconsistency in results between the two countries
9. Different questionnaires used

[19;21;25;30;33-36] and RCTs only (36 min [5.89, 65.14], I²=98%, 6 studies).[30;32-36] For the outcome intra-operative blood loss, 10 studies were pooled for analyze and no difference was observed between TLH and VH (30 mL ([-67.3, 7.6], I²=82%, 10 studies, and 38 mL when analyzing the six RCTs ([-96.70, 21.31], I²=83%)).[13;14;16;19;21;30;33-36] In the 12 studies analyzed, a non-significant shorter length of hospital stay was found in the TLH group (-0.61 day [-1.23, 0.01], I²=98%, and for RCTs -0.32 day, [-0.85, 0.20], I²=90%).[14;16-19;25;26;30;33-36]

Complications

Fifteen of the studies included in the analysis mentioned complications.[13;15;16;18;19;21;22;25;28;30;31;33-36] When dividing the complications into major and minor, no difference was observed between groups (major complications OR 1.49 [0.78, 2.85], I²=62%, 15 studies;[13;15;16;18;19;21;22;25;28;30;31;33-36] minor complications OR 0.83 [0.53, 1.28], I²=0%, 12 studies[15;16;18;19;21;25;28;30;31;33-35]). Subanalysis for the 7 RCTs only did not show a significant difference either (major complications OR 0.59 [0.30, 1.15], I²=0%, minor complications OR 0.85 [0.16, 4.56], I²=49%),[29-35] and subanalysis of the different types of complications showed no significant difference between groups, other than for risk of vaginal cuff dehiscence.[13;15;16;18;19;21;22;25;28;30;31;33-36]

In our meta-analysis, based on 7 studies,[18;19;21;22;27;31;33] TLH was associated with a higher risk of vaginal cuff dehiscence (OR=6.28, [2.37, 16.57], I²=0%[18;19;21;22;27;31;33]), varying up to 7.5% after LH and less than 1% for VH. Regarding specifically ureter and bladder injuries in 12 studies, no difference between LH and VH was observed (overall OR 0.81, [0.34, 1.92], I²=8%, bladder injuries OR 0.49 [0.19, 1.27], I²=9%, ureter injuries OR 1.31 [0.26, 6.58], I²=0%).[15;16;18;21;25;28;30;31;33-36] Conversion risk to laparotomy was higher in the TLH group (OR 3.89, [2.18, 6.95], I²=0%, 12 studies).[13;14;18;19;25;30-36] However, only one study showed a significant difference.25 When analyzing the 7 RCTs only, no difference was observed (OR 1.00 [0.10, 9.89], I²=0%).[29-35]

Post-operative pain scores, costs and sexual function

Five randomized controlled studies and one prospective study reported on patient pain scores at different postoperative times using the VAS score.[17;30;32;34-36] In the study by Ghezzi et al., patients who underwent VH experienced more pain at each evaluated time point (1, 3, 8 and 24 hours after surgery).[32] Candiani et al. compared pain scores on the first, second and third postoperative day.[34] A significant difference was observed in favor of the TLH group only on the first postoperative day (p=0.23). Similarly, Allam et al. demonstrated significantly less pain in the TLH group on the first day after surgery (p<.001).[35] Sesti et al. described 53% of the TLH and 47% of the VH patients had a postoperative VAS score of 0

(signifying that no pain was experienced).[30] Roy et al. reported no experienced pain difference between TLH, VH and LAVH groups (p=0.8).[36] In the prospective study by Radosa et al., no significant difference was demonstrated in VAS scores six weeks after surgery (p=0.26).[17] Data on postoperative VAS scores 24 hours after surgery were extracted for meta-analysis and showed that the TLH group had lower pain scores (1.1 [-1.74, -0.42], I^2=52%, 3 studies[32;34;35]). Also, the duration and amount of analgesics needed after surgery were studied. Ghezzi et al. reported a significantly smaller dose needed (morphine 10mg subcutaneously) after TLH (p<.001), whereas Roy et al. found no difference for the given injectable analgesics.[32;36] Our meta-analysis, based on three studies, demonstrated that in the TLH group analgesics were used during inpatient care for a shorter period of time (0.64 day, [-1.06, -0.22], I^2=0%).[16;34;35]

Regarding surgery costs, three studies compared the total costs associated with TLH and VH but two of these studies had overlapping patient cohorts and therefore we excluded the smallest studies.[13;21;26] Meta-analysis demonstrated that VH was less expensive than TLH (3389.9 U.S. dollars, [-2120.3,8900.0], I^2=94%),[13;21] although this difference was non-significant (p=0.23). The two Korean studies showed a mean difference between the two procedures ranging from 715 to 745 US dollars compared with 6378 US dollars in the study from the United States.[13;21;26]

Sexual function outcome and patient satisfaction data could not be pooled. Seven of the 24 studies reported on sexual function after hysterectomy.[17;18;20;24;29;34;36] Two RCTs showed no significant patient reported sexual function difference between the two types of surgery 6 weeks, 3 months, 6 months, and one year after surgery,[34;36] based on physician-developed questionnaires. Radosa et al. used the validated Female Sexual Function Index (FSFI) questionnaire and showed no difference between the 2 types of surgery.[17] Muller et al. asked patients up to six year after surgery regarding change of sexual function after surgery; 24 of the 75 patients in the TLH group (35.9%) and 15 of 44 in the VH group (32%) stated that there was a change in sexual function but the study did not note whether the change was positive or negative.[18] Based on the same cohort, Lerman et al. compared the prevalence of hypoactive sexual desire disorder after hysterectomy using the Brief Profile of Female Sexual Function and showed no difference in outcome between surgical techniques.[20] In the study by Ayoubi et al. improvement of dyspareunia was seen after both TLH and VH and authors reported that the impact of VH and TLH on sexuality is less than after abdominal hysterectomy.[29] Finally, Ercan et al. used the validated Pelvic Organs Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ-12) questionnaires and reported no difference in sexual function between types of hysterectomy.[24] Though, patients after all types of hysterectomy were found to have less favorable results compared with controls who did not undergo surgery.[24]

Four studies reported on patient satisfaction.[17;18;34;36] Roy et al., Muller et al. and Radosa et al. showed a similar overall patient satisfaction rate between TLH and VH using the Health-Related Quality of Life Questionnaire (HR-QOL), a five-point scale and EuroQol five dimensions questionnaire (EQ-5D), respectively.[17;18;36] Candiani et al. collected data on patient satisfaction but did not include in the paper.[34]

Table 3.3 gives an overview of the main findings as discussed above and in Appendix 3.3 (available online) the forest plots of the results are detailed.[13-36]

Table 3.3: Overview of the main findings of the meta-analysis TLH vs VH

	Number of studies	TLH	VH	Mean difference or Odds ratio (OR)	95% confidence interval
Operative time	14		In favor	+42 min	[29.34, 55.91]
Operative time (RCTs only)	6		In favor	+36 min	[5.89, 65.14]
Blood loss	10		Similar	-30 mL	[-67.34, 7.60]
Blood loss (RCTs only)	6		Similar	-38 mL	[-96.7, 21.31]
Length of stay	12		Similar	-0.61 days	[-1.23, -0.01]
Length of stay (RCTs only)	6		Similar	-0.32 days	[-0.85, 0.20]
Major complications	14		Similar	OR 1.49	[0.78, 1.28]
Major complications (RCTs only)	7		Similar	OR 0.59	[0.30, 1.15]
Vaginal cuff	7		In favor	OR 6.28	[2.37, 16.57]
Ureter/bladder injury	12		Similar	OR 0.81	[0.34, 1.92]
Minor complication	12		Similar	OR 0.83	[0.53, 1.28]
Minor complication (RCTs only)	7		Similar	OR 0.85	[0.16, 4.56]
Conversion	7		In favor	OR 3.89	[2.18, 6.95]
Conversion (RCTs only)	7		Similar	OR 1	[0.10, 9.89]
VAS at 24 hours postoperatively	3	In favor		-1.1 VAS score	[-1.74, -0.42]
Days of analgesia use	4	In favor		-0.9 days	[-1.13, -0.75]
Costs	3		In favor	3889.9 US dollars	[2120.3, 8900.0]

Discussion

The results of our meta-analysis showed no difference between the two groups for overall risk of complications, risk of ureter and bladder injuries, intraoperative blood loss, length of hospital stay, patient satisfaction, and sexual function after surgery. VH was associated

with a shorter operative time, a lower risk of conversion to laparotomy and a lower risk of vaginal cuff dehiscence. Patients in the TLH group had lower postoperative pain scores and required less analgesia.

When looking specifically at RCTs,[30-36] operative time was shorter for VH and VAS pain scores were lower in patients undergoing TLH; all other outcomes were similar and noted no differences between procedures. This is similar to the outcomes of the Cochrane review[5] although they found a higher risk of ureter and bladder injury during LH (when compared with abdominal hysterectomy).

Kluivers et al. reported that complication rate was the most important factor for patients when considering the route of hysterectomy (LH or AH).[38] In our review, the rate of major complications between TLH and VH did not differ. Sub analysis showed though, an increased risk of vaginal cuff dehiscence when the cuff was closed laparoscopically. Although several hypothesizes have been suggested, the etiology of this rare, though severe complication in the laparoscopic group remains unclear.[39] The study by Hur et al. is the largest cohort currently available to study the incidence of vaginal cuff dehiscence after TLH and VH.[22] Despite a higher risk of cuff dehiscence in the TLH group (1.35% versus 0.08%), Hur et al. concluded that TLH remains an acceptable method to offer to patients.[22] Of the 24 studies, the highest incidence of vaginal cuff dehiscence was observed in one of the RCTs where 3 of 40 patients were affected for an unspecified reason.[33]

Another concern of the laparoscopic approach is the increased risk for urinary tract injuries. The first studies demonstrated an increased risk of bladder and/or ureter injuries after laparoscopy.[40;41] In our meta-analysis no difference was found between the LH and VH groups, which is in line with a recent systematic review on this topic.[42] The risk of conversion to laparotomy was significantly higher in the TLH group in the present meta-analysis. David et al. was the only study with a significant difference and concluded that a high risk of conversion to laparotomy was related to lack of surgical experience.[25] When excluding this study from our meta-analysis or when analyzing the RCTs only, the difference between the groups disappeared.

Other than complication rates, patient satisfaction and pain perception are important factors when comparing different surgical approaches. Few studies on patient satisfaction have been published comparing TLH and VH. In our review, four studies compared patient satisfaction and showed no difference in satisfaction between LH and VH.[17;18;34;36] Several studies have reported on postoperative VAS pain scores and results were overall in favor of the TLH group.[32;34;35] It might at first seem surprising that TLH is associated with lower pain scores as one would expect less pain in the group without abdominal scars. Yet this has

been repetitively found in various studies, including well-designed RCTs.[32;34] The difference in VAS scores between the groups after 24 hours was on average one point lower on a 10-point scale, making the clinical relevance of this finding questionable. Yet, in the RCTs of Ghezzi et al. and Candiani et al.[32;34] a significant difference of almost 3 points for the VAS score immediately postoperatively was observed (p=0.23 and p<.001). Furthermore, lower pain scores in the TLH group have also resulted in a decreased use of pain medication as was observed in our meta-analysis. The explanations for the difference in pain scores are probably multi-factorial and could be related to the severity of vaginal descensus, the traction applied on the ligaments during the procedure but also the variance in given anesthesia or postoperative pain management. Studies have shown that LH vessel sealing is associated with less pain than knotting, usually used during VH.[43] However, a recent RCT by Allam et al.,[35] noted that even when using vessel sealing in both procedures, the TLH group had significantly less pain after surgery (p<.001).[13;21;26] In spite of the small study population and wide differences in costs in the studies reviewed, we concluded that VH is less expensive than LH. Kim et al. and Cho et al., two South Korean studies showed the cost difference was relative to operative costs and anesthesia (epidural for VH versus general anesthesia for TLH) and not admission costs.[21;26] This finding should be interpreted with caution as absolute costs are often difficult to calculate given the usual non-transparent data and reimbursement variations between countries and/or hospitals. A systematic review on this topic concluded that the cost-effectiveness of hysterectomy has been poorly studied.[44] Based on the available evidence, the laparoscopic technique was the least cost-effective approach primarily owing to the expensive disposable instruments and longer operative time.[44] The prolonged operative time during TLH was also found in our review, with an overall additional operative time of 37 minutes compared with VH. In the last 5 years, the operative time during LH has shortened by 16 minutes based on data of a prospective national cohort.[45] It can be speculated that as TLH becomes more routine, operative time will decrease even more.

The consequences of the rapid implementation of LH should be addressed globally, especially regarding training and skills of the VH for the residents. Experience and preference of the surgeon are decisive factors for patients when deciding the route of hysterectomy. Consequently, if LH is being utilized more than VH, the next generation of gynecologists will be considerably less skilled in performing VH leading to a more profound decrease. In 2011, the AAGL wrote on this topic concluding that laparotomy should be avoided when possible and that most hysterectomies for benign disease should be performed either vaginally or laparoscopically,[46] although it was not mentioned which minimally invasive technique is superior. With the increased implementation of LH, it seems that the preference for VH is decreasing. Yet, based on our review, it was demonstrated that when both procedures are technically feasible, VH is still associated with greater advantages.

Limitations

One of the limitations of our study is the inclusion of different types of study designs, resulting in methodological and clinical heterogeneity and low quality of evidence according to the GRADE methodology. Most of the RCTs are small, had a single-center design, and none were blinded. Operative time was the only outcome with a moderate level of evidence.

For cohort studies, it should be taken into consideration that some studies reported differences in baseline characteristics and/or indications for surgery adding to variability in outcome data. Additionally, it cannot be excluded that in those studies other factors such as type of anesthesia, instrument used, or postoperative pain management also influence the standardization of outcomes data. Though, the inclusion of all studies can also be seen as strength as it gives an overview of all current literature. This is specifically interesting for complication rates, which are often underpowered in RCTs. Indeed, when performing sub-analyses with only RCTs, a very low number of events were observed for outcomes such as 'vaginal cuff dehiscence' and 'conversion risk', resulting in non-significant differences. Strengths of this study were that the quality of evidence was assessed systematically according to GRADE methodology, a strict definition of TLH was used, and only studies published after the year 2000 were included, thereby limiting learning curve bias. Ideally, studies would have been selected based on surgical experience but in most studies these data are not available.

Conclusion and implications

Laparoscopic hysterectomy in the field of minimally invasive gynecology has changed gynecological surgical practice, making this topic important to address. In our meta-analysis, most outcomes were similar for TLH and VH, except for operative time, the risk of vaginal cuff dehiscence, potentiality of conversion to laparotomy, the costs and postoperative pain and management. Operative time is shorter for VH; the risk of vaginal cuff dehiscence is a serious complication that although rare is notably less in VH than TLH; postoperative pain is greater in VH. The actual difference in costs between TLH and VH is unclear in most countries as few reliable studies on this topic have been published.[44] Regardless of the developments, we believe that data on costs should be transparent in each country and an important aspect to take into consideration when deciding the surgical approach.

Defining the best surgical approach requires frequent re-evaluation based on actual data that reflect current practice. Many factors influencing patient choice for one of the surgical approaches to hysterectomy and therefore shared decision making is recommended.

The overall results of this meta-analysis demonstrated that when both surgical approaches are feasible, VH should remain the surgery of choice for benign hysterectomy. Large, randomized, clinical trials are needed to compare and clarify differences in VH and LH outcomes regarding postoperative pain, patient satisfaction, and accurate and transparent cost.

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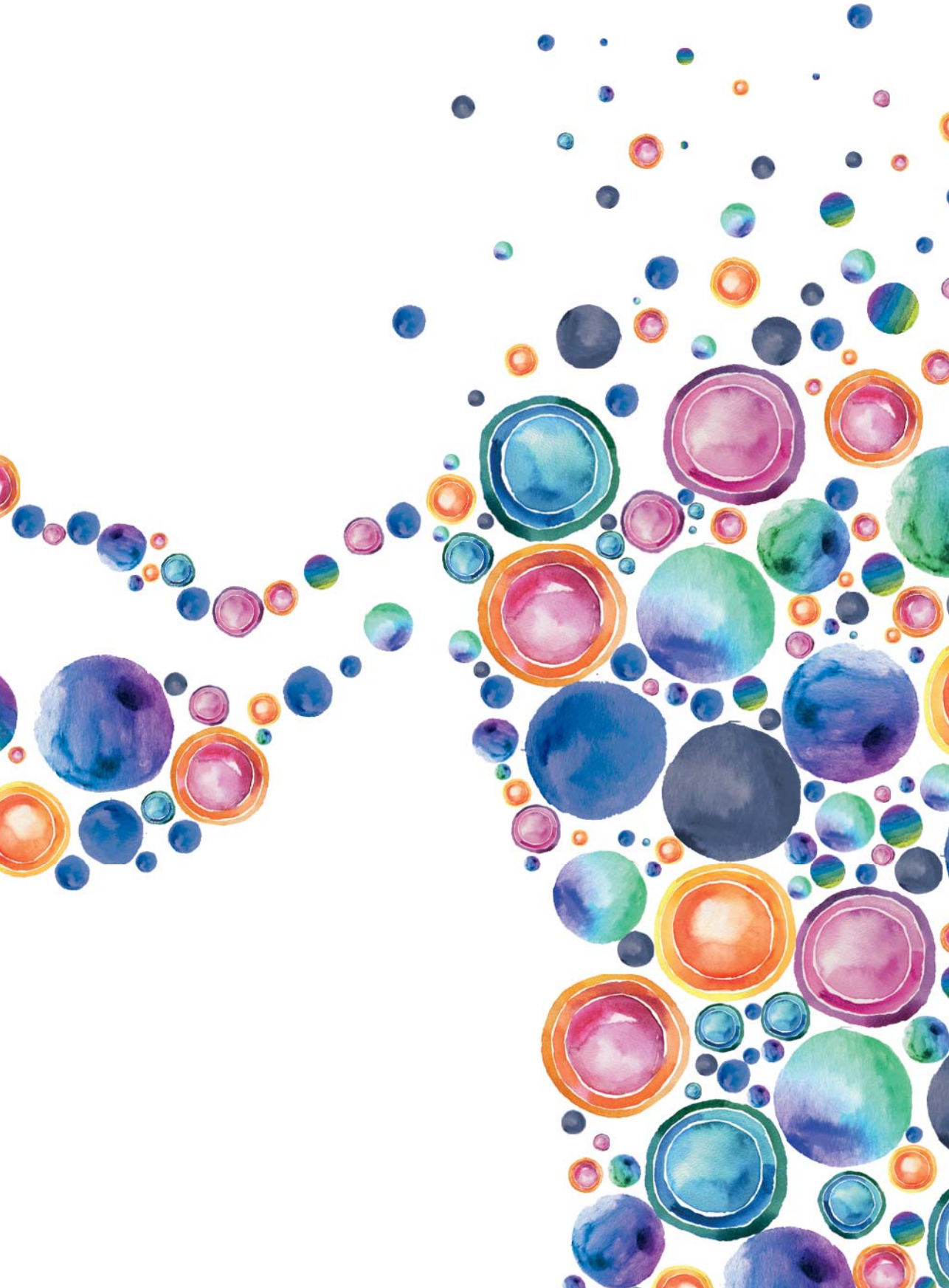
Appendix 3.1: Literature search TLH versus VH

1st of January 2000 up to 1st of March 2016

("laparoscopic hysterectomies"[tw] OR "laparoscopic hysterectomy"[tw] OR "laparoscopically assisted hysterectomies"[tw] OR "laparoscopically assisted hysterectomy"[tw] OR "laparoscopically assisted vaginal hysterectomies"[tw] OR "laparoscopically assisted vaginal hysterectomy"[tw] OR "laparoscopically assisted vaginal radical hysterectomy"[tw] OR "laparoscopical hysterectomy"[tw] OR (("Laparoscopy"[Mesh] OR "laparoscopy"[tw] OR "laparoscopic"[tw] OR laparoscop*[tw]) AND ("Hysterectomy"[Mesh] OR "hysterectomy"[tw] OR "hysterectomic"[tw] OR hysterectom*[tw]))) AND ("Hysterectomy, Vaginal"[Mesh] OR "vaginal hysterectomies"[tw] OR "vaginal hysterectomy"[tw] OR "vagina hysterectomy"[tw] OR (("vaginal"[ti] OR "vagina"[ti] OR vagina*[ti]) AND ("Hysterectomy"[Majr] OR "hysterectomy"[ti] OR "hysterectomic"[ti] OR hysterectom*[ti]))) AND ("Cohort Studies"[Mesh] OR "cohort"[tw] OR "cohorts"[tw] OR "Comparative Study"[Publication Type] OR "Comparative"[tw] OR compar*[tw] OR "Randomized Controlled Trial"[Publication Type] OR random*[tw] OR rct*[tw]) NOT ("Humans"[mesh] NOT "Animals"[mesh]) AND ("2000/01/01"[PDAT] : "3000/12/31"[PDAT])



Chapter 4

Laparoendoscopic single-site surgery versus conventional laparoscopy for hysterectomy: a systematic review and meta-analysis

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Abstract

Purpose: To assess the safety and effectiveness of LESS compared to conventional hysterectomy.

Methods: The systematic review and meta-analysis was performed according to the MOOSE guideline, and quality of evidence was assessed using GRADE. Different databases were searched up to 4th of August 2016. Randomized controlled trials and cohort studies comparing LESS to the conventional laparoscopic hysterectomy were considered for inclusion.

Results: Of the 668 unique articles, 23 were found relevant. We investigated safety by analyzing the complication rate and found no significant differences between both groups [OR 0.94 (0.61, 1.44), I^2=19%]. We assessed effectiveness by analyzing conversion risk, postoperative pain, and patient satisfaction. For conversion rates to laparotomy, no differences were identified [OR 1.60 (0.40, 6.38), I^2=45%]. In 3.5% of the cases in the LESS group, an additional port was needed during LESS. For postoperative pain scores and patient satisfaction, some of the included studies reported favourable results for LESS, but the clinical relevance was non-significant. Concerning secondary outcomes, only a difference in operative time was found in favor of the conventional group [MD 11.3 min (5.45–17.17), I^2=89%]. The quality of evidence for our primary outcomes was low or very low due to the study designs and lack of power for the specified outcomes. Therefore, caution is urged when interpreting the results.

Conclusion: The single-port technique for benign hysterectomy is feasible, safe, and equally effective compared to the conventional technique. No clinically relevant advantages were identified, and as no data on cost effectiveness are available, there are currently not enough valid arguments to broadly implement LESS for hysterectomy.

Introduction

Since the early 1990s, "minimally invasive surgery" (MIS) has been rapidly implemented into a variety of surgical disciplines. The main advantage of minimally invasive procedures is the absence of a large abdominal wound, which results in fewer wound-related complications, less postoperative pain, and a shorter hospital stay.[1] In an effort to extend these benefits, an increasing enthusiasm has emerged for the laparoendoscopic single-site surgery (LESS). In LESS, multiple laparoscopic instruments are placed through one single abdominal incision at the place of the umbilicus. The hypothesis is that single incision technique might offer advantages over the standard multi- port laparoscopy as abdominal wall trauma is decreased, potentially leading to less postoperative pain and improved cosmesis.[2-4] The potential drawbacks of the single-port approach are a larger umbilical incision and the proximity of the instruments resulting in a technical challenge, especially for advanced surgery.[5;6] It was only in 1991 that Pelosi et al. performed the first LESS hysterectomy,[7] more than 20 years after the first publication on the LESS procedure in 1969.[6] Reports have currently shown the feasibility of LESS surgery in many benign gynecologic procedures.[8;9] However, it remains debatable whether this new technology has added value over the existing conventional laparoscopic technique and whether it should be broadly implemented for hysterectomy.

The proportion of laparoscopic hysterectomies (LH) has significantly increased the last decades: from 3% in 2002 to 36% in 2012 in the Netherlands,[10] and similar numbers have been observed in other countries (United States[11] and Finland[12]). Regarding the proportion of hysterectomies performed using the LESS approach, no national overviews have been published on this topic so far. In some parts of the world, single-port hysterectomy seems well implemented. A retrospective single-hospital study from Korea showed for example that in 2013, 80% of their hysterectomies were LESS hysterectomies.[13] Hysterectomy in general is one of the most performed advanced surgeries in gynecology with approximately 600,000 procedures a year in the United States.[11] As a result, defining the surgical approach with the most advantages is essential. In this light, the aim of this study is to provide a systematic review and meta-analysis of the current comparative studies evaluating specifically LESS hysterectomy and conventional laparoscopy. We particularly focused on the safety and effectiveness of the two techniques.

Materials and methods

Eligibility criteria, information source, search strategy

This systematic review was conducted according to the MOOSE guidelines.[14] We identified original published studies through a search of Medline (PubMed version), EMBASE (Ovid version), Cochrane, Web of Science, Central, CINAHL, Academic Search Premier and Science Direct up to 4th of Augustus 2016 without restriction. The search terms included 'gynecology', 'hysterectomy', and all acronyms of LESS. The exact search terms are presented in supplemented material (Appendix 4.1). In addition, relevant studies cited in the reference lists of the selected papers were evaluated. Only comparative studies (randomized controlled trials, prospective and retrospective cohort studies) evaluating LESS versus hysterectomy for benign indications were considered for inclusion. LESS procedures had to be strictly performed through one single (umbilical) port as opposed to the conventional laparoscopic hysterectomy performed through more than one port. Studies on animals or patients aged <18 years were excluded as well as studies comprising endoscopic surgery with different techniques (e.g., hand- or robot-assisted, isobaric pneumoperitoneum). We also excluded descriptive review articles, surveys, technical reports, published abstracts without a full manuscript, reports from meetings, and trials with less than ten included participants per arm or 20 in total.

Study selection

Two reviewers independently screened the titles and abstracts for their relevance (ES and CC). Potentially relevant studies were obtained in full text and assessed for inclusion. We included studies wherein the effectiveness and/or safety of LESS compared to conventional laparoscopy for hysterectomy were investigated. To assess the safety of a procedure, we considered complication rates as primary outcome. Effectiveness refers to the potential success of a surgical procedure, and therefore, we considered: success rate (defined by the chance for a successful procedure without conversion to laparotomy and for the use of an additional port in the single-site group), postoperative pain scores, cosmetic outcomes, and patient satisfaction (including sexual function) as relevant primary outcomes. The following secondary perioperative outcomes were considered: operative time, intraoperative blood loss, and length of hospital stay. Although less important, these are also relevant identifiers for the effectiveness of a procedure.

Complications were defined according to the classification of the Dutch Society of Obstetrics and Gynecology and further divided into 'major complications' and 'minor complications'.[15] Major complications included: major hemorrhage or hematoma (requiring transfusion);

urinary tract or bowel injury; pulmonary embolism; major anesthesia problems; vaginal cuff dehiscence; port site hernia; and re-operation. Minor complications were defined as hemorrhage (not requiring transfusion) or hematoma (with spontaneous drainage); infection to the chest, urinary tract, wound, pelvic, other, or pyrexia 38 °C; deep vein thrombosis; and other minor complication requiring treatment (including voiding dysfunction and ileus). We distinguished two types of conversion: an unintended conversion to laparotomy and the need for an additional port in the single-site group. The postoperative pain should be expressed on a self-reported scale[16] (e.g., visual analogous scale (VAS), numerical rating scale (NRS)), and for cosmetic outcomes, validated questionnaires should be used.

Data extraction

Outcome data as mentioned in the previous heading as well as study and patient characteristics were extracted from the included studies. These baseline findings included study design, number of included participants, country where the study was conducted, source of funding, relevant characteristics of the participants (age, body mass index, and uterine weight), description of the procedural setting, and experience of the physician. Data related to the defined outcomes were assessed for inclusion in the meta-analysis. Sensitivity analyses were performed for randomized studies and cohort studies when relevant subgroup analyses were accomplished for TLH and LAVH.

Assessment of risk of bias

The study limitations in randomized trials and observational studies were assessed using the checklists adapted from Guyatt et al.:[17] (1) random sequence generation; (2) allocation concealment; (3) blinding of participants, surgeons, and investigators; (4) attrition bias: loss to follow- up (5) reporting bias: selective reporting and/or missing per protocol analysis; (6) other, e.g., use of non-validated outcome measures, difference in baseline characteristics between the groups and influence of co-interventions, or differing surgical experience in the compared procedures. For the first three points of the checklist, retrospective studies were rated as 'high risk', whereas attrition bias and reporting bias were marked as 'unclear', unless there was an additional reason to judge them as 'high risk'. The quality of evidence was then rated following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[18] The quality of evidence was classified into one of four categories: high quality, moderate quality, low quality, or very low quality. We used the online GRADE program (GRADEpro Guideline Development Tool [Software], McMaster University, 2015, developed by Evidence Prime, Inc., available from gradepro.org). Any discrepancies between reviewers were addressed by an open discussion.

Evidence synthesis and statistical analysis

Meta-analysis was conducted using Review Manager (Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). For continuous data, we calculated mean differences (MDs) and standard deviations (SDs); for dichotomous data, we calculated odds ratio (OD) with their 95% confidence intervals (CIs). When summary data were missing, e.g., only the median and range were available, data were transformed as appropriate according to the definitions described by Hozo.[19] We applied the random-effects model to combine data for meta-analysis.

Results

Study selection

Figure 4.1 shows the flow diagram of the literature selection for this review. The initial search yielded 668 unique references, and twenty-three studies fulfilled our inclusion criteria. Eleven studies compared LESS hysterectomy to conventional TLH,[13;20-29] eleven studies compared LESS hysterectomy to LAVH,[30-40] and in one study, both procedures were included.[41] Two studies also included supra-cervical hysterectomies.[20;21] The study by Koyanagi[42] was excluded as all data were already included in another study by the same author.[40] The selected papers were published between 2010 and 2015.

Study characteristics

A total of 1,985 women in the LESS group and 2,466 women in the conventional hysterectomy were included in six randomized controlled trials,[23;24;26;30;39;41] five prospective cohort studies,[21;27;32;36;37] and 12 retrospective cohort studies.[13;20;22;25;28;29;31;33-35;38,40] Twenty of the studies (86.9%) were performed in Asia (fifteen in Korea,[13;23-25;27;28;31;32;34;35;37-39;41] one in China,[26] two in Japan,[29;40] and two in Taiwan,[30;33] and the other three studies originated from the United States,[20] Italy,[22] and France.[21] Fourteen studies had a single center design,[20-24;26-30;33;36;37;39] one RCT was multi-center,[41] and in the other eight studies, the setting was unclear.[13;25;31;32;34;35;38;40] Fifteen studies stated that there was no potential conflict of interest to disclose,[13;20-27;30-33;35;38] five studies reported financial support (from a grant of Samsung Medical Center,[39] from a grant of Korea Health Care technology,[36;37] from Covidien,[41] and from Kyung Hee University Research Fund[34]), and three studies remained unclear about their potential conflicts.[28;29;40]

Women in the LESS group aged between 40.3 and 53 years, their BMI ranged from 22.0 to 28.7 kg/m^2, and their uterine weight ranged from 105 to 642 grams. In the conventional

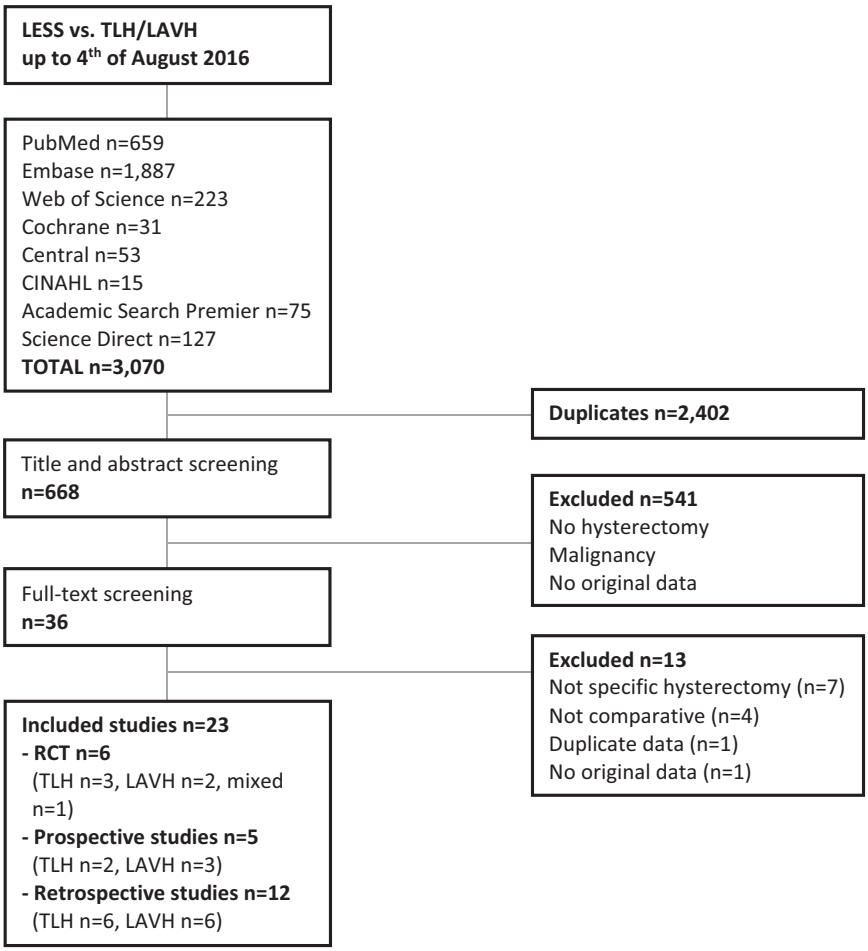

Figure 4.1: Flow diagram of the study selection.

group, the age range of the patients, their BMI, and uterine weight varied, respectively, between 41.26 and 63 years; 22.0–28.8 kg/m^2 and 9–613 g. In two studies from Lee et al., the same cohort was partially used: the smaller cohort study focused on outcomes of sexual function. We used the data from the largest cohort,[37] but for analysis of the outcome 'sexual function', we extracted the data from the partial cohort.[36]

Risk of bias of the included studies

A summary of risk of bias for the individual studies is depicted in Figure 4.2. For the overview of GRADE findings, see Table 4.1.

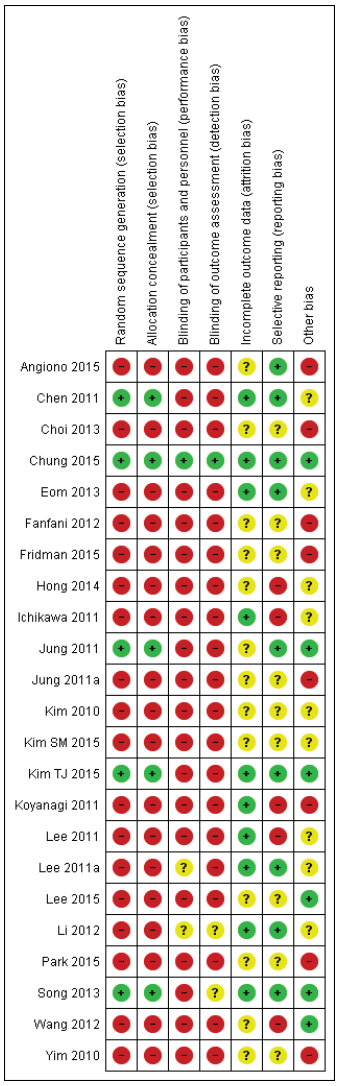

Figure 4.2a: Risk of bias per study, LESS versus conventional laparoscopic hysterectomy.

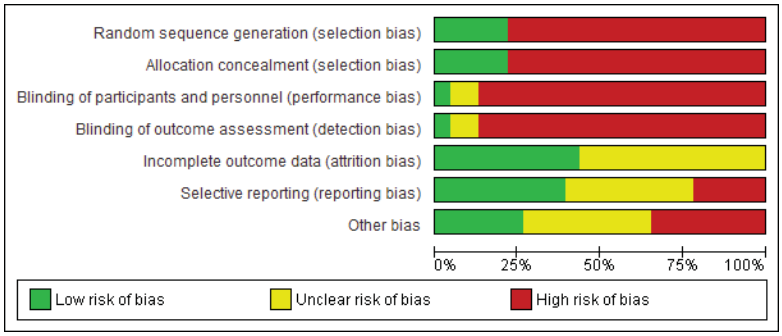

Figure 4.2b: Risk of bias summary LESS versus conventional laparoscopic hysterectomy.

Table 4.1: GRADE evidence LESS versus conventional laparoscopic hysterectomy

LESS compared to conventional laparoscopic hysterectomy											
Quality assessment							Summary of findings				
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With conventional	With LESS		Risk with conventional	Risk difference with LESS
Complications major											
3,943 (23 observational studies)	serious [1]	not serious	not serious	serious [2]	none	⊕OOO VERY LOW	121/2,153 (5.6%)	94/1,790 (5.3%)	OR 0.94 (0.61 to 1.44)	56 per 1,000	3 fewer per 1,000 (21 fewer to 23 more)
Complications minor											
2,555 (13 observational studies)	serious [1]	not serious	not serious	serious [2]	none	⊕OOO VERY LOW	61/1,368 (4.5%)	40/1,187 (3.4%)	OR 0.76 (0.46 to 1.27)	45 per 1,000	10 fewer per 1,000 (24 fewer to 11 more)
Conversion to laparotomy											
4,124 (21 observational studies)	serious [1]	not serious	not serious	very serious [2]	none	⊕OOO VERY LOW	8/2,289 (0.3%)	22/1,835 (1.2%)	OR 1.60 (0.40 to 6.38)	3 per 1,000	2 more per 1,000 (2 fewer to 18 more)

Table 4.1 continues on next page

Table 4.1: *Continued*

LESS compared to conventional laparoscopic hysterectomy											
Quality assessment							Summary of findings				
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With conventional	With LESS		Risk with conventional	Risk difference with LESS
VAS score 24 h postoperatively											
512 (5 RCTs)	serious [3]	serious [4]	not serious	not serious	none	⊕⊕OO LOW	257	255	-	The mean VAS score 24 hours postoperatively was -0.15 VAS	MD 0.14 VAS lower (0.58 lower to 0.28 higher)
Cosmetic outcomes											
353 (3 RCTs)	serious [3]	not serious	not serious	serious [5,6]	none	⊕⊕OO LOW	179	174	-	The mean cosmetic outcomes was 0	MD 0 (0 to 0)
Operative time											
620 (5 RCTs)	not serious	not serious	not serious	serious [7]	none	⊕⊕⊕O MODERATE	313	307	-	The mean operative time was 119.6 min	MD 13.14 min more (1.69 more to 24.59 more)

LESS compared to conventional laparoscopic hysterectomy											
Quality assessment							Summary of findings				
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With conventional	With LESS		Risk with conventional	Risk difference with LESS
620 (6 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	313	307	-	The mean blood loss was 158 mL	MD 5.62 mL more (0.42 more to 10.82 more)
Length of stay											
562 (4 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	284	278	-	The mean length of stay was 3.81 days	MD 0.29 days fewer (0.74 fewer to 0.17 more)

CI: Confidence interval; OR: Odds ratio; MD: Mean difference.
[1] Majority of studies are retrospective cohort studies.
[2] Wide confidence interval, crossing the line of no effect.
[3] No blinding.
[4] Differences between studies (in favor of conventional LH; in favor of LESS).
[5] Different questionnaires.
[6] Underpowered.
[7] For TLH vs LESS a significant difference of 21 min was observed. For LAVH vs LESS a non significant difference of 2 min was observed.

Safety: complications

We found no differences between complication rates when comparing LESS hysterectomy to conventional hysterectomy when clustering into major complications (23 studies, OR 0.94 (0.61, 1.44), I^2=19%, Figure 4.3a) and minor complications (13 studies, OR 0.76 (0.46–1.27), I^2=11%, Figure 4.3b). Sub-analysis specific for TLH and LAVH showed no difference (data not shown). None of the studies reported a port site herniation, though only one study mentioned that they had collected data on herniation.[26]

Effectiveness: success rate, postoperative pain scores, cosmetic results, and patient satisfaction

Conversion to laparotomy occurred in 22 of 1,835 patients (1.2%) in the LESS group, compared to 8 of 2,289 (0.35%) patients in the conventional group, which was not statistically significant (total 21 studies, OR 1.60 (0.40, 6.38), I^2=45%, Figure 4.3c). The six RCTs included reported two conversions in both groups. For the 15 cohort studies, 17 of the 20 conversions in the LESS group were observed in one study.[13] Reason for

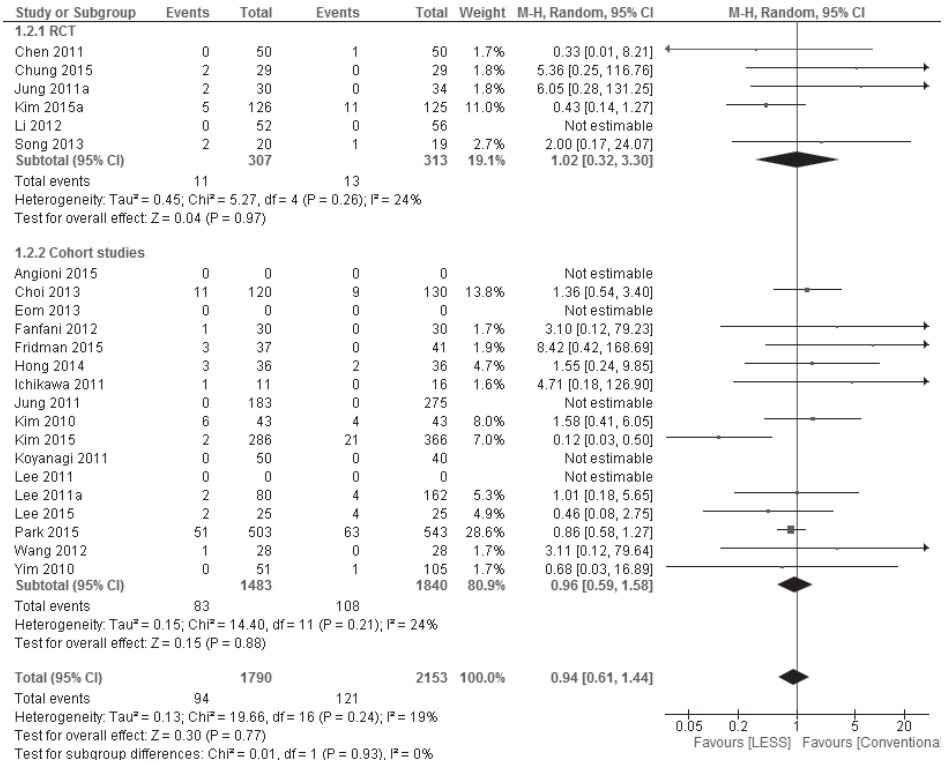

Figure 4.3a: Major complications, LESS versus conventional laparoscopic hysterectomy.

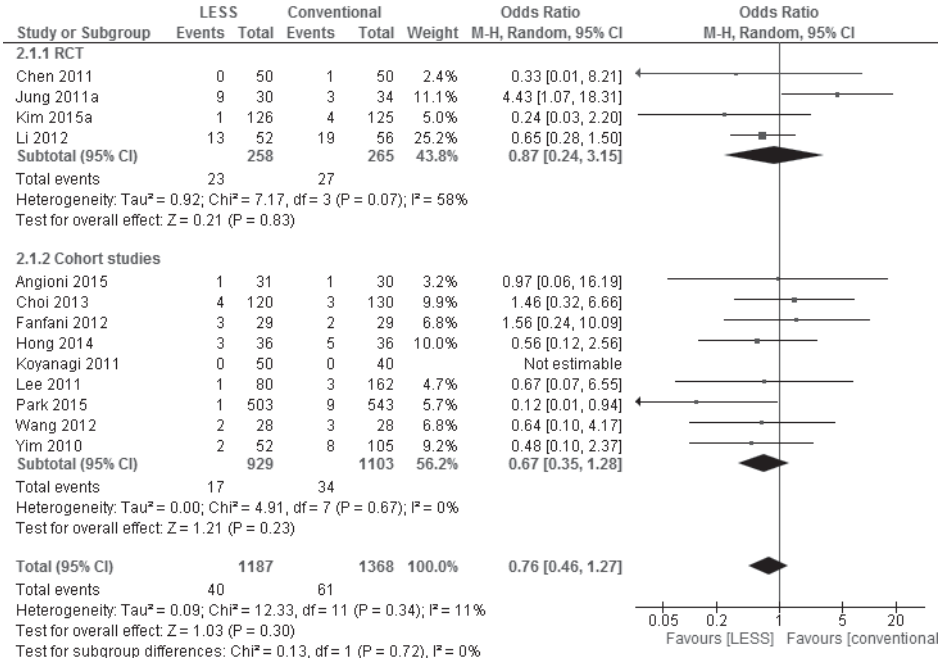

Figure 4.3b: Minor complications, LESS versus conventional laparoscopic hysterectomy.

conversions was extensive adhesions (n=18), bladder injury (n=1), bladder and bowel injury (n=1), retroperitoneal bleeding (n=1), and unspecified (n=9). When evaluating the rate of additional ports needed during LESS surgery, 48 of the 1,344 (3.5%) patients included had at least one additional port during LESS surgery versus one in the conventional group (0.06%).[38] Fourteen of these cases can be attributed to Fridman et al. where additional port was needed in 38% of the cases.[20] In the study by Jung et al. one patient had an additional port due to an incidental finding of an appendiceal mucinous adenoma.[34]

Thirteen studies assessed the pain scores of their patients at various postoperative moments (direct after surgery up to one week) using VAS scores. Five of these studies were RCTs and one had appropriate double blinding. That specific RCT found no difference between the two groups at any of the reported moments (direct, 12, 24, and 48 h post-operative).[23] The pain scores direct, 12 and 24 h after surgery were most frequently studied and, therefore, pooled for meta-analysis. Data that analyzed pain scores in the recovery unit, thus immediately after surgery, showed significantly lower pain scores after LESS hysterectomy compared to conventional hysterectomy (5 studies, MD -1.09 (-1.66, -0.52), I^2=80%, Figure 4.4a).[21-23;28] The only randomized controlled trial included in this sub-analysis showed no difference between the two groups. At 12 h, a non-significant difference was

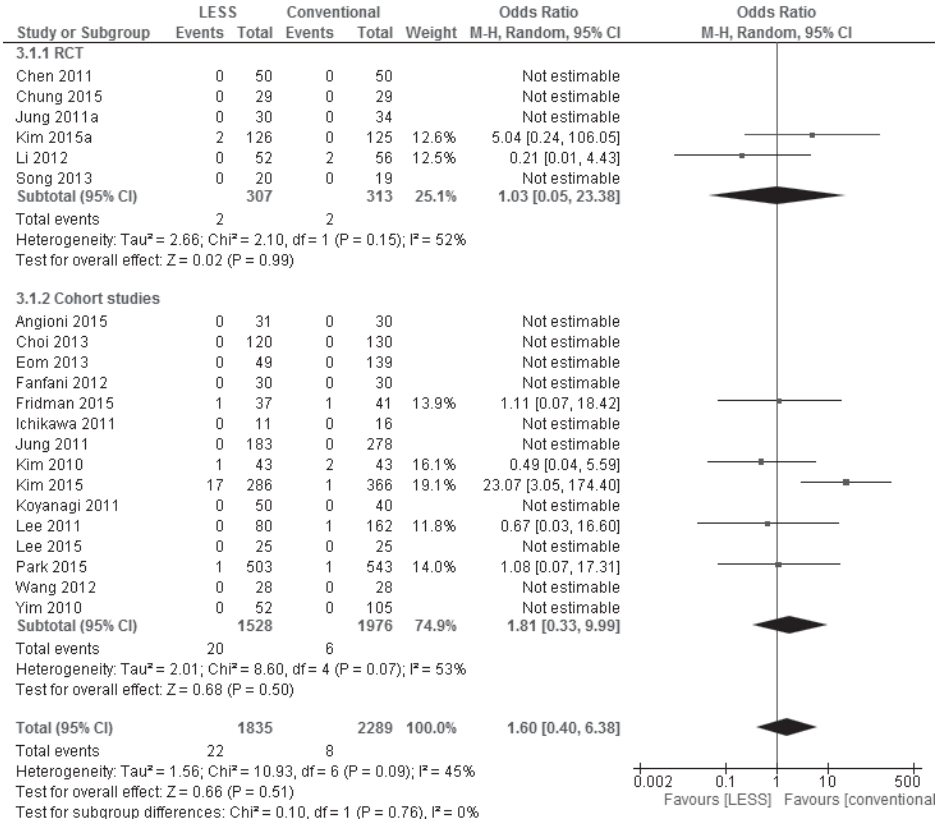

Figure 4.3c: Conversion to laparotomy, LESS versus conventional laparoscopic hysterectomy.

observed (5 studies, MD -0.19 (-0.41, 0.03), I^2=0%, Figure 4.4b). At 24 h, meta-analysis showed a significant difference between the two groups (11 studies, MD -0.45 (-0.87, -0.03), I^2=90%, Figure 4.4c).[21;23;25;28] Though, the subgroup analysis including five RCTs showed non-significant results (MD -0.15 [-0.58, 0.28]. I^2=64%). Ten studies reported on data regarding analgesic use.[22-25;28;30;33;38;39;41] Chung et al. and Jung et al. showed that the LESS group requested significantly more (additional) analgesics, but the VAS scores revealed no difference.[23;24] In contrast, the (rescue) analgesic requirement was significantly lower in the LESS group in four studies.[22;28;30;38] Similarly, Hong et al. calculated a pain-relief score based on the amount and type of analgesic used and the effectiveness on pain relief and their results were also in favor of the single-port surgery.[33] Finally, Lee et al., Kim et al. and Song et al. showed no difference in analgesic use between the two groups.[25;39;41]

Three studies reported on cosmetic results,[21;39;41] and two used the validated Body Image Questionnaire at one, four and 24 week postoperative. Patients in the LESS group were

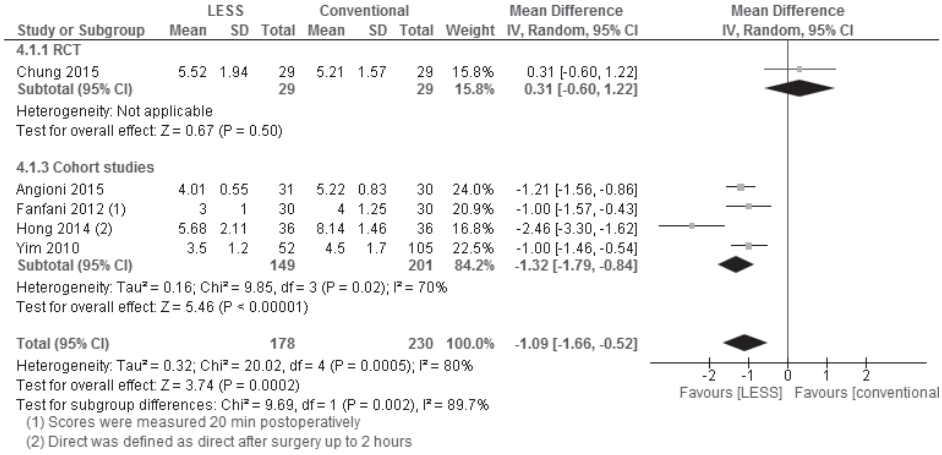

Figure 4.4a: Pain scores direct postoperative, LESS versus conventional laparoscopic hysterectomy.

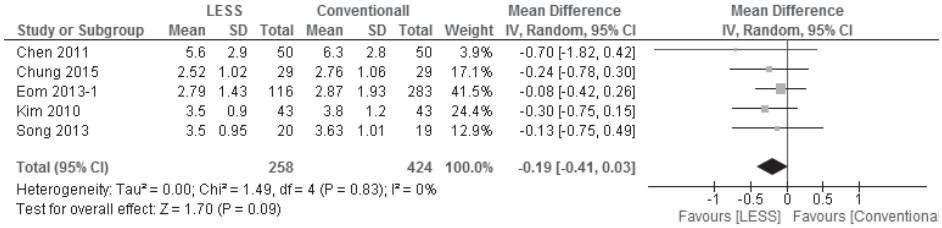

Figure 4.4b: Pain scores 12 hours postoperative, LESS versus conventional laparoscopic hysterectomy.

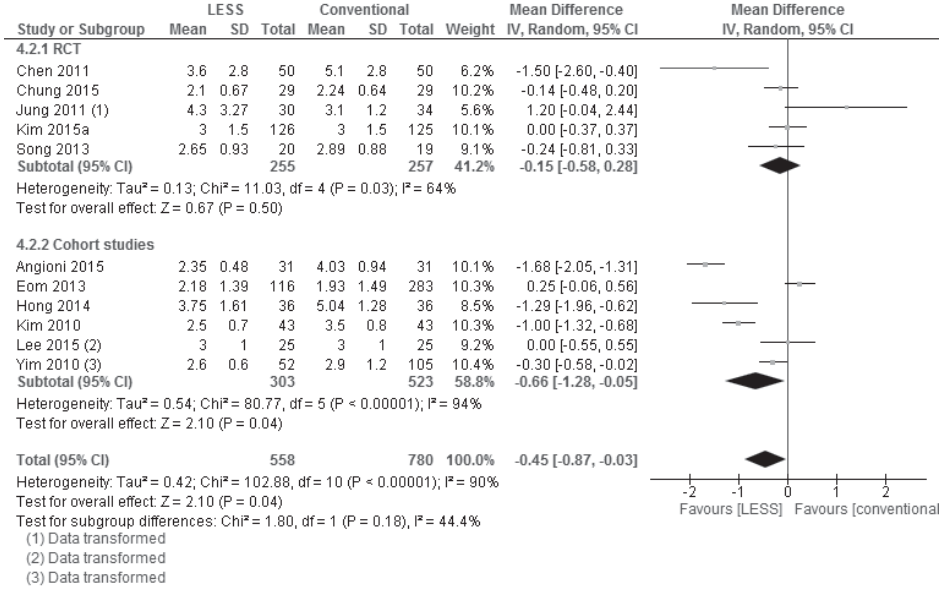

Figure 4.4c: Pain scores 24 hours postoperative, LESS versus conventional laparoscopic hysterectomy.

significantly more satisfied with their scars and had higher satisfaction with their own body at the three measured moments. Kim et al. studied the scar satisfaction using the patient and observer scar assessment scale (POSAS) one week and two months after surgery and showed no difference between the single-site group and the multi-port one. Li et al. studied patient satisfaction and demonstrated a higher patient satisfaction rate in the single-port group, although it was unclear which questionnaire was used.[26] Lee et al. compared the sexual function of premenopausal women by using the female sexual function index and showed no difference between women that underwent LESS compared to LAVH.[36]

Secondary outcomes

The operative time was significantly longer in the single-port group compared to the multi-port group (20 studies, MD 11.3 min (5.45–17.17), I^2=89%, Figure 4.5a. When comparing separately TLH and LAVH, a significant difference of 21 minutes was seen in favor of the

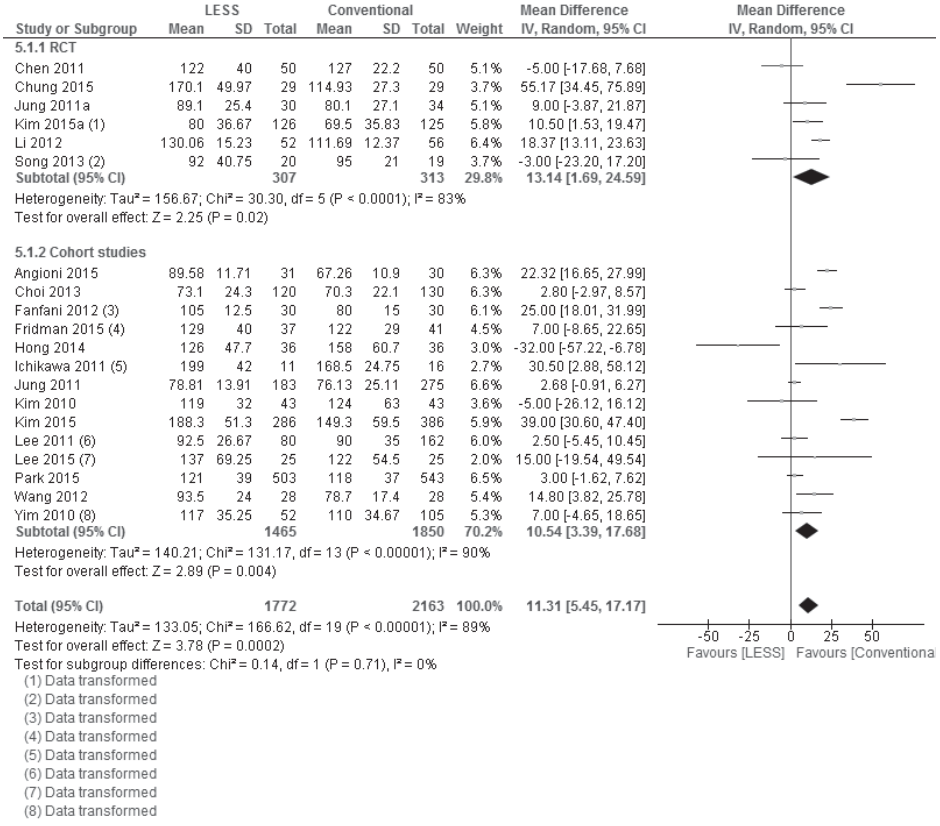

Figure 4.5a: Operative time, LESS versus conventional laparoscopic hysterectomy.

TLH group, compared to a non-significant difference of two minutes after LAVH (data not shown). No difference was seen for the intraoperative blood loss (19 studies, MD 1 mL (-6.03, -7.81), I^2=27%, Figure 4.5b). For the length of hospital stay, a small significant difference was seen (15 studies, MD -0.22 (-0.43, -0.01), I^2=86%, Figure 4.5c). This difference was not seen when looking separately at the RCTs and cohort studies.

Discussion

Main findings

In this systematic review, we evaluated the safety and effectiveness of LESS hysterectomy compared to the conventional laparoscopic hysterectomy (TLH and LAVH). Twenty-three studies on LESS versus conventional hysterectomy showed no differences for safety with very low quality evidence. Concerning effectiveness, very low quality evidence indicated no difference for the risk of conversion to laparotomy in the LESS group compared to

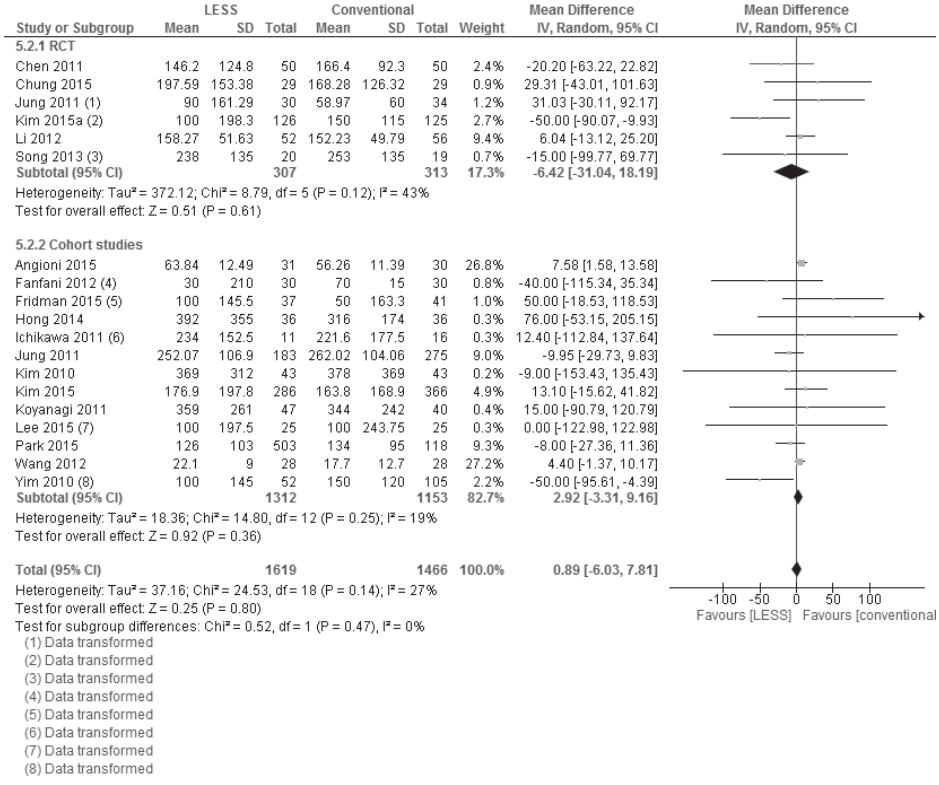

Figure 4.5b: Total blood loss, LESS versus conventional laparoscopic hysterectomy.

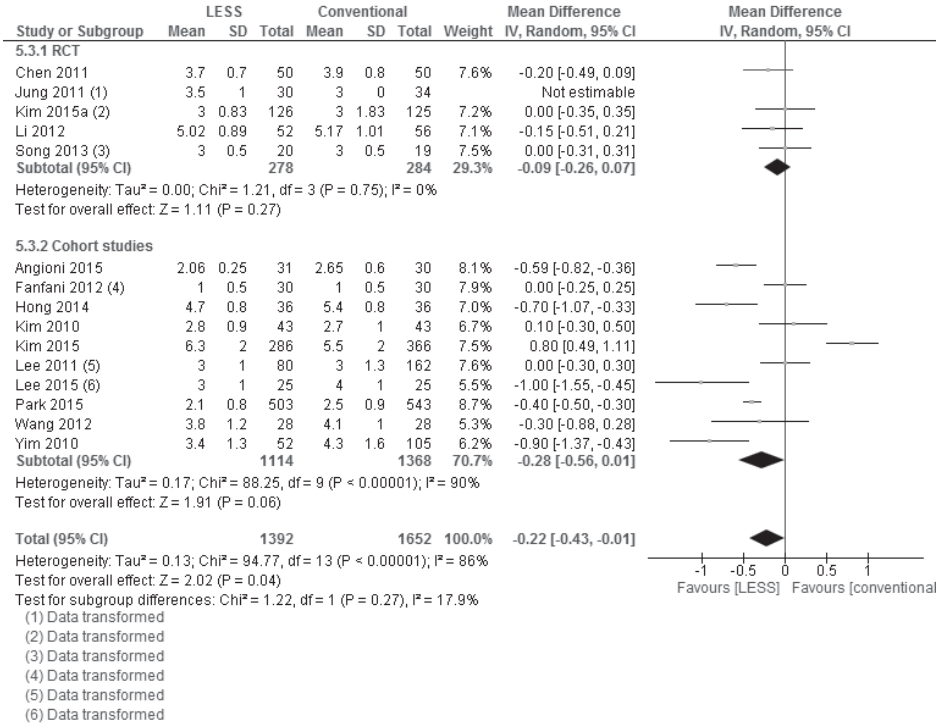

Figure 4.5c: Length of hospital stay, LESS versus conventional laparoscopic hysterectomy.

TLH and LAVH. In 3.5%, the LESS approach failed as an additional port was needed. For postoperative pain, low quality of evidence indicated a lower VAS score of 1.09 and 0.45, respectively, directly and 24 h after LESS hysterectomy, though with substantial statistical heterogeneity. Two out of three studies with low-quality evidence indicated a better cosmetic outcome after LESS versus conventional hysterectomy. A major shortcoming in these studies is the lack of a pre-operative assessment. Without a pre-operative assessment, it remains unclear whether there were any differences between the groups prior to their surgery. The third study, a RCT showed no difference with respect to scar satisfaction.

Strengths and limitations

Though there are some RCTs available comparing LESS to conventional hysterectomy, we decided to include other comparative study designs as well. The inclusion of non-RCT designs results in less homogenous groups, but when outcomes of interest are infrequent (e.g., conversion to laparotomy risk, complication risks); RCTs are rarely large and lengthy enough to measure infrequent outcomes accurately. Cohort studies facilitate a larger

study population and adequate power to identify significant differences. Therefore, the inclusion of study designs other than RCTs can be seen as a limitation but also as strength. In addition, to limit bias, we performed sensitivity analysis for the study design for the meta-analysis. Another strength of this review is the assessment of the quality of evidence using GRADE methodology. We believe that the use of GRADE results in additional clinical value of this review: GRADE optimizes the presentation of evidence for clinical practice. The results of this systematic review are strengthened through the findings of other reviews published on the subject that as well found no significant difference in the frequency of perioperative complications and postoperative pain scores.[8;9;43] Though, other reviews described a higher rate of 'failures' in the LESS group. These studies defined 'failure' as the need to convert to laparotomy and/ or to add an extra port, without differentiating. We found that in 3.5% of the LESS procedures, an additional port was needed compared to <1% in the conventional procedures.

Interpretation

The feasibility of LESS surgery for benign gynecologic procedures seems proven.[8;9] The meta-analyses in this review showed no significant differences in complication and conversion rate to laparotomy between LESS and conventional hysterectomy. Without substantial statistical heterogeneity, we consider these findings reliable. Besides complication risk, the pain experienced after surgery is an important consideration and usually an important argument in favor of LESS. Though, we did not find any clinically significant differences in postoperative pain. Directly and 24 h after LESS hysterectomy, a significant lower VAS score was observed. This difference was not observed when analyzing only the RCTs. Furthermore, the mean difference did not exceed 1.09 and studies have shown that a mean difference of 2 points on a 10-point scale should be considered as clinically relevant.[44] In addition, it cannot be excluded that enrolled patients in the study are biased with respect to their pain outcomes as, except in one study, the included patients were not blinded to the type of surgery. One single randomized controlled trial applied accurate blinding:[23] patients and anesthesiology staff who measured the postoperative pain scores did not know which type of approached had been performed and similar pain scores were found. Cosmetic outcomes are also suggested as important improvement in the single-site approach but surprisingly few studies on LESS hysterectomy reported on this topic.[21;39;41] We judged the assessment in the two studies on patient satisfaction insufficient, since baseline assessment of body image and cosmetic satisfaction was not performed. The largest RCT published so far for hysterectomy reported no significant differences regarding scar satisfaction between the LESS and 'conventional' hysterectomy

group.[41] When looking at studies published in other fields than benign gynecology, inconsistent results are found for the self-scar rating in patients who underwent LESS or conventional laparoscopic surgery.[45-47] In Tuschy et al. patients who underwent conventional gynecological laparoscopy were asked which scar they would prefer to eliminate, and for most patients, it was the umbilical one.[48] In the study by Bush et al. patients were asked their aesthetic preference regarding scars, and no differences were observed between the single-site and conventional incisions.[6] In LESS surgery, higher forces are applied on the umbilical port during tissue handling and irreversible umbilical deformation has been described.[29] It is also suggested that LESS would lead to a higher risk of port herniation as the opening of the umbilical port is larger.[49-51] Though, this could not be confirmed in the current literature, as within the short study follow-up, only one case of port herniation was reported.[31]

Evaluating the secondary surgical outcomes, a notable finding is the increased operative time found in the LESS versus conventional hysterectomy group: an overall mean difference of 11 minutes was observed, though with substantial heterogeneity. For the TLH, the mean difference was 21 minutes, whereas for the LAVH, a non-significant difference of two minutes was observed. The reason for the prolonged operative time during TLH is most probably related to the difference in surgical experience. For the LAVH, it makes sense that the operative time was similar as a large part of the LESS and conventional procedure is performed vaginally, thus using exactly similar techniques. It is well known that LESS surgery is technically more challenging[8;9;43] and studies reporting on the learning curve in LESS have suggested that sufficient skills are acquired after 10 to 15[3] up to 40 cases,[52] especially when surgeons are already well-trained in laparoscopy. In five studies included in this review, the surgical experience of the surgeons was not described.[13;28;30;35;38] In the other included studies, the experience of surgeons was defined by terms, such as 'very experienced', 'senior surgeon', or by the number of laparoscopic and/or LESS surgeries performed in one's career. Hence, it is difficult to interpret the impact of the skills on the outcomes. It is noteworthy mentioning that we found substantial differences in baseline characteristics between compared groups in the non-randomized studies (uterine weight,[20;21;28] age,[20] BMI,[31] previous surgeries, and co-morbidities[28;38]). This could be explained by the surgeon's specific selection when performing a new technique in a non-randomized setting. Yet, an increased uterine weight, a high BMI, and/or previous surgical interventions are known to directly influence surgical outcomes[53] and this could lead to an overestimation of effectiveness, safety, and secondary outcomes (e.g., operative time, blood loss) for LESS outcomes. In addition, it should also be taken into account that 20 of the 23 studies originated from Asian, and therefore, the impact of Asian demographics should not be underestimated.

Remarkably, none of the included studies has taken the costs of the surgery into account, and currently, it is unknown if the LESS approach is cost effective. Despite the lack of data for LESS versus conventional hysterectomy, it can be reasoned that implementing the LESS technique in a hospital is costly as the conventional instruments do not fit and new instruments need to be purchased.

As seen with previous devices and or techniques,[54] implementing new technologies in the medical field is a challenge. In contrast to the introduction of new drugs, the latest techniques and devices are usually implemented in clinical practice without proper systematic evaluation regarding their safety, effectiveness, costs, and benefits. Advantages and disadvantages only become clear with the passage of time and after the implantation phase. Considering this, it is complex to answer the question whether the single-port surgery should be an additional possibility for the minimally invasive surgery. Most of studies in the review were single center and from the same region in the world, where a lot of experienced has already been acquired with the LESS technique. Despite the amount of experience with LESS in these centers, there is still no clear added value.

In conclusion, current evidence shows that the single-port technique for benign hysterectomy (TLH and LAVH) is feasible, safe, and equally effective compared to the conventional technique. Caution is urged when interpreting the results of studies on LESS because the evidence is of *low* to *very low* quality. Potential benefits are sought in patient satisfaction, cosmetic satisfaction, and postoperative pain, but the small differences for these outcomes appear not to be of clinical relevance. Furthermore, surgeons and patients should be aware that in up to 3.5% of LESS hysterectomies an additional port is required resulting in failure of the "single-site" approach and affecting the less invasive purpose. As no clinically relevant advantages were identified, and no data on cost effectiveness were available, there are currently no solid arguments to implement the single-port technique worldwide.

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Appendix 4.1: Literature search LESS versus conventional hysterectomy
Search up to 4th of August 2016

PubMed:
("gynaecology"[All Fields] OR "gynecology"[MeSH Terms] OR "gynecology"[All Fields] OR gynaecologic[All Fields] OR gynecologic[All Fields] OR "Genital Diseases, Female"[Mesh] OR "female genital disease"[all fields] OR "female genital diseases"[all fields] OR "Gynecologic Surgical Procedures"[Mesh]) AND (("Single Incision Laparoscopic Surgery"[All Fields] OR "laparo-endoscopic single-site surgery"[all fields] OR "One port umbilical surgery"[all fields] OR "Natural orifice transluminal endoscopic surgery"[all fields] OR "Single-incision minimally invasive surgery"[all fields] OR "Single laparoscopic incision transabdominal surgery"[all fields] OR "Single-port access"[all fields] OR "Single-port laparoscopy"[all fields] OR "Single-port incisionless conventional equipment-utilizing surgery"[all fields] OR "Umbilical laparoendoscopic single-site surgery"[all fields]) OR (("laparoscopy"[MeSH Terms] OR "laparoscopy"[All Fields] OR "laparoscopic"[All Fields] OR laparoendoscopic[All Fields]) AND (("single"[All Fields] AND (site[All Fields] OR port[all fields] OR incision[all fields] OR umbilical[all fields] OR transumbilical[all fields])) OR (single-port[all fields] OR single-site[all fields] OR single-incision[all fields])) AND ("surgery"[Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms]))) AND ("2012/05/01"[PDAT] : "3000/12/31"[PDAT])

Embase:
(gynaecolog*.mp. OR gynecolog*.mp. OR exp gynecology/ OR exp gynecologic disease/ OR female genital disease*.mp. OR exp gynecologic surgery/) AND (("Single Incision Laparoscopic Surgery".mp. OR "laparo-endoscopic single-site surgery".mp. OR "One port umbilical surgery".mp. OR "Natural orifice transluminal endoscopic surgery".mp. OR "Single-incision minimally invasive surgery".mp. OR "Single laparoscopic incision transabdominal surgery".mp. OR "Single-port access".mp. OR "Single-port laparoscopy".mp. OR "Single-port incisionless conventional equipment-utilizing surgery".mp. OR "Umbilical laparoendoscopic single-site surgery".mp.) OR ((exp laparoscopy/ OR exp laparoscopic surgery/ OR "laparoscopy".mp. OR "laparoscopic".mp. OR laparoendoscopic.mp.) AND (("single".mp. AND (site.mp. OR port.mp. OR incision.mp. OR umbilical.mp. OR transumbilical.mp.)) OR (single-port.mp. OR single-site.mp. OR single-incision.mp.)) AND (exp surgical technique/ OR surgery.mp. OR surgical.mp.))) AND (201236 OR 201237 OR 201238 OR 201239 OR 20124* OR 20125* OR 2013* OR 2014* OR 2015* OR 2016*).ew

Chapter 5

Utility of cystoscopy during hysterectomy

E.M. Sandberg, S.L. Cohen, S. Hurwitz, J.I. Einarsson

Obstet Gynecol 2012;120:1363-1370

Abstract

Objective: To estimate the incidence of cystoscopy use at time of hysterectomy and its use to detect urinary tract injury.

Methods: This was a retrospective cohort study in a tertiary care academic center of 1982 patients who underwent a hysterectomy for any indication (excluding obstetric) between January 2009 and December 2010. Medical records were reviewed for baseline and perioperative characteristics, cystoscopy use, and information about bladder or ureteral injury related to hysterectomy.

Results: Two hundred fifty-one women (12.66%, 95% confidence interval [CI] 11.23–14.21%) underwent a cystoscopy at the time of hysterectomy with no reported complications resulting from the cystoscopy procedure. Cystoscopy was most frequently used by low-volume surgeons and in cases involving prolapse or vaginal mode of access. Fourteen patients (0.71%, 95% CI 0.39–1.19%) experienced bladder injury and five patients (0.25%, 95% CI 0.08–0.58%) sustained ureteral injury. None of these complications were detected by cystoscopy; cystoscopy was either normal at the time of hysterectomy or was omitted. The presence of adhesions was significantly associated with bladder injury at the time of hysterectomy (p=.006). Low-volume surgeon and laparoscopic or robotic mode of access were both significantly associated with ureteral injury (p=.023 and p=.042, respectively).

Conclusions: Our data support selective rather than universal cystoscopy at the time of hysterectomy.

Introduction

Hysterectomy is the most common major gynecologic surgical procedure performed worldwide.[1] Regardless of the route of hysterectomy, potential for injury to the urinary tract remains a major concern. Injuries not identified at the time of surgery can have serious postoperative consequences; therefore, it is of utmost importance to recognize and repair injuries intraoperatively if possible.[2] According to a review by Gilmour and a large retrospective study performed in Finland by Brummer, the incidence of urinary tract injuries during hysterectomy ranges from 0.2 to 12.1 per 1,000 for bladder injury[3;4] and from 0.2 to 13.9 per 1,000 for ureteral injury.[4]

Historically, surgeons relied on clinical suspicion alone to diagnose intraoperative injury to the ureters or bladder.[5] The first cystoscopy was described by German urologist M.C.F. Nitze in 1879; however, it was not until later that gynecologic surgeons began to perform cystoscopy concomitantly with their primary procedure.[6] As surgeons strive to lower the risk of complications related to gynecologic surgery, it has been debated whether cystoscopy should routinely be performed at the time of hysterectomy. Many authors advocate that cystoscopy should be a universal screening tool, because its relatively low cost is accompanied by a high injury detection rate superior to simple visual inspection.[7] The use of cystoscopy can help detect injuries that might otherwise have been unidentified, thus decreasing morbidity and potentially avoiding further complications.[2] Advocates of universal, rather than selective, cystoscopy point to the fact that using cystoscopy only with complicated cases may lead to underdiagnosis; it has been reported that up to 75% of urinary tract injuries are associated with uncomplicated hysterectomies.[8] Additionally, serious complications related to cystoscopy are rare.[9]

However, one should also take into account the potential disadvantages of performing universal cystoscopy at the time of hysterectomy, including increased operative time, procedure cost, and incidence of minor complications such as bladder trauma or urinary tract infection. Although extremely rare, severe complications associated with intravenous dye use during cystoscopy have also been reported.[5] Although cystoscopy has a high sensitivity and specificity, it will not detect all injuries, particularly those caused by thermal damage, which may take several weeks to develop.[8;10] It has also been suggested that some urinary tract injuries are asymptomatic and resolve spontaneously, meaning that universal cystoscopy could lead to overdiagnosis and unnecessary intervention in some cases.[3] As a result of these considerations, many surgeons perform selective cystoscopy in more complex cases, basing their decisions on training, surgical experience, and individual rate of injuries.[11]

To minimize hysterectomy-associated urinary tract complications, it is important to carefully evaluate the use of cystoscopy. The aim of this study is to estimate the incidence of cystoscopy use at the time of hysterectomy and its use to detect urinary tract injury at a large academic tertiary-care hospital in the northeastern United States. In our hospital, there is no specific protocol in place across specialties regarding the use of cystoscopy, and the vast majority of health care providers practice selective cystoscopy.

Material and methods

This retrospective study was approved by Partner's Research Management Institutional Review Board, our local institutional review board. The study cohort included the 1,982 patients who underwent a hysterectomy for any nonobstetric indication from January 2009 through December 2010 at Brigham and Women's Hospital. All modes of hysterectomy (abdominal, vaginal, laparoscopic, robotic) and each subtype (total, subtotal, radical) were included. Patients who underwent a gravid or postpartum hysterectomy were excluded; however, oncologic hysterectomy cases were included.

The following data were abstracted from the medical record: age, parity, race, body mass index (calculated as weight (kg)/[height (m)]^2), indication for surgery, history of prior surgeries, annual hysterectomy volume of operating surgeon (low volume defined as less than 10 hysterectomies per year, medium volume as 11–50 hysterectomies per year, high volume as greater than 51 hysterectomies per year), operative findings, intraoperative complications, postoperative complications, readmission, reoperation, presence of urinary tract injury, operative time (listed as time in and out of the operating room), length of hospital stay (same day discharges coded as 0 days), estimated blood loss, total hospital cost and operative cost (as reported by hospital accounting ledgers), performance of cystoscopy, and complications related to cystoscopy. Intraoperative complications included injuries to the urinary tract, nerves, vessels, or bowel as well as estimated blood loss of more than 1,000 mL or major anesthesia-related issues. The postoperative complications were divided into major and minor complications based on previously described criteria;[12] major complications included injuries to the urinary tract, nerves, vessels, or bowel, which were diagnosed postoperatively, as well as hemorrhage requiring transfusion, hematoma requiring drainage, pulmonary embolus, or wound dehiscence; minor postoperative complications included hemorrhage not requiring transfusion, infection or fever, spontaneously resolving hematoma, deep vein thrombosis, minor anesthesia issues, or other mild complications requiring treatment.

Statistical analyses were performed using SAS 9.2 software. Data were summarized and extreme values were verified to be correct. Comparisons of the patients who

underwent cystoscopy at the time of hysterectomy, compared with those who did not, were performed using the Wilcoxon rank-sum test for continuous and ordered variables because distributional normality could not be assumed according to results of standard tests of normality (SAS implementation of Shapiro-Wilk). The X^2 was used for nonordered categorical variables. P-values were not adjusted for multiple testing in this exploratory data analysis context.

Results

Of the 1,982 patients included in this study, 251 women (12.66%, 95% confidence interval [CI] 11.23–14.21%) underwent a cystoscopy at the time of their hysterectomy with no reported complications resulting from the cystoscopy procedure. Baseline and operative characteristics are displayed in Table 5.1. Patients who underwent a cystoscopy were found to be younger on average compared with patients who did not undergo cystoscopy. Discrepancies were also found with regard to race, lower body mass index, and higher parity in the group who underwent cystoscopy. No significant difference was found between the two groups in terms of history of laparotomy or laparoscopy.

Concerning the indication for hysterectomy, there were 775 oncologic and 1,207 benign cases. Cystoscopy was performed less frequently in the oncologic cases (frequency 1.68%, 95% CI 0.90–2.85%) in oncologic cases compared with (19.72%, 95% CI 17.51–22.08%) in benign cases ($p<.001$). There were 216 prolapse and 1,766 nonprolapse cases; cystoscopy was performed more frequently in cases involving prolapse (frequency 38.89%, 95% CI 32.35–45.74% compared with 9.46%, 95% CI 10.74–13.85%; $p<.001$). No significant difference was found with regard to cystoscopy use in cases involving leiomyomata or endometriosis.

Perioperative outcomes and complications were also examined (Table 5.1). Estimated blood loss was lower in the cystoscopy group, although there was no statistically significant difference seen with regard to uterine weight between the groups. Operative time was longer in the cystoscopy group with a corresponding higher operative cost as well. Length of stay was found to be shorter in the cystoscopy group; this may reflect the preponderance of oncologic cases in the noncystoscopy group, which are associated with more complex medical issues and comorbidities that result in longer hospitalization. Intraoperative complications, major postoperative complications, readmissions, and reoperations were not significantly different between the two groups. However, when analyzing subcategories of intraoperative or major postoperative complications, the cystoscopy group was found to have a significantly lower incidence of estimate blood

Table 5.1: Baseline characteristics, perioperative outcomes and complications of hysterectomy cohort

	Cystoscopy n=251	No cystoscopy n=1,731	p-value
Age (y)	49.7±11.5 (48 [19.4–87])	53.4±11.9 (51 [18–92])	<.001
BMI (kg/m^2)	28.0±6.0 (27 [18.1–52.7])	29.9±8.3 (27.9 [15.8–69.4])	.02
Race			.05
White	179 (73)	1332 (79)	
Black	34 (14)	194 (12)	
Other§	33 (13)	155 (9)	
Parity	2.1±1.6 (2 [0–11])	1.83±1.5 (2 [0–12])	.009
Prior laparoscopy	71 (29.8)	400 (24.3)	.07
Prior laparotomy	91 (38.1)	654 (39.6)	.65
Indication/findings*			
Cancer	13 (5.2)	762 (44.0)	<.001
Prolapse	84 (33.5)	132 (7.6)	<.001
Leiomyomata	134 (53.4)	886 (51.2)	.51
Endometriosis	16 (6.4)	117 (6.8)	.82
Adhesive Disease	50 (19.9)	451 (26.1)	<.001
OR time (min)	206.7±78.3 (195 [79–692])	191.4±67.5 (180 [29–618])	.004
Estimated blood loss (mL)	150.5±196.6 (100 [0–1800])	205.6±327.0 (100 [0–4800])	.03
Uterine weight (grams)	247±269.5 (141 [24–17775])	280.3±462.4 (139 [20–8000])	.93
Length of Stay (d)	1.5±4.2 (1 [0–65])	2.0±2.2 (1 [0–34])	<.001
Total OR cost (USD)	14,170.3±9,834.1 (9927.5 [3252–54999])	11,136.0±7,434.8 (9322 [1498–88453])	<.001
Total cost (USD)	24,854.2±33,224.4 (19968.1 [964.1–496237])	23,876.4±13,940.7 (23532.51 [2254.4–125603.5])	.36
Intra-operative complication*	13 (5.2)	53 (3.1)	.08
Readmission	18 (7.2)	87 (5.1)	.16
Reoperation	6 (2.4)	41 (2.4)	.99
Major postoperative complication	15 (6)	84 (4.9)	.45
Minor postoperative complication	93 (38.8)	318 (19.1)	<.001

BMI, body mass index; Data are mean + standard deviation or number (%).
* Each was compared with all others combined; § Includes 102 Hispanics, 77 Asians and 9 others.

loss greater than 1,000 mL (0.8% compared with 3%; p=.045) but a higher incidence of bladder injury (2% compared with 0.3%; p<.001) and bowel injury (1.6% compared with 0.5%; p=.049). The minor postoperative complications were more common in the cystoscopy group, perhaps reflecting associated urinary tract symptoms in the patients who underwent cystoscopy.

Table 5.2 outlines the frequency of cystoscopy listed by procedure and surgeon characteristics. Cystoscopy was performed most often in vaginal hysterectomies followed by laparoscopic and robotic. Of note, there was no significant difference found between frequency of cystoscopy in the laparoscopic and robotic subgroups (p=.19). It also was seen that cystoscopy was performed less frequently if the hysterectomy was completed by a higher-volume surgeon. However, when surgeons were further categorized into generalists or specialists (defined as having completed fellowship training in urogynecology, gynecologic oncology, reproductive endocrinology and infertility, or minimally invasive surgery), no significant difference was found with regard to cystoscopy use.

Nineteen patients experienced a urinary tract injury; 14 patients (0.71%, 95% CI 0.39–1.19%) incurred bladder injuries and five patients (0.25%, 95% CI 0.08–0.58%) sustained ureteral injuries. The bladder injury cases are outlined in Table 5.3 separated into the 10 cases that were identified intraoperatively and the four that were discovered postoperatively (Table 5.3). Cystoscopy did not aid in the intraoperative detection of any bladder injuries.

Table 5.2: Proportion who underwent cystoscopy according to procedure and surgeon characteristics in 1,982 hysterectomy patients

	n	Cystoscopy n (%)	p-value
Mode of hysterectomy			<.001
Abdominal	644	12 (1.9)	
Vaginal	250	69 (27.6)	
Laparoscopic	1,011	162 (16.0)	
Robotic	77	8 (10.4)	
Subtype of hysterectomy			<.001
Supracervical	391	74 (18.9)	
Total	1,511	177 (11.7)	
Radical	79	0 (0.0)	
Surgeon type			.91
Generalist	297	37 (12.5)	
Specialist	1,685	214 (12.7)	
Surgeon volume*			<.001
Low	196	51 (26.0)	
Medium	518	110 (21.2)	
High	1,268	90 (7.1)	

* Low volume > 10; medium 21–50; high 51–80 cases/year.

Table 5.3: Description of bladder injuries

Case	Type of hysterectomy	Low-volume surgeon	Cancer	Adhesions	Endometriosis	Uterine weight (g)	Prior surgery	Cystoscopy use	Comments
Identified intraoperatively n=10									
1	TAH		x	x		122	x	No	**Cystotomy** visualized & repaired
2	SAH	x		x		495	x	No	**Cystotomy** visualized & repaired
3	TLH			x		167	x	No	Blood-tinged urine noted, bladder back-filled and **cystotomy** identified & repaired
4	TLH converted to TAH			x	x	833		No	**Cystotomy** visualized & repaired
5	TAH					1,144		No	Blood-tinged urine noted, bladder back-filled and **cystotomy** identified & repaired
6	TAH		x	x		406	x	No	**Cystotomy** visualized & repaired
7	TVH	x				129	x	After repair of injury	Fluid leakage into field, bladder back-filled and **cystotomy** identified & repaired
8	TLH			x		155	x	After repair of injury	**Cystotomy** visualized & repaired
9	TVH					114		After repair of injury	Fluid leakage into field, **cystotomy** identified & repaired
10	TLH			x		746	x	After repair of injury	**Cystotomy** visualized & repaired

Case	Type of hysterectomy	Low-volume surgeon	Cancer	Adhesions	Endometriosis	Uterine weight (g)	Prior surgery	Cystoscopy use	Comments
Identified postoperatively n=4									
11	TAH		x			84		No	Tumor plaque dissected off surface of bladder. 1 week postoperatively developed ascites, when drained found to be urine. **Vesicovaginal fistula** identified, prolonged bladder drainage and interval transperitoneal fistula repair performed
12	TLH		x			164	x	No	4 days postoperatively developed pain, ascites. CT cystogram demonstrated **cystotomy**, repaired via laparotomy
13	TLH					387		Normal at time of hysterectomy	Intraoperatively backfilled bladder to confirm location during dissection. 1 week postoperatively fluid leakage per vagina. CT urogram confirmed **vesicovaginal fistula**, repaired via laparotomy
14	TLH	x		x		168	x	Normal at time of hysterectomy	Intraoperatively backfilled bladder to confirm location during dissection. 10 days postoperatively developed vaginal leakage. CT urogram confirmed **vesicovaginal fistula**, repaired via laparotomy

TAH, total abdominal hysterectomy; SAH, supracervical abdominal hysterectomy; TLH, total laparoscopic hysterectomy; TVH, total vaginal hysterectomy; CT, computed tomography.

Table 5.4: Description of ureter injuries

Case	Type of hysterectomy	Low-volume surgeon	Cancer	Adhesions	Endometriosis	Uterine weight (g)	Prior surgery	Cystoscopy use	Comments
	Identified intraoperatively n=0								
	Identified postoperatively n=5								
1	RRH		x			81		No	Developed urine leakage postoperatively, cystoscopy normal. Continued leakage led to CT urogram and retrograde pyelogram, left ureteral injury diagnosed and stented. Continued leakage led to repeat CT urogram and laparotomy to reimplant left ureter. Faiulre to improve led to third CT urogram which diagnosed right ureteral injury, reimplanted via laparotomy.
2	TLH	x				442		No	Left ureter noted to be in close proximity to coagulated edges of vaginal cuff. Postoperative urine leak into abdomen led to diagnosis of ureteral stricture which was stented. Required laparotomy and reimplantation.
3	TLH	x		x		221	x	No	2 weeks postoperatively developed vaginal leakage. Cystogram normal, CT urogram showed ureteral obstruction, stented.
4	TLH					303		No	2 days postoperatively developed vaginal leakage. Cystogram normal, CT urogram showed ureteral leakage and kinking, stented.
5	TLH		x	x	x	250	x	No	2 days postoperatively developed vaginal leakage. CT urogram showed ureteral injury, unable to stent. Nephrostomy placed, interval re-implantation with psoas hitch.

RRH, robotic radical hysterectomy; TLH, total laparoscopic hysterectomy; CT, computed tomography.

Instead, surgeons recognized the injuries by direct visualization of a cystotomy or presence or blood-tinged urine and fluid leakage into the field. In the four intraoperatively detected injuries wherein cystoscopy was used, it was solely used as a postrepair check. In two of the four cases of bladder injury identified postoperatively, a cystoscopy had been performed at the time of the hysterectomy without any abnormal findings. Table 5.4 outlines the five ureteral injuries that occurred. In all five cases, intraoperative cystoscopy was not performed and the ureteral injury was detected postoperatively.

Regarding risk factors for genitourinary injury at the time of hysterectomy, the following variables were investigated: low-volume surgeon, laparoscopic or robotic mode of access, total hysterectomy, oncologic indication, presence of adhesions, and history of laparotomy or laparoscopy. Of these factors, only the presence of adhesions was significantly associated with bladder injury at the time of hysterectomy (p=.006). Low-volume surgeon and laparoscopic or robotic mode of access were both significantly associated with ureteral injury at the time of hysterectomy (p=.023 and .042, respectively).

Discussion

Cystoscopy has been described as a useful tool in the detection of urinary tract injuries, which may occur during hysterectomy. Evaluation of the patients undergoing hysterectomy from our institution over a two-year study period found that gynecologic surgeons performed selective (rather than universal) cystoscopy at the time of hysterectomy. Surprisingly, cystoscopy was performed more commonly in subtotal hysterectomy than it was in total or radical types. This may in part reflect the performance of a joint procedure of supracervical hysterectomy and sacrocervicopexy, which is commonly used for treatment of apical prolapse and is often accompanied by a cystoscopy. Additionally, the gynecologic oncology surgeons were less likely to perform cystoscopy and almost exclusively perform total or radical hysterectomies. This difference among specialists is interesting and demonstrates that there are wide variations in philosophy regarding its cystoscopy use.

The absolute rate of hysterectomy-associated urinary tract injury was low. Although there is no substitute for prevention of injury with meticulous surgical technique and thorough knowledge of anatomy, timely detection of injury is also essential. In examination of the cases of bladder injury in our cohort, cystoscopy did not help detect any injuries intraoperatively. Furthermore, three of the four delayed recognition bladder injuries involved fistula formation. The tissue necrosis that leads to fistula development is typically the result of thermal or other mode of injury, which may not be visible on intraoperative cystoscopy.[13] Given these considerations and the low baseline incidence of bladder injury,

it is not clear that a strategy of universal cystoscopy would have substantially improved outcomes for these patients. Rather, these findings reinforce that, whether performing cystoscopy or not, it is not always possible to identify damage that occurs at the time of surgery.

Inferences regarding ureteral injury are more complex, because all five ureteral injuries in the cohort were identified postoperatively and not associated with cystoscopy screening at the time of hysterectomy. It is open to speculation whether or not universal cystoscopy would have identified any or all of these ureteral injuries earlier, allowing for more timely intervention and repair. However, it is interesting to note that in one of the ureteral injury cases (case 1 from Table 5.4), persistent vaginal drainage led to a cystoscopy two weeks after surgery that did not reveal any urinary tract defects. At the time of postoperative cystoscopy, indigo carmine was administered intravenously and bilateral ureteral jets seen. Failure to improve led to further urologic work-up and the patient was subsequently diagnosed with bilateral ureteral injuries. This case exemplifies the imperfect sensitivity of cystoscopy for injury detection and highlights the difficulty that may be encountered in diagnosis of ureteral injury. Even with the use of cystoscopy, one may fail to identify ureteral injury, particularly in cases of partial obstruction or thermal injury.[10] Visco et al. evaluated the cost-effectiveness of cystoscopy for detection of ureteral injury and concluded that universal cystoscopy is cost-effective when the incidence of ureteral injury at the time of hysterectomy exceeds 1.5–2%.[14] These recommendations should be interpreted with caution as a result of evolving techniques and changes in practice patterns in the intervening decade since the study was published; however, it is notable that the ureteral injury incidence in our study population was well below the cost-effectiveness threshold.

Although this study was not designed to analyze the predictive ability of risk factors for hysterectomy related urinary tract injury, it is interesting to examine these results in light of what has previously been reported in the literature. The rate of urinary tract injury in our cohort was 9.6 per 1,000 cases overall (9.3 per 1,000 for abdominal, 10.1 per 1,000 cases for laparoscopic or robotic, and eight per 1,000 for vaginal mode of access), which is comparable to reported incidence in the literature.[1] The increased risk of ureteral injury with the laparoscopic or robotic approach is consistent with previous findings, although must be interpreted with caution in a noncontrolled study because confounding factors may be present, which influence both choice of mode and risk of injury.[15;16] Surgical volume has been reported to be an important predictor of perioperative outcomes and was associated with ureteral injury occurrence in our cohort as well.[17] Additionally, the presence of adhesions was associated with incidence of bladder injury in this study, as has been reported previously.[4;18] As a result of the low baseline incidence of urinary tract

injury in our patient population, it is not possible to confirm the noted associations as definitive risk factors; a larger study design targeting this issue is needed to confirm these findings. Despite this caveat, surgeons who are prospectively assessing particular patient cases may find it useful to reflect on the presence of these factors (low-volume surgeon, laparoscopic or robotic access, adhesions) and further individualize decisions regarding urinary tract evaluation.

Limitations to this study include its retrospective nature. The rate of urinary tract injury may have been underestimated if patients presented to outside institutions for treatment or remained asymptomatic during the follow-up period that was observed (range 2–3 years). Strengths of this work include the large number of patients and surgeons present. Because this study was performed at an academic institution, health care providers represent a variety of surgical experience ranging from trainees to fellowship-trained attending surgeons. Additionally, both benign and oncologic hysterectomy cases were included. This patient and health care provider diversity lends generalizability to our findings, although it may also introduce confounding variables that are not fully accounted for by the study design.

Based on the low absolute risk of urinary tract injury, selective cystoscopy at the time of hysterectomy appears to be acceptable as currently practiced at Brigham and Women's Hospital. It may well be that outcomes regarding cystoscopy use and its use may vary in different populations or hospital settings. Although our data support selective rather than universal cystoscopy at the time of hysterectomy, the authors maintain that the threshold to perform a cystoscopy should be low, and in cases involving low-volume surgeons, significant pelvic pathology, or both, cystoscopy should be performed liberally. Surgeons should also be aware that a normal cystoscopy does not negate the possibility of urinary tract injury and maintain vigilance during the postoperative period. Additionally, it is important for gynecologic surgeons who perform advanced pelvic surgery to be trained and have privileges for performance of diagnostic cystoscopy. A Canadian study found that the most common reason for omitting cystoscopy at the time of laparoscopic hysterectomy was lack of training.[19] Although continually striving to improve early detection of bladder and ureteral injury at time of hysterectomy, there is no substitute for primary prevention through surgeon experience and comfort with pelvic anatomy.

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Chapter 6

Urinary catheterization management after laparoscopic hysterectomy: a national overview and a nurse preference survey

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Abstract

The aim of this study was to evaluate catheterization regimes after laparoscopic hysterectomy (LH) in Dutch hospitals and to assess nurses' opinion on this topic. This was particularly relevant as no consensus exists on the best moment to remove urinary catheter after LH. All 89 Dutch hospitals were successfully contacted and provided information on their catheterization regime after LH: 69 (77.5%) reported removing the catheter the next morning after LH, while nine hospitals (10.1%) removed it directly at the end of the procedure. The other 11 hospitals had different policies (four hours up to two days). Additionally, all nurses working at the gynaecologic departments of the hospitals affiliated to Leiden University were asked to fill in a self-developed questionnaire. Of the 111 nurses who completed the questionnaire (response rate 81%), 90% was convinced that direct removal was feasible and 78% would recommend it to a family member or friend.

Impact statement

- Although an indwelling catheter is routinely placed during hysterectomy, it is unclear what the best moment is to remove it after LH specifically. To fully benefit from the advantages associated with this minimally invasive approach, postoperative catheter management, should be, amongst others, optimal and LH-specific. A few studies have demonstrated that direct removal of urinary catheter after uncomplicated LH is feasible, but evidence is limited.
- While waiting for the results of randomised trials, this present study provides insight into nationwide catheterization management after LH. Despite the lack of consensus on the topic, catheterization management was quite uniform in the Netherlands: most Dutch hospitals removed the urinary catheter one day after LH. Yet, this was not in line with the opinion of the surveyed nurses, as the majority would recommend direct removal. This is interesting as nurses are closely involved in patients' postoperative care.
- Although randomised trials are necessary to determine optimal catheterization management, the findings of this present study are valuable if a new urinary catheter regime has to be implemented.

Introduction

Compared with abdominal hysterectomy, laparoscopic hysterectomy (LH) is associated with many well-known advantages, including quicker hospital discharge and faster return to normal activities.[1] To fully benefit from the advantages associated with this minimally invasive approach, post-operative patient care, including postoperative catheter management, should be optimal and LH-specific. Although an indwelling catheter is routinely placed during hysterectomy, it is specifically for LH unclear what the best moment is to remove it after surgery. Clinical practice guidelines on LH such as the ones published by the American Association of Gynecologic Laparoscopists (AAGL) or the National Institute for Health and Care Excellence (NICE) do not formulate any recommendations on when to remove the urinary catheter after LH.[2;3;4;5] The hysterectomy patient leaflet of the Royal College of Obstetrics and Gynecology (RCOG) only mention that the urinary catheter is usually in place for up to 24 hours and the Dutch Society of Obstetrics and Gynaecology (NVOG) state it will be removed 'after a certain amount of time'.[6;7] Looking at the literature, a few studies have demonstrated that direct removal of urinary catheter after uncomplicated LH is feasible, but evidence is limited.[8;9;10;11] As such, a randomised controlled trial (RCT) is currently being conducted in six hospitals in the Netherlands comparing direct versus delayed removal of urinary catheter after LH (MUCH trial, registration number at Clinicaltrials.gov:NCT02742636).

While waiting for the results of the trial, it is valuable to get insight into nationwide catheterization management after LH. This is particularly interesting since Hakvoort et al. published in 2009 a nationwide survey regarding catheterization regimes after vaginal prolapse surgery and demonstrated high practice variation among hospitals due to insufficient evidence.[12] Furthermore, the opinion of nurses on this topic is also relevant to study, as nurses are closely involved in patients' postoperative care. Being aware of the national policies and the attitude of the nurses is valuable if a new policy has to be widely implemented. In this light, the aim of this study was firstly to evaluate catheterization regimes after LH in all Dutch hospitals and secondly to survey all nurses working in one of the hospitals participating in the MUCH trial regarding the best time to remove urinary catheter after LH.

Material and methods

Telephone consultation

All Dutch gynaecologic inpatient departments were contacted by phone. One of the chief nurses was asked to provide information on the urinary catheter regime after LH in their hospital. The nurse was also asked whether their catheter policy was written in a guideline.

Nurse preference survey

All nurses working at a gynaecologic department of one of the six hospitals participating in the MUCH trial, all affiliated to Leiden University, were asked to fill in anonymously a self-developed questionnaire. The survey was developed by the gynaecologic department of Leiden University Medical Centre (LUMC), together with the department of Medical Decision Making and included 19 questions (6 open questions and 13 multiple-choice). A pilot study was performed at the gynaecologic department of LUMC by asking five nurses to fill in the questionnaires. Questions were reviewed and adapted afterwards if necessary. Topics covered in the survey were baseline characteristics of the responding nurses, current catheter management in their hospital and their personal opinion regarding direct or delayed removal of the catheter. To put their answers into context, nurses were also asked to estimate the overall incidence of urinary tract infections and urinary retention after LH. In Appendix 6.1 a summary of the topics that were covered in the survey can be found as well as the questionnaire (translated from Dutch into English).

The survey was available online (using the program NetQhttps://www.netqhealthcare.nl/) or on-paper. The questionnaire was sent out to all nurses by e-mail via the chief nurse of each hospital. Paper-based copies were also available in the nurses' stations of the different hospitals. Two and four weeks after the first request, a reminder was sent out by e-mail.

Statistics

Data analysis was performed using SPSS 23 (SPSS Statistics UK, Spss Inc, Chicago, IL, USA). Continuous data were expressed as median with range (minimum-maximum), while categorical data were expressed as numbers and percentages (%). We qualitatively analysed all open-ended responses from our survey and arranged these answers in thematic groups. Sub-analysis by age and experience was performed using independent t-test. A p-value $<.05$ was considered as significant.

Ethical approval

Because of the nature of the study, Institutional Review Board (IRB) approval did not apply.

Results

Telephone consultation

All 89 Dutch hospitals, including eight academic hospitals, 34 teaching hospitals and 47 non-teaching hospitals, were contacted by phone. All hospitals provided us with information on their urinary catheter management after LH (response rate 100%). As can be seen in Figure 6.1, a total of 69 hospitals (77.5%) reported removing the catheter the next morning after surgery, while 9 hospitals (10.1%) removed the catheter directly at the end of the operation. Seven hospitals (7.9%) removed the catheter on the same day but with a delay of four to six hours after surgery. Three hospitals (3.4%) removed the catheter 24 hours after operation. One hospital (1.1%) left the catheter in place up to two days after procedure, based on their guideline for vaginal hysterectomy.

All hospitals affirmed that they possessed a protocol describing when to remove the urinary catheter after LH. In 75 hospitals (84.2%), this was a standard postoperative care guideline used after all type of gynaecological surgical interventions and not specifically designed for LH. In 14 hospitals (15.7%) a specific guideline for LH existed with information on post-operative catheter management.

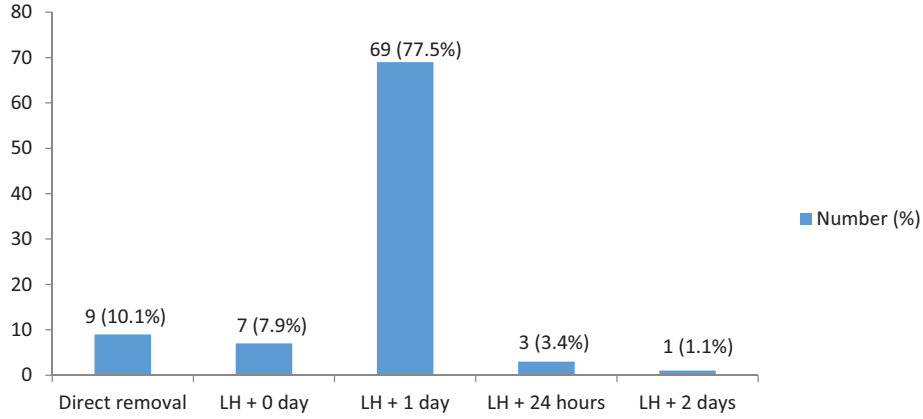

Figure 6.1: Moment of urinary catheter removal after laparoscopic hysterectomy in Dutch hospitals.
LH, laparoscopic hysterectomy. LH+0: the urinary catheter is removed on the same day as LH but with a delay of 4 to 6 hours.

Nurse preference survey

The survey was sent to 137 nurses working at one of the six gynaecological inpatient departments of the included hospitals. These included one academic hospital (LUMC), four teaching hospitals and one non-teaching hospital. A total of 111 nurses completed the entire questionnaire (response rate of 81%). The response rate varied per hospital from 57.6% up to 90.9%.

Table 6.1 presents the baseline characteristics of the responding nurses. The nurses working in one of the five non-academic hospitals reported that before the trial urinary catheter was usually left in place until the next morning. In the academic hospital, the policy was to directly remove the catheter after surgery.

Table 6.1: Baseline characteristics of the responding nurses

Characteristics	
Gender	
Male	2 (1.8)
Female	109 (98.2)
Age (years)	34.0 (19–61)
Graduated	
Yes	95 (85.6)
No	16 (14.4)
Work experience (years)	
As a nurse	7 (0–41)
On a gynecology ward	2 (0–37)
Hours per week at work	32 (16–36)

Data are presented as median (range) or as number (percentage).

As demonstrated in Table 6.2, most nurses (90.1%) believed that it was feasible to directly remove the catheter after procedure. Eighty-seven nurses (78.4%) mentioned that if a friend or family member would undergo a LH, they would advise direct removal. For both questions, sub-analysis by age demonstrated that nurses favouring direct catheter removal were significantly younger than the group that preferred delayed removal ($p=.022$ and $p=.008$, Table 6.2). Similarly, the group of nurses that believed in direct removal had significantly less working experience on a gynaecological ward compared to the nurses preferring delayed removal ($p=.008$ and $p<.001$, Table 6.2). The age of the nurses and their working experience were directly correlated (person correlation 0.9, $p<.001$). Of note, an additional sub-analysis for these questions revealed no significant difference in the answers given by the nurses working in the LUMC where before the trial direct catheter removal policy was in place, compared to the nurses from the other hospitals.

Table 6.2: The opinion of nurses on timing of urinary catheter removal after LH

	Number (%)	Mean age ± SD (years)	p-value	Mean working experience on gynecologic ward ± (years)	p-value
Is direct removal feasible?					
Yes	100 (90.1)	35.4±12.6	.022	5.0±7.6	.008
No	11 (9.9)	44.7±12.8		12.4±14.9	
Recommendation to family					
Direct removal	87 (78.4)	34.4±12.3	.008	3.8±5.7	<.001
Delayed removal	21 (18.9)	42.7±13.7		11.7±14.2	
Other	3 (2.7)				
Age dependent	2 (1.8)				
Patient health	1 (0.9)				
Situations where it would be better not to remove the catheter directly					
In all cases direct removal is better	47 (42.3)	--	--	--	--
The level of activity of the service	5 (4.5)				
Patient with BMI >30	22 (19.8)				
Patient age >65 years	38 (34.2)				
Other	30 (27.0)				
Physical difficulties	15 (13.5)				
General well-being	8 (7.2)				
Epidural use	3 (2.7)				
Level of severity of the procedure	4 (3.6)				

BMI, Body Mass Index. Statistics: Independent T-test. Data are presented as mean ± standard deviation (SD) or as number (percentage).

A total of 42.3% of the nurses believed that direct removal was in all cases better, whereas 57.7% thought that in specific situations direct removal might be contra-indicated. Specific factors against direct removal were the age of the patient (>65 years) (34.2%); a BMI >30 (19.8%); physical difficulties (13.5%) or the general well-being of the patient (7.2%). Other mentioned criteria included the level of activity of the service (4.5%), the level of severity of the procedure (e.g. adhesions) (3.6%) and the use of an epidural as analgesic (2.7%).

Nurses reported that compared to delayed removal, direct removal was associated with advantages such as a decreased risk of urinary tract infections (75.7%), earlier post-operative mobilization (73.9%) and faster hospital discharge (58.6%) (Table 6.3). Regarding the risk of urinary retention, the opinion was divided: 45.9% reported that direct removal was associated with an increased risk, 28.8% thought the moment of catheter removal was not of influence on the risk of urinary retention and 25.2% said that direct removal

Table 6.3: Influence of timing of urinary catheter removal on several outcomes, according to the nurses

Influence of direct removal (compared with delayed removal)	No influence	Increases	Decreases
Risk of urinary tract infections	14 (12.6)	13 (11.7)	84 (75.7)
Risk of urinary retention	32 (28.8)	51 (45.9)	28 (25.2)
Post-operative pain	63 (56.8)	35 (31.5)	13 (11.7)
Workload of the nurses	58 (52.3)	43 (38.7)	10 (9.0)

Influence of direct removal (compared to delayed removal)	No influence	Later	Earlier	Too early
Mobility	20 (18.0)	7 (6.3)	82 (73.9)	2 (1.8)
Discharge	41 (36.9)	5 (4.5)	65 (58.6)	0 (0)

Data are presented as number (percentage).

decreased the risk. While the majority of the nurses reported that direct removal had no influence on postoperative pain (56.8%) or on their own workload (52.3%), more than one third thought that direct removal of the catheter did negatively affect these outcomes (31.5% and 38.7%). Nurses reporting that direct removal was associated with more workload had significantly more working experience (mean 8.8 (11.2) years versus 3.9 (6.5) years, p=.007) but were not significantly older than the nurses reporting no difference in workload (mean 38.6 (13.3) versus 34.7 (12.8), p=.142).

Finally, nurses estimated that overall 10.5% (12.6) of the women undergoing LH in their hospital will have urinary retention and that 9% (13.5) will get a urinary tract infection.

Discussion

Telephone consultation

The national overview of catheter management after LH presented in this study demonstrated that the majority of Dutch hospitals (78%) have the policy to leave the urinary catheter in place until the next morning. Despite the lack of evidence-based recommendations on this topic, it is interesting to observe that practice variation regarding catheter management was minimal in the Netherlands. This is in discordance with previous studies that showed that without a convenient standard of care, doctors are more prone to adopt their own medical practices that are based on personal experience.[13;14] How the hospitals guidelines on urinary catheterization were developed and by which evidence it was supported, is unclear though.

Reviewing the literature, only a few studies have been published on the best moment to remove urinary catheter after hysterectomy and most do not differentiate between the different types of approaches (open, vaginal and laparoscopic).[8;9;10;11] Despite the limited evidence, the available studies all favour direct catheter removal after the different types of hysterectomy as it was associated with a lower risk of urinary tract infections, a quicker mobilization and an earlier hospital discharge.[8;9;10;11] The only RCT that exclusively included 150 LHs concluded that women in the direct catheter removal group had a significant lower risk of urinary infection (4% versus 18%, p=.034).[11] Another RCT comparing direct versus delayed catheter removal, including 16 LHs, 43 vaginal hysterectomies and 37 abdominal ones, demonstrated a reduced mean ambulation time (p<.05), a shorter hospital stay of nearly 19 hours (36.5 hours versus 55.2 hours, p<.05) and a lower but non-significant risk for urinary tract infection (3.1% versus 15.6%, p=NS).[8] Though, in this study no specific sub-analysis was performed for the types of approach.

The most important argument against direct urinary catheter removal is the potential increased risk of urinary retention after surgery.[8;9;10;11] In the RCT by Liang et al. the rate of urinary retention after LH was 34% in the direct removal group compared to 12% in the group where catheter was removed the next day.[11] Ghezzi et al. demonstrated in their prospective study with 142 LHs, a urinary retention rate of 14% when directly removing catheter after the laparoscopic procedure.[15]

Catheter management after LH is an important topic to address in the field of minimally invasive gynaecology as in more and more hospitals throughout the world patients are being discharged on the same-day of surgery.[16] A recent systematic review on this topic observed that one of the factors associated with a successful same-day discharge was a reduced time before voiding following catheter removal.[17] Interestingly, the inability to void was never a reason of re-admission.[17] Assumptions can be made that voiding dysfunctions are in most cases detected during admission and that these patients are most probably not discharged on the same day. To start implementing same-day discharge after LH, an optimal and LH-specific catheter policy is essential. With this in mind, it is notable to mention that most hospitals in the Netherlands did not have a specific protocol for LH but rather used a general surgical protocol. By applying the policies of open surgery, the benefits associated with this minimally invasive approach might be undone. As such, we recommend a protocol specific for LH in every hospital regarding urinary catheter policy.

Nurse survey

In the second part of this study, the opinion of the nurses regarding catheter management was assessed. Assessing their opinion is valuable as nurses do not decided when to remove

the urinary catheter but they do closely monitor the patients in the postoperative period and have as a result much clinical experience on this topic. Furthermore, it seems relevant to study the attitude of the nurses when it comes to implementing (new) evidence-based recommendations on catheter removal.

Although the results of the randomized controlled trial are not yet available that compare direct versus delayed catheter removal after LH (MUCH trial), it seems that the nurses deemed clinical advantages with the direct removal regimen. From our survey, we observed that 90% of the surveyed nurses, all working on a gynaecological ward where both catheterization policies were in place due to the MUCH trial, indicated that direct removal was feasible (90%) and 78% would recommend it to a friend or family member.

Also, it was interesting to note that nurses' opinion on urinary retention and timing of catheter removal varied. Almost half of the nurses reported that direct removal was associated with an increased risk of urinary retention (45.9%) whereas the other half was convinced that that direct removal had no influence (25.2%) or even a decreased risk (28.8%) on voiding dysfunction. This variety in responses should also serve as a general reflection in terms of education on this topic. Indeed, there is currently sufficiently literature available demonstrating that direct catheter removal is not associated with a decreased risk of urinary retention.[9;15;18]

Regarding risk factors associated with voiding dysfunction after laparoscopic gynaecologic surgery, several studies have been published with varying results.[13;19] Although some characteristics such as diabetes and age have been appointed as risk factors after hysterectomy, a study demonstrated that it was for LH often unpredictable to determine which patient will develop urinary retention.[19] As a result, it remains challenging to select beforehand the low-risk patients. In our survey, a total of 57.7% of the nurses appointed specific criteria where direct removal of catheter might be contra-indicated, including (pre-operative) physical co-morbidities and complications.

Finally, the results of our survey also revealed that particularly the nurses with more experience, who appeared to be the older nurses, had a tendency to favour delayed removal. Possible explanations could be the fact that they have been working with this policy for years with good outcomes. Also, the possible increased workload associated with direct removal did seem to be influenced by experience, as shown in our sub-analysis. These findings are relevant to take into consideration when implementing catheter removal policies in the future.

Limitations

One of the limitations of our study was that for the telephonic consultation we did not collect the protocols of each hospital but rather asked over the phone what the catheterization management of that specific hospital was. Yet, as we interviewed the head nurses that were working according to these guidelines, we believe our findings are reliable. Furthermore, we did not explicitly evaluate if all surgeons within one hospital followed the same protocol. As a result, individual differences within one hospital may be present. In addition, these national data should be compared with caution to the data of the nurse survey as the latter was limited to six hospitals. Finally, as the MUCH trial was being conducted at the time of the survey, the opinion of the nurses might be influenced by it. On the other hand, it can also be considered as a strength that the nurses had the opportunity to work with both catheter policies. Other strengths of the study were the fact that we had a 100% response rate for our telephone consultation and that 81% of the nurses responded to our survey.

Conclusion

To conclude, most Dutch hospitals removed the urinary catheter one day after LH (78%). Of the survey nurses, 78% recommend direct removal. Although randomised trials are necessary to determine optimal catheterization management, our findings are helpful if a new urinary catheter policy has to be implemented.

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Chapter 7

Immediate versus delayed removal of urinary catheter after laparoscopic hysterectomy: a randomized-controlled trial

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Submitted

Abstract

Background: In many hospitals, it is standard care to leave the indwelling catheter in place until the next day after uncomplicated laparoscopic hysterectomy. However, scientific support for this policy is lacking.

Objective: In many hospitals, it is standard care to leave the indwelling catheter in place until the next day after uncomplicated laparoscopic hysterectomy. However, scientific support for this policy is lacking.

Study design: Non-inferiority randomized controlled trial in six hospitals in the Netherlands. Primary outcome was the inability to void within six hours after catheter removal.

Results: Between May 2016 and July 2017, 155 patients were randomized to either immediate removal (n=74) or delayed (n=81). The intention-to-treat and per-protocol analysis did not demonstrate the non-inferiority of immediate removal for the primary outcome (p=.81, p=.80): ten patients with immediate catheter removal could not urinate spontaneously within six hours (13.5% [7.3;23.3]) compared to none in the delayed group. Though, of these ten patients, seven could void spontaneously within nine hours without additional intervention. Regarding the secondary outcomes, eight patients from the delayed group requested earlier catheter removal because of unbearable complaints (9.9%). Three patients with immediate removal (4.1%) had a urinary tract infection postoperatively versus eight with delayed removal (9.9%, p=.596). Patients with immediate removal mobilized significantly earlier (5.7 hours (0.8–23.3) versus 21.0 (1.4-29.9), p<.001). No significant difference was observed for hospital stay, postoperative pain and patient satisfaction.

Conclusion: The non-inferiority of immediate catheter removal could not be demonstrated by more than 10% in terms of urinary retention six hours after procedure. However, 70% of the patients with voiding difficulties in the immediate group could void spontaneously within nine hours and therefore it is questionable if all observed urinary retention cases where clinically relevant. As a result, the clinical advantages of immediate removal seem to outweigh the risk of bladder retention.

Introduction

During laparoscopic hysterectomy (LH), it is standard care to place an indwelling catheter to avoid iatrogenic injuries of the bladder, monitor urinary output and check for hematuria.[1] However, it remains unclear what the best moment is to remove the catheter after an uncomplicated LH. Most specific guidelines on LH report limited information on this topic.[2;3] A recent telephonic survey in the Netherlands demonstrated that after LH 78% of the Dutch hospitals have the policy to leave the catheter in place until the next morning (data unpublished). Though, no scientific support exists for this regime; the few available studies on this topic in fact all favor direct catheter removal after hysterectomy.[4-6]

The Infectious Diseases Society of America recommends not leaving the catheter longer in place than necessary after any type of surgery.[7] A prolonged catheterization is known to be associated with increased risk of urinary tract infection as well as delayed mobilization and prolonged hospital stay.[4;6] Additionally, patients have reported that they find the indwelling catheter inconvenient.[8;9] On the other hand, immediate removal of the catheter after surgery has been associated with higher rates of urinary retention which can result in re-catheterization and other morbidities. Specifically for LH, urinary retention rates up to 14% to 34% have been reported after immediate removal.[4;5]

To fully benefit from the advantages of minimally invasive surgery, all postoperative complications and side effects leading to prolonged recovery should be minimized.[10] As a result, an adequate catheter management can be valuable for patients and their recovery. With this in mind, the aim of our study was to evaluate if immediate catheter removal (ICR) after LH was associated with similar (or better) outcomes compared with delayed catheter removal (DCR). As the advantages associated with a reduced catheterization time are well-known (early mobilization and reduced risk of urinary tract infection),[8] we specifically aimed to demonstrate that the risk of bladder retention is non-inferior in the ICR group compared to the DCR.

Material and methods

A multi-center non-inferiority randomized controlled trial (RCT) was conducted following the CONSORT recommendations.[12] The protocol was approved by the Ethics Committee of Leiden University Medical Centre (LUMC) in Leiden, the Netherlands (P15.382/NL55504.058.15) and the boards of all participating hospitals. The trial was registered in clinicalgov.org (NCT02742636). The study was conducted in LUMC, an academic hospital in the Netherlands and its five affiliated teaching hospitals (Alrijne Ziekenhuis, Groene Hart Ziekenhuis, Haaglanden Medisch Centrum, HagaZiekenhuis and Reinier de Graaf Gasthuis).

All patients undergoing LH for benign indication or low-grade cervical or endometrial malignancies were asked to participate if fulfilling study criteria. Women had to be older than 18 years and scheduled for LH. Women with concomitant procedures such as prolapse surgery, extensive endometriosis surgery or advanced oncologic dissection including nodal dissection, were excluded, as well as patients with stress and urge incontinency, or other systemic diseases potentially influencing their ability to void (e.g. multiple sclerosis). Women were counselled by their gynecologist during an outpatient visit prior to surgery and were given written information. If, after consideration, they agreed to participate, written informed consent was obtained and they were enrolled in the study. LH was performed according to standard local protocol and under general anesthesia.

In the operating room, at the end of the surgery, patients were randomized (1:1 ratio) to either ICR or DCR. Patients randomized to ICR had their catheter removed in the operating room while patients with DCR had their catheter removed between 18 and 24 hours after surgery (regular treatment in all participating hospitals). If intraoperative injury occurred and the gynecologist judged that prolonged catheterization was necessary, patients were considered dropouts.

The randomization was done by the operating gynecologist through an online and secured program called Promise (www.msbi.nl/much). To assure group balance within centers, the randomization sequence was computer-generated with variable blocks of two and four, stratified by center. The allocation code was disclosed directly on the website after entering patient identification number and confirming inclusion criteria. Nor the patients nor the medical staff were blinded for the allocated treatment. At any time, a patient could decide to opt out. The secured program Promise was also used for data collection.

Primary outcome of the study was urinary retention defined as the inability to void completely within six hours after catheter removal.[5] If a patient could not void within given time a bladder scan was performed to assess the amount of retention, as described in Figure 7.1. Further actions were undertaken accordingly. Before discharge patients in both groups had a bladder scan after voiding to ensure no patient was sent home with retention.

Secondary outcomes were (suspicion of) urinary tract infection (based on the results of a standard urine test for nitrite and leucocytes in combination with clinical symptoms); time of mobilization (defined as the first time out of bed after surgery) and the length of hospital stay (same day discharged coded as 0). Additionally, patients were asked to fill in these questionnaires 6 and 24 hours after surgery, and after 6 weeks during the outpatient follow-up visit. Questions regarding pain and discomfort of the urinary catheter were asked as well as patient satisfaction. The visual-analogue score (VAS) was used (0–10) to evaluate pain and satisfaction.

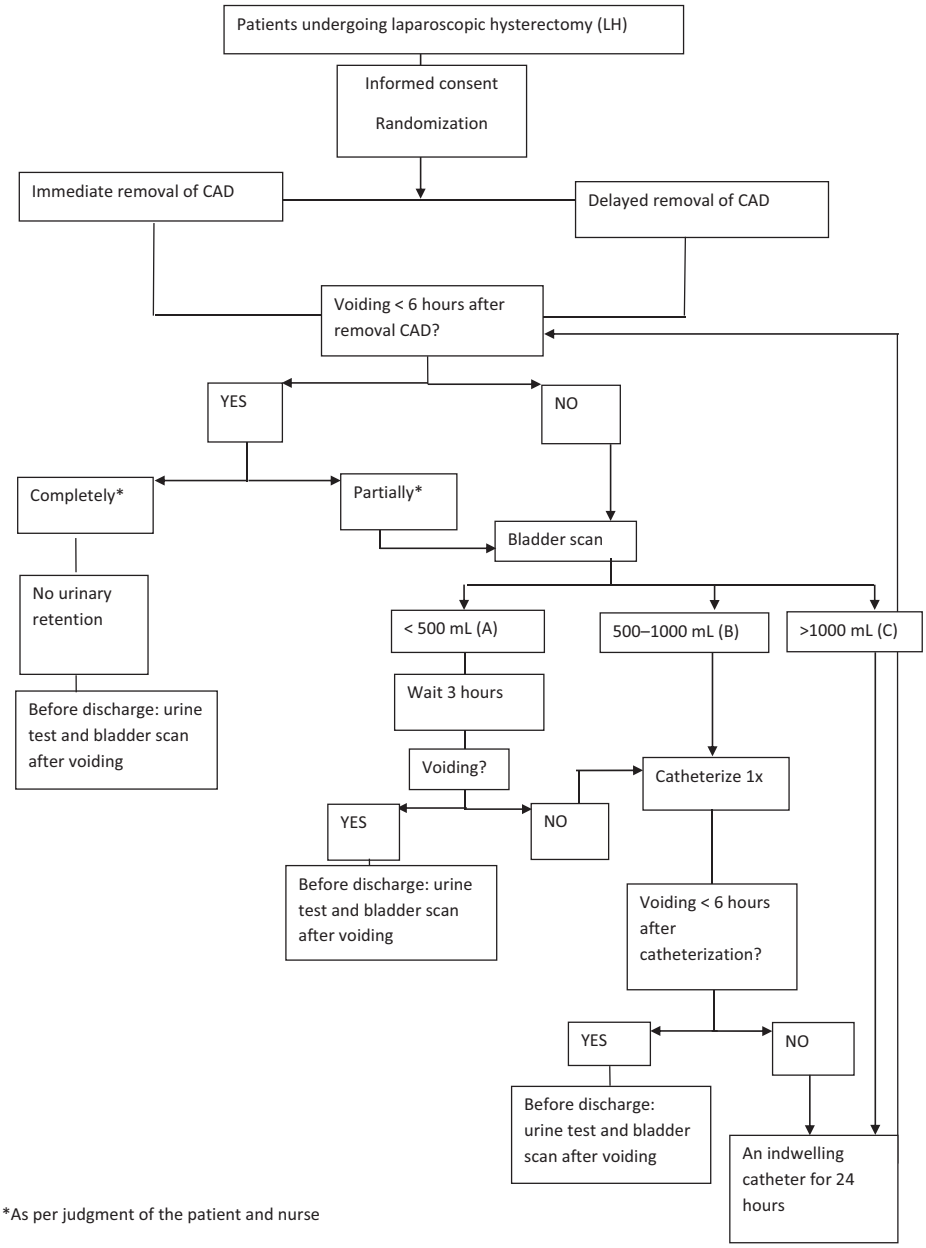

Figure 7.1: Study flow-chart.

Patient and surgical baseline characteristics were extracted from the medical records. Patient characteristics included age at surgery, BMI (kg/m^2), ASA classification, history of previous abdominal procedures and indication for hysterectomy. The type of surgery (total, supra-cervical or laparoscopic assisted vaginal hysterectomy (LAVH)) and any concomitant

procedures such as adnexal surgery were also recorded. Surgical outcomes included intra-operative blood loss, operative time (skin incision to skin closure), uterine weight and complications (recorded up to six weeks after surgery). Complications were defined according to the internationally recognized classification of the Dutch Society of Obstetrics and Gynecology (NVOG)[11] and were further divided into major and minor complications. After completion of the study, source data verification from the medical charts was performed in all hospitals by the principle investigator (EMS) and two research nurses.

Statistics

A non-inferiority study design was used. To ascertain the required group size, a power calculation was performed. We hypothesized that DCR was associated with 5% retention and we expected a higher risk when catheter was removed immediately. A non-inferiority margin of 10% was used; we wanted to exclude a difference of more than 10% in favor of DCR. Thus, using a one-sided Z-test (alpha error 0.025, beta error 0.20), two groups of 75 women were needed to demonstrate the non-inferiority of ICR. An additional 10 patients were included to intercept any unanticipated drop-outs. As a result, a sample-size of 160 patients was needed. Statistical analysis was performed using SPSS software (BM SPSS Statistics for Windows, version 20.0, Chicago). Data were summarized and extreme values were verified to be correct. All statistical analyses were performed by intention-to-treat and per protocol approach, as stated in the CONSORT recommendations for non-inferiority RCTs.[12] To determine the non-inferiority of the immediate catheter removal policy, rates of urinary retention (primary outcome) were compared using the one sided non-inferiority Z test for difference in proportions (pooled variance). Non-inferiority was confirmed if the confidence interval did not cross the predefined margin of 10%. For the other variables, we assessed normality; continuous data were presented as mean with standard deviation (SD) or as median (range) and categorical data as frequency (percentage). The outcomes of the two groups were compared to each other with superiority tests as we aimed to demonstrate, similar to the literature, the well-known advantages of ICR.[8] Tests used were the student t-test or Mann-Whitney test and Chi-square or Fisher's exact test as appropriate. P-value and 95% confidence interval (95% CI) were reported. A p-value of <.05 was considered significant.

Results

Between 31st of May 2016 and 22nd of July 2017, 162 eligible patients were included in the trial (Figure 7.2). Three patients withdraw consent after randomization and four

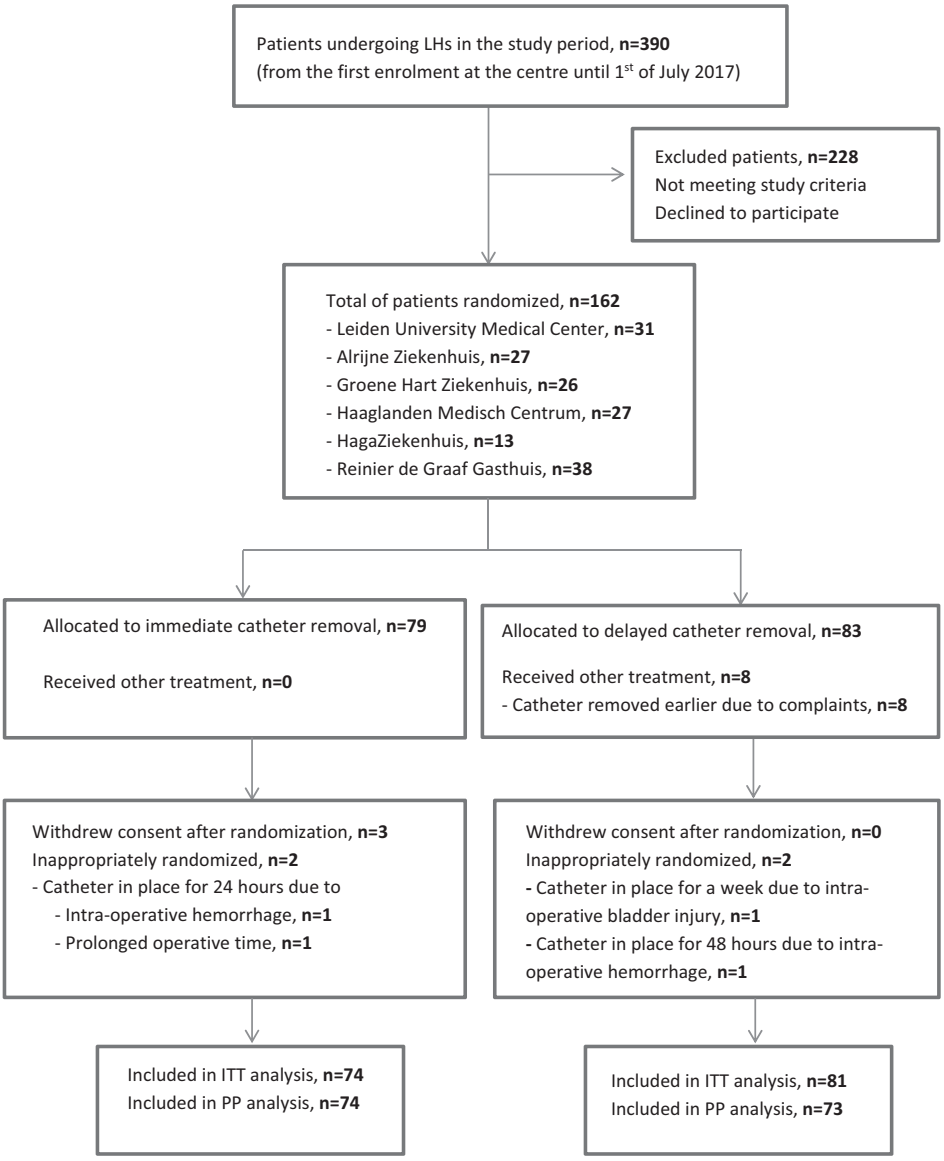

Figure 7.2: CONSORT flow diagram of included patient.

patients were randomized despite the fact that the gynecologist decided immediately at the end of the surgery that prolonged catheterization was necessary regardless of the randomization result. These cases were considered dropouts. As a result, a total of 74 patients were analyzed in the group with ICR and 81 patients in the group with DCR. Of the patients randomized to DCR, eight requested earlier catheter removal (between 2 and 12

hours after surgery) because of unbearable complaints (9.9%). Baseline characteristics and surgical outcomes of the included patients are listed in Table 7.1 and were well balanced.

Regarding the primary outcome, it was for five patients (n=1 in the ICR group; n=4 in the DCR group) not reported if they had urinated specifically within six hours. As in none of the medical charts urinary problems were reported, we assumed that these patients did

Table 7.1: Baseline characteristics and surgical outcomes – intention-to-treat analysis

	Immediate catheter removal (n=74)	Delayed catheter removal (n=81)
Baseline characteristics		
Age, years , mean (SD)	49.3 (10.5)	51.5 (11.9)
BMI, kg/m^2, mean (SD) (n=154)	26.4 (5.5)	28.5 (5.6)
ASA classification, n (%)		
ASA I	32 (43.2)	37 (45.7)
ASA II	40 (54.1)	43 (53.1)
ASA III	2 (2.7)	1 (1.2)
ASA IV	0	0
Previous procedures, n (%)		
Laparoscopic	13 (17.6)	18 (22.2)
Laparotomic	12 (16.2)	16 (19.8)
Indication(s) for LH, n (%)		
Heavy or irregular menstrual bleeding	37 (50)	43 (53.1)
Pain	14 (18.9)	16 (19.8)
Fibroids	21 (28.4)	15 (18.5)
Malignancy	25 (33.8)	34 (42.0)
Cervix	11	12
Endometrium	14	22
Other	3 (4.1)	9 (11.1)
Preventive (genetics)	2	5
Adenomyosis/endometriosis	0	4
Bicornuate uterus	1	0
Type hysterectomy, n (%)		
TLH	73 (98.6)	78 (96.3)
LAVH	1 (1.4)	3 (3.7)
SLH	0	0
BSO, n (%)	35 (47.3)	38 (46.9)
Tubectomy, n (%)	12 (16.2)	12 (14.8)
Uterine weight, grams, mean (SD), (n=148)	213.8 (170.7)	217.9 (227.9)
Surgical outcomes		
Operative time, minutes, mean (SD)	116.0 (44.0)	105.4 (29.6)
Intra-operative blood loss, mL, mean (SD)	131.8 (136.9)	108.1 (122.3)

Table 7.1 continues on next page

Table 7.1: *Continued*

	Immediate catheter removal (n=74)	Delayed catheter removal (n=81)
Complications, n (%)		
Major complications	1 (1.4)	6 (7.4)
Ureter injury	1	1
Bladder injury	0	0
Post-operative hemorrhage (re-operation)	0	3
Vaginal cuff abscess (drainage)	0	1
Re-operation*	0	1
Minor complications	5 (6.8)	10 (12.3)
Infection (wound)	1	2
Fever eci (>38C)	0	1
Hemorrhage/hematoma/abscess/defect (vaginal cuff)	3	4
Hematoom abdomen	1	1
Transient kidney failure eci	0	1
Gauze left in vagina	0	1

Indications: patients could have more than one indication.
* Re-operation due to suspicion of herniation but this was not the case.
TLH, total laparoscopic hysterectomy; LAVH, laparoscopic assisted vaginal hysterectomy; SLH, supracervical laparoscopic hysterectomy; (B)SO, (bilateral) salpingo-oophorectomy.

not have voiding problems postoperative. Of the analyzed patients, ten patients in the ICR group could not urinate spontaneously within six hours (13.5%) compared to none in the DCR group (Table 7.2). The intention-to-treat analysis and per-protocol analysis did not demonstrate the non-inferiority of ICR over DCR (p=.81 and p=.80). The difference of 13.5% [7.3;23.3] between the groups did not fell within the inferiority margin. Also, the superiority test demonstrated that ICR was associated with significant more voiding problems (<.001).

Of the ten patients with voiding dysfunction in the ICR group, seven were able to urinate spontaneously within nine hours after catheter removal without any additional interventions. The other three patients required re-catheterization as they could not void spontaneously despite several attempts. The first patient was intermittent catheterized after the bladder scan revealed a urinary retention of 908 mL. The second one received directly an indwelling catheter overnight (urinary retention 550 mL). Both patients urinated spontaneously after catheter removal and did not encounter any further problems. The last patient also received an indwelling catheter overnight. The next day, this catheter was removed but patient could still not urinate spontaneously and the decision was made to discharge her with an indwelling catheter. After seven days, the catheter was removed and patient could immediately void spontaneously. Bladder scan showed no urinary retention.

Table 7.2: Primary and secondary outcomes of the trial – intention-to-treat analysis

	Immediate catheter removal (n=74)	Delayed catheter removal (n=81)	Difference in percentages	p-value	[95% CI]
Primary outcome					
Unable to void within 6 hours after catheter removal, n (%), (n=155)	10 (13.5)	0	[7.3;23.3]	.82**	
Additional interventions required	3*	0			
Secondary outcomes					
Urinary tract infection treated with antibiotics, n (%)	3 (4.1)	8 (9.9)	[0.9; 11.7]	.215	
During hospitalization	0	4			
After discharge	3	4			
Urine test positive for nitrite and/or leucocytes, n (%), (n=98)	25 (48.1)	24 (52.2)	[-15.1; 23]	.840	
Mobilization, hours, median (range), (n=134)	5.7 (0.8–23.3)	21.0 (1.4–29.9)		<.001	
Length of hospital stay, days, median (range)	1.5 (0–4)	1 (1–4)		.954	
Exploratory outcomes					
Bladder scan at discharge, mL, mean (SD), (n=116)	46.6 (70.7)	37.5 (64.7)		.471	[-15.8; 34.0]
Questionnaires 6 hours after surgery (n=103)					
Overall VAS score, mean (SD)	3.2 (2.0)	3.5 (2.4)		.426	[-1.2; 0.5]
VAS score specific for the catheter, mean (SD)	0	2.9 (2.9)		--	
Excepted discharge time according to patient, n (%)				.621	
Today	2 (4.5)	1 (1.9)			
Tomorrow	14 (31.8)	22 (41.5)			
The day after tomorrow	15 (34.1)	15 (28.3)			
Not any time soon	2 (4.5)	5 (9.4)			
I don't know	11 (25.0)	10 (18.9)			

	Immediate catheter removal (n=74)	Delayed catheter removal (n=81)	Difference in percentages	p-value	[95% CI]
Questionnaires 24 hours after surgery (n=101)					
Overall VAS score, mean (SD)	2.9 (2.0)	2.8 (2.3)		.719	[-0.7; 1.0]
Expected VAS score specific for the catheter for patients without, mean (SD)	4.7 (2.9)	3.0 (2.9)		.004	[0.6; 3.0]
Questionnaires 6 weeks after surgery (n=70)					
Satisfaction with treatment, VAS score, mean (SD)	8.9 (0.9)	9.0 (1.7)		.709	[-0.8; 0.5]
Satisfaction with hospitalization, VAS score, mean (SD)	8.5 (1.5)	9.1 (1.1)		.056	[-1.2; 0.2]

* One patient was discharged with an indwelling catheter.
Data are presented as mean (standard deviation), as median (range) or as number (percentage)
[95% CI] is 95% confidence interval.
Statistics:
** One sided non-inferiority Z test for difference in proportions (pooled variance).
For the other variables: independent T-test or Mann Whitney U (continuous data); chi-square of fisher exact test (categorical data).
UTI, urinary tract infection.

In Table 7.3, detailed information regarding the ten patients with voiding dysfunction was provided. Also patient and surgical characteristics of the patients with voiding dysfunction were compared to the patients from the ICR group without voiding difficulties. No differences were observed between the two groups except that patients with voiding dysfunction had significantly more blood loss during surgery (250 (25–600) versus 100 (10–600), p=.032).

For the secondary outcomes (Table 7.2), we observed that after ICR and DCR respectively three (4.1%) and eights patients (9.9%) had a suspicion of urinary tract infection postoperatively requiring antibiotics. No significant difference was observed between the two groups (p=.215). In the ICR group, all three patients were treated approximately two weeks after surgery. In the DCR group, four patients were treated with antibiotics after discharge while four patients were treated directly one or two days after surgery. No significant difference was observed between the two groups for the results of the urine test (p=.840) or the post-voiding residual at discharge (p=.471). Patients in the ICR group mobilized significantly earlier than the group with DCR (median of 5.7 hours (0.8–23.3) versus 21 (1.4–29.9), p<.001). The length of hospital stay did not differ between the two groups (p=.954).

The overall pain-VAS was similar between the two groups six and 24 hours after LH (Table 7.2). The group with an indwelling catheter in place reported six hours after surgery a VAS specific for the indwelling catheter of 2.9 (2.9). No difference was observed regarding the number of days a patient expected to stay in the hospital when asked six hours after surgery (p=.621). Twenty-four hours after surgery, the patients without catheter were asked to assess their VAS for the catheter as if they still had one. Patients in the ICR group reported a significant higher expected VAS than the DCR group (4.7 (2.9) versus 3.0 (2.9), p=.004, 95% CI [0.6; 3.0]). Six weeks after surgery, patients in both groups were equally satisfied with the procedure (p=.731) and the hospitalization (p=.052).

The results of the per protocol analysis are available in Appendix 1 (available online). The eight patients who had been randomized to DCR but requested earlier catheter removal were excluded. No relevant differences were observed compared with the intention-to-treat analysis.

Table 7.3: Detailed overview of the patients with voiding dysfunction compared to patients without from the immediate catheter removal group

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	TOTAL voiding dysfunction (n=10)	TOTAL no voiding dysfunction (n=63)	p-value
Age	55	48	43	60	53	44	45	41	47	45	48.1 (6.0)	49.2 (11.0)	.752
BMI	23.1	23.5	30.4	28.5	27.7	29.8	20.1	23.3	23.6	27.1	25.7 (3.4)	26.3 (5.7)	.718
ASA I ASA II ASA III	2	2	2	1	2	1	1	1	2	2	4 (40) 6 (60) 0	28 (44.4) 33 (52.4) 2 (3.2)	.798
Indication for LH	Micro invasive cervix carcinoma	Fibroids	Fibroids	Endometrium carcinoma	Endometrium carcinoma	Endometrium carcinoma	Fibroids	Cervix dysplasia	Fibroids	Heavy bleeding	-	--	--
TLH LAVH	TLH	TLH	TLH	TLH	TLH	TLH	TLH	TLH	TLH	TLH	10 0	62 1	1.000
Operative time	152	108	118	77	179	166	79	86	120	240	119 (77–240)	110 (48–241)	.304
Intra-operative blood loss	300	250	250	25	365	600	30	50	600	150	250 (25–600)	100 (10–600)	.032
Uterine weight	60	420	607	103	172	267	40	98	410	82	137.5 (40–607)	166.5 (54–962)	.821
Complications	No	No	No	No	No	No	No	No	No	No	0	8 (12.7)	.588
Length of stay	3	1	2	2	2	2	1	2	1	3	2 (1–3)	1 (0-4)	.487
Mobilization	3.8	8.9	9.5	6.8	2.3	7.8	7.6	11	5.7	2.9	7.2 (2.3–11)	5.4 (0.8–23.3)	.275
Voiding within 6 hours	After 6 hours without voiding, CAD was placed over night. Next day, CAD was removed but patient was still unable to void. Discharged home with a CAD for 1 week.	Patient voided spontaneously 9 hours after CAD removal. No bladder scan was performed.	Patient voided spontaneously 9 hours after CAD removal. No bladder scan was performed.	Patient voided spontaneously 6.5 hours after CAD removal. After 6 hours, bladder scan revealed 135 mL	Patient voided spontaneously 8 hours after CAD removal. After 6 hours, bladder scan revealed 225 mL.	Patient voided spontaneously more than 6 hours after CAD removal (exact time unclear). After 6 hours, bladder scan revealed 300 mL.	Patient voided spontaneously 7.5 hours after CAD removal. No bladder scan was performed.	Patient voided spontaneously 9.5 hours after CAD removal. After 6 hours, bladder scan revealed 140 mL.	Patient was catheterized after 6 hours without voiding after bladder scan revealed 908 mL. Voided spontaneously within 6 hours.	After 6 hours without voiding, CAD was placed over night. Bladder scan revealed 550 cc. Next day, CAD was removed and patient voided spontaneously within 6 hours.	--	--	--

LH, laparoscopic hysterectomy.
Statistics: independent T-test or Mann Whitney U (continuous data); chi-square of fisher exact test (categorical data).

Discussion

Although the majority of the hospitals in the Netherlands leave the urinary catheter in place until the next day after LH, the scientific support for this management is absent. Indeed, the few available studies on this topic all favor immediate removal after different types of hysterectomy.[4;6;13] The potential drawback of immediate catheter removal is the increased risk of urinary retention, which has been reported up to 34% after LAVH.= In the present RCT comparing 74 patients with immediate catheter removal (ICR) after LH to 81 patients with delayed catheter removal (DCR), ten patients, all allocated to the ICR group, could no void within six hours (13.7%). This retention rate was in line with a prospective cohort study that demonstrated a retention rate of 14% after analyzing 140 patients undergoing LH with ICR.[5]

In our study, the risk of urinary retention after ICR was not demonstrated to be non-inferior to delayed catheter removal as the difference exceeded the predefined margin of 10%. However, of the ten patients with voiding dysfunctions, only three patients required re-catheterization. The other seven patients voided spontaneously within nine hours without additional interventions. It is therefore debatable if these latest voiding difficulties were clinically relevant for the patients and should be considered as 'real' urinary retention. In the literature, several definitions are in use to define 'urinary retention'. If considering only the patients requiring re-catheterization, the urinary retention rate for the ICR group would be only 4.1% in our study and non-inferior to DCR.

In the context of same-day discharge after LH, it is nevertheless important to take into consideration that a proportion of patients with ICR voided with delay. Indeed, a recent systematic review demonstrated that a reduced time before voiding after catheter removal was directly associated with a successful same-day discharge.[14] For instance, it might be too late to discharge patients on the same-day if they can only void between six and nine hours after surgery. A study demonstrated that it was difficult to predict preoperatively which patients are at risk of voiding dysfunction.[15] Although our study was not designed to study the risk factors associated with urinary retention, we observed that patients who were confronted with voiding difficulties had significantly more intra-operative blood loss. Yet, it was not possible to determine a cut-off.

Another aspect to consider when determining the optimal moment to remove the catheter is the risk of urinary tract infections. Studies have shown that the overall risk of urinary tract infection with an indwelling catheter is 3 to 7% per day of catheterization.[7;16] Similarly to the RCT of Liang et al. reporting on voiding outcomes of 150 patients undergoing LAVH, we did not observe a significant difference in the risk for urinary tract infections up to six

weeks after surgery.[4] Though, it was interesting to observe that already during the short time of admission, four patients from the DCR group were diagnosed and treated for urinary tract infections (4.9%) compared to none in the ICR group. It is however important to realize that health care givers were not blinded to the use of catheter and therefore a bias toward the concern for dysuria in patients for DCR cannot be excluded.

Direct catheter removal has also been associated with early mobilization after surgery.[6;13] This was also observed in our study; patients with ICR mobilized on average 15 hours earlier than the group with DCR. Patients with ICR are forced to get out of bed to void, which is a positive side effect of this regime as early mobilization has been associated with quicker recovery and decreased morbidity.[10] In theory, patients with an indwelling catheter in place could also start mobilizing, yet they often have no incentive to do so. Despite the faster mobilization, ICR did, in our study, not result in earlier hospital discharge. This is in contrast with previously published studies.[6]

Finally, it is relevant to assess patient's well-being on catheter removal. Studies have reported that patients experience more urethral or vesical pain with prolonged catheterization.[8] In our study, eight patients (9.6%) from the DCR group requested catheter removal a few hours after surgery because of unbearable discomfort, which is from a patient's perspective an important finding against prolonged catheterization. On the other hand, patients who had a catheter in place until the next morning reported on average a low VAS specific for the catheter (2.9 (SD 2.9)). In addition, the overall pain scores were not higher compared with the group without catheter. It seems thus that the degree of discomfort varies according to the individual patient.

Limitations of our study were that patients and caregivers were not blinded to the catheter policy, which could result in bias of outcomes. This could be particularly the case for outcomes related to patients, as psychological factors might be of influence.[17] Yet, for this topic, a double blinded study would not have been possible. Strengths of the study include its randomized controlled design and the inclusion of a large population of patients undergoing LH. To our knowledge, no other RCT specific for LH has been conducted so far. Furthermore, the trial was performed in six different hospitals, which adds to the generalizability of the outcomes.

Compared with open surgery, LH has been associated with many well-known advantages such as quicker hospital discharge and faster recovery.[18] Although catheter management is probably not the main priority of a surgeon, the consequences of a suboptimal regimen may undo the benefits associated with the minimally invasive approach. The consequences related to poor catheterization policy might significantly impact patient's post-operative

recovery as well as lead to increased hospital costs, aspects that are increasingly being considered in our era of Valued Based Health Care.

In conclusion, our trial demonstrated that in terms of inability to void six hours after catheter removal, ICR was not non-inferior by more than 10% compared to DCR management. However, 70% of the patients with voiding dysfunctions could void spontaneously within nine hours without further interventions. ICR was also associated with faster mobilization and, although not significant, with lower rates of treatment for urinary tract infections (4.1% versus 9.9%). Furthermore, 9.9% of the patients from the DCR group requested earlier removal because of discomfort. As a result, the advantages associated with ICR seem to outweigh the disadvantage of clinically relevant voiding dysfunction.

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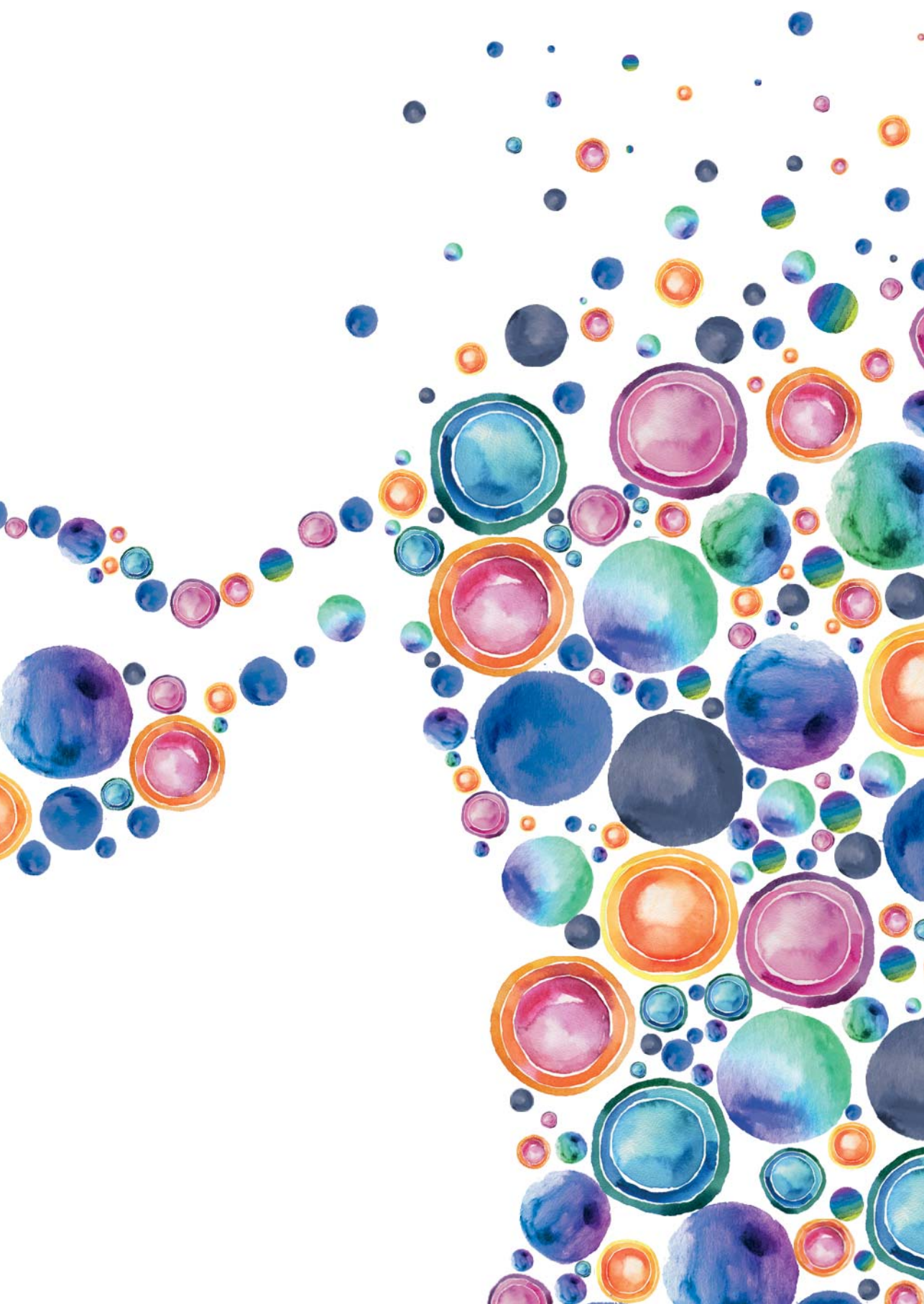

Chapter 8

Disseminated leiomyoma cells can be identified following conventional myomectomy

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Abstract

Objective: Uncontained morcellation of leiomyomas during laparoscopic surgery has recently been discouraged, as undetected malignant tumours, namely leiomyosarcomas, could be fragmented which may result in upstaged disease. However, enucleating leiomyomas per se may be inappropriate from an oncological perspective because complete, radical resection of malignant tumours to prevent further tumour growth or recurrence is not achieved. Thus, the aim of this study was to determine whether spillage of leiomyoma cells occurs during laparotomic myomectomy.

Design: Observational study.

Setting: Tertiary academic centre in the Netherlands.

Population: Women undergoing laparotomic myomectomy were included in the study.

Methods: Peritoneal abdominal washings were obtained on two occasions during the myomectomy procedure; the first one immediately after opening the abdomen and the second one after resection of the leiomyoma(s). Cytological evaluation of the fluids was performed.

Main outcome measures: The presence of leiomyoma cells in any of the washings.

Results: Five patients were included in this pilot study. All first washings were negative for leiomyoma cells. However, cytology positive for the presence of leiomyoma cells was found in three of the five second, post-myomectomy washings.

Conclusion: Tissue spillage from leiomyoma(s) occurs during conventional open myomectomy. The clinical relevance of tissue dissemination after myomectomy is unclear but it cannot be excluded that this may negatively affect the patient's outcome if there is malignant change within the enucleated leiomyoma(s). Therefore, it is questionable whether morcellation in specially designed containment bags after laparoscopic myomectomy, guarantees any additional oncological safety.

Introduction

The introduction of power morcellation in the field of gynaecology has contributed to the wider implementation of minimally invasive surgery by enabling laparoscopic extraction of large specimens. Although warnings regarding its oncological safety were published more than a decade ago,[1,2] it was only in 2014 that the Food and Drug Administration (FDA) issued a press release discouraging the use of morcellation during laparoscopic gynaecologic surgery, namely hysterectomy and myomectomy, in the presence of leiomyomas.[3] This FDA statement was issued in response to reports of cases of morcellation of presumed benign tumours that subsequently turned out to be leiomyosarcoma(s). This in turn led to concerns that tissue dissemination of occult malignancy after morcellation could lead to an upstage of the disease.[4] Furthermore, preoperative prediction of malignant change within leiomyomas is unreliable in the absence of prognostic patient characteristics or discriminatory diagnostic tests.

One of the basic principles of surgical oncology is that malignant tumours should always be resected radically and in toto to prevent further tumour growth and/or recurrence. If all malignant tissue spillage is considered potentially harmful, as many authors advocate,[4-6] it can be questioned whether, from an oncological point of view, myomectomy for presumed leiomyomas is safe altogether. Indeed, the cleavage plane is almost never radical during myomectomy, regardless of the type of approach. Furthermore, leiomyosarcomas are heterogeneous tumours, meaning that malignant cells could be located anywhere inside the growth.

In light of these considerations we hypothesised that dissemination of leiomyomatous tissue occurs during resection of leiomyomas and not just as a result of subsequent morcellation of extracted tissue. Therefore, the aim of the current study was to detect the presence of leiomyoma spillage during laparotomic myomectomy by performing peritoneal washings.

Methods

During the study period, all patients undergoing abdominal myomectomy at the Leiden University Medical Centre (Leiden, the Netherlands) were asked to participate. The study was exempted from Institutional Review Board approval, but patients were informed about the study procedure and gave oral consent. Inclusion criteria were women of 18 years or older, diagnosed with symptomatic leiomyomas and eligible to undergo abdominal myomectomy as per the judgment of the surgeon. Exclusion criteria were suspected malignancy and inability to give consent.

The abdominal myomectomy procedure was performed according to standard techniques. As part of the study, the entire abdomen was washed two times with 500 ml of normal saline during the procedure: the first washing was performed as a control, immediately after opening the abdomen, and the second washing after resection of the leiomyoma(s). After every washing, the abdominal fluid was completely aspirated and collected in two separate bags for cytological evaluation. The main outcome of the study was to evaluate the presence of leiomyoma cells in any of the washings.

Before embedding the cells collected from the washings in paraffin, an erythrocyte lysis buffer (155 mM NH_4Cl, 10 mM $KHCO_3$, 1 mM EDTA, pH 7.4) was used to limit the amount of red blood cells which would impair visualisation during analyses. For each patient, two sets of formalin-fixed paraffin-embedded samples were obtained from the first and second washing. These samples were then cut at different levels and the tissue was stained with haematoxylin and eosin (HE stain). Next, the specimen slides were reviewed by an experienced pathologist (T.B.) to detect the presence of leiomyoma cells. In case of doubt, an additional staining with desmin was performed.

Data from the medical record of the patients were also abstracted and included: patient age and body mass index (BMI), indications for myomectomy, the number and weight of removed fibroids, and surgical outcomes such as operative time, intra-operative blood loss and complications. Complications were defined based on the classification of the Dutch Society of Obstetrics and Gynaecology.[7]

Results

Five patients were recruited to the study between April and October 2015. Patients were on average 34.6 years old (29–40), with a BMI of 27.7 (22–34.1). Reasons for the surgery were heavy bleeding (n=2) and/or infertility problems (n=3) and/or pelvic pressure and pain (n=2). On average, 3.8 fibroids (3–6) were removed and the removed specimens weighed 599.4 g (256–1040). All procedures were successfully completed, with an operative time of 108 min (91–134) and intra-operative blood loss of 685 ml (275–1300). Two patients experienced intraoperative haemorrhage of more than 1000 ml. One of them received two packages of red blood cells postoperatively. No other complications occurred and the postoperative course was otherwise uneventful in all cases (Table 8.1). All peritoneal washings obtained directly after opening the abdomen were negative, whereas three of the five peritoneal washings acquired after resection of the leiomyomas were positive for leiomyoma cells (Table 8.1, Figure 8.1). In one case the presence of leiomyoma cells was confirmed after performing an additional staining with desmin.

Table 8.1: Baseline characteristics, surgical outcomes and outcomes of cytology peritoneal washings

	Age (years)	BMI (kg/m^2)	Indication surgery	Operative time (min)	Intra-operative blood loss (mL)	Specimen weight (gram)	Number of fibroids (n)	Complications	First washing	Second washing
Patient 1	38	22.0	Infertility	100	275	256	3	--	Negative	Negative
Patient 2	31	27.8	Blood loss	103	1065	1040	3	>1000 mL blood loss + two RBCs	Negative	Positive*
Patient 3	29	26.1	Pressure + infertility	111	350	811	6	--	Negative	Positive
Patient 4	35	34.1	Blood loss + infertility	91	430	500	4	--	Negative	Positive
Patient 5	40	28.4	Pressure	134	1300	390	3	>1000 mL blood loss	Negative	Negative
Mean	**34.6**	**27.7**	--	**108**	**684**	**599.4**	**3.8**	--	--	--

* Desmin stain conclusive.

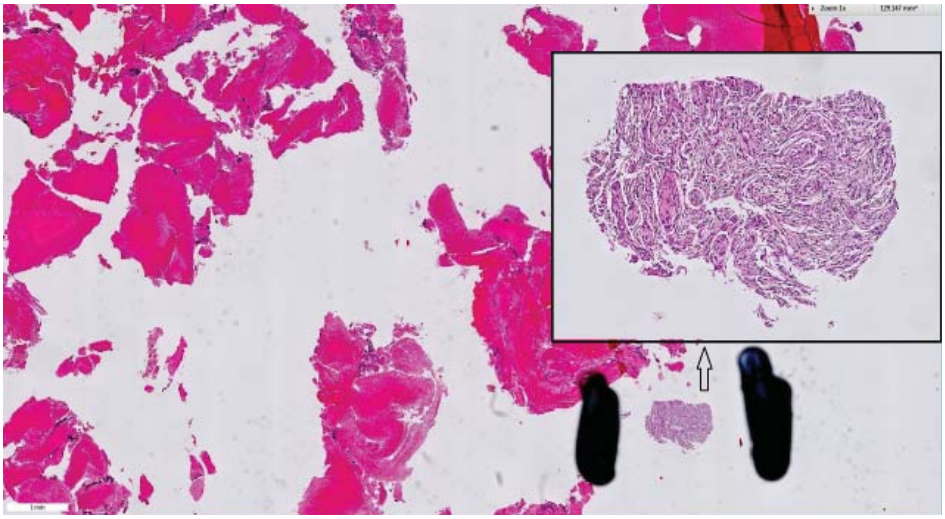

Figure 8.1: Leiomyoma cells (arrow) in the second peritoneal washing of patient 4 (HE stain).

Discussion

Main findings

There is evidence of micro-spillage of leiomyoma cells after conventional, open myomectomy but it is unclear whether these positive cytology results hold any clinical relevance if malignant change within the enucleated leiomyoma(s) is subsequently diagnosed following histological analysis.

Strengths and limitations

One limitation of our study could be the restriction of analysis to a conventional open abdominal myomectomy. However, the process of mechanically enucleating fibroids is similar during laparoscopic surgery and so one would expect the likelihood of tissue dissemination during myomectomy to be the same. The finding that tissue dissemination was not consistent following myomectomy, as no leiomyoma cells were detected in two of the five study cases, could be explained by the known limitations of the peritoneal washings technique[8] and so does not completely exclude their presence. In any case, even one positive cytology result would have been sufficient to support our hypothesis that dissemination of leiomyomatous tissue can occur during resection of leiomyomas. Our study analysed tumour dissemination of benign leiomyoma cells and not of leiomyosarcomas. Dissemination of leiomyosarcomas might also depend on whether small foci of sarcoma

are at the edges of the excised specimen and/or breaches were made on the surface. Of note, in this study we focused only on myomectomy and so our conclusion can not be extrapolated to hysterectomy in the presence of uterine leiomyomas.

Interpretation

The present study sheds new light on the current morcellation debate. In reaction to the FDA report warning of the use of power morcellation in the presence of uterine leiomyomas, gynaecologists throughout the world have sought to develop techniques to reduce the risk of potential spread, while conserving the less invasive laparoscopic approach. In addition to reducing surgical morbidity, preservation of the laparoscopic route of surgery seems reasonable given the low prevalence of leiomyosarcoma compared with that of leiomyoma.[9]

One of the suggested surgical options is 'contained power morcellation': after resection of the uterus or fibroid, a bag is inserted into the abdomen and the specimen is morcellated in the bag and removed.[10;11] In many clinics, contained power morcellation has been rapidly adopted and the first studies have shown that, despite a prolonged operative time of approximately 20–30 minutes, the technique is feasible.[12-14] Even though this technique is in its early phase of development, it can be questioned whether containment after extensive resection without a bag will ever provide any additional safety during myomectomy, as our study showed that during leiomyoma resection, tissue dissemination already occurs. Furthermore, studies evaluating the leakage during contained tissue extraction with power morcellation noted spillage of tissue from the bag in 9.2–33% of cases.[15;16] However, in all those cases the containment bags were visually intact.

In light of this, it is important to evaluate the impact of intra-abdominal malignant tissue dissemination on patient outcomes. Several studies have suggested that spread of uterine sarcomas leads to an upstaging of the disease and dramatically worsens the five-year survival rate when compared with surgery where no morcellation was performed.[4-6] Although the assumption that malignant tissue dissemination is associated with poorer outcomes seems instinctively plausible, we should be careful with the concept of upstaging used in the studies. Indeed, it implies that during initial surgery all leiomyosarcomas were stage I and that staging was based on a proper inspection of the abdomen, which seems unlikely when a benign tumour is expected.[17] Other studies have found no differences in survival rates between the morcellated and non-morcellated group, or have stated a lack of reliable evidence regarding the clinically relevance of the spread, especially as generally speaking the overall prognosis of a leiomyosarcoma is poor.[17;18] Furthermore, it is unknown whether a relation exists between the amount of tissue dissemination and the recurrence

and/or survival rate, especially as advanced research demonstrated already detectable circulating tumour cells in the blood of patients with early-stage localised tumours.[19]

The influence of non-radical procedures on the recurrence and survival rate has also been investigated in other malignant tumours. For endometrial carcinoma, similar washing studies have been performed, showing an increased percentage of positive cytology after dissemination of tissue from the endometrial cavity into the peritoneal cavity[20] but with inconsistent results regarding the prognosis and recurrence of the disease.[8;20] Also for ovarian carcinoma, controversy exists regarding the magnitude of harm of tumour leakage.[21] In a meta-analysis on early-stage ovarian cancer, pre-operative ruptures were associated with poorer outcomes compared with intra-operative ruptures, probably due to the duration and the amount of leakage in the abdomen.[21-23]

From a benign perspective, a condition called parasitic leiomyomas has been reported and although the exact aetiology remains unclear, it is believed to be caused by retained intra-abdominal tissue fragments.[24] The overall risk of parasitic leiomyomas after uncontained morcellation has recently been reported as between 0.12 and 0.95%.[24] It would be interesting to know whether the prevalence changes with contained morcellation. Assuming that containment keeps macro-spread to a minimum during surgery, it cannot be excluded that micro-spread contributes to this rare condition. One recent published report recommended extensive washings after surgery to minimise the risk of retained tissue.[18]

Thus, it is apparent that the impact of tissue dissemination on clinical outcomes is unclear, as is the protective value of contained extraction. Therefore, we believe that the gynaecological community should be cautious in widely adopting the peri-operative use of containment bags, which are most likely used off-label and without a proper systematic evaluation prior to implementation. Otherwise, there is a risk of offering a false sense of security. Furthermore, containment extraction should not distract us from seeking improved diagnosis of leiomyosarcomas and a better understanding of tumour biology including the impact of tissue dissemination on clinical outcomes.[25]

Conclusion

During open myomectomy, spillage of leiomyoma cells occurs. Although the clinical relevance of tissue dissemination after myomectomy is unclear, it cannot be excluded that it does negatively affect the patient's outcome, especially in the presence of malignancy. As a result, it can be questioned whether contained morcellation, as currently performed after laparoscopic myomectomy, guarantees any additional oncological safety.

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Chapter 9

Analysis of risk factors for intraoperative conversion of laparoscopic myomectomy

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Abstract

Objectives: To report the surgical outcomes of laparoscopic myomectomy (LM) and abdominal myomectomy (AM) at a high-volume tertiary care hospital, to evaluate the risk of conversion during LM, and to analyze the associated risk factors.

Design: Retrospective cohort study (Canadian Task Force classification II).

Patients: All patients who underwent LM and AM in a tertiary academic center in Boston, Massachusetts between 2009 and 2012.

Intervention: Medical records were reviewed for baseline characteristics and perioperative outcomes. Robot-assisted laparoscopy was considered a subtype of LM.

Results: A total of 966 patients underwent myomectomy during the study period, including 731 LM cases (75.67%) and 235 AM cases (24.33%). Compared with patients undergoing LM, those undergoing AM had more myomas removed and heavier specimens (mean number of myomas, 12.60 vs 3.54, p<.001; mean weight, 592.75 g vs 263.4 g, p<.001). Conversion was necessary in 8 LM cases (1.09%). All conversions were reactive in nature and were associated with greater blood loss (mean, 1381.25 vs 167.95 mL; p<.001) and longer hospital stay (mean days 3.13 vs 0.55, p<.001) compared with cases without conversion. Factors associated with conversion included both the number and the weight of myomas removed (mean number, 9.75 vs 3.48, p=.003; mean weight, 667.9 vs 259.25 g, p=.015), especially with myomas weighing more than 500 grams (odds ratio: 8.551, p=.005).

Conclusion: The risk of conversion for LM was low (1.09%) in this cohort, and was associated both with the number and the weight of myomas removed. LM is a feasible approach for surgical management of myomas in the majority of cases; however, when myomas are expected to weigh more than 500 grams, it may be prudent to consider referring those cases to specialized centers with highly experienced teams.

Introduction

An estimated 20% to 40% of reproductive-aged women have symptomatic uterine myomas.[1] For women who desire uterine conservation, laparoscopic myomectomy (LM) is a safe and feasible option.[2-4] This minimally invasive procedure is associated with better postoperative outcomes, including less postoperative pain, quicker recovery, and fewer overall complications, compared with abdominal myomectomy (AM).[5;6] However, it is a technically challenging and potentially complicated procedure. As such, the selection criteria for patients who are candidates for a laparoscopic approach to myomectomy remain a matter of debate.[7-9]

The main complications seen during LM are excessive blood loss and conversion to an abdominal approach, which is especially closely associated with worse postoperative outcomes.[10;11] Depending on the reason for conversion, the procedure may be considered as strategic or reactive (owing to complications).[12] The incidence of conversion may reflect the preoperative indications for LM and/or intra-operative complications, and can be considered a quality indicator. Compared with laparoscopic hysterectomy, little has been published on the conversion rate of LM. The frequency of conversion has been historically cited as ranging from 0 to 41.4% at the time of LM,[3;7;13] and in more recent studies, rates have varied from 1% to 3% for high-volume surgeons.[9;14;15]

The objectives of the present study were to report the surgical outcomes of LM and AM at a high-volume tertiary care hospital, to evaluate the incidence of conversion during LM, and to analyze the risk factors associated with the need to convert to laparotomy.

Methods

The retrospective cohort study included all consecutive cases of myomectomy performed between January 2009 and December 2012 at Brigham and Women's Hospital, a tertiary care academic center in Boston, Massachusetts. The study was reviewed and approved by Partners Institutional Review Board. The cases were identified through a centralized hospital database.

Data abstracted from the medical record included age, parity, race, body mass index, history of previous surgeries, mode of myomectomy (laparoscopic, robotic, or abdominal), operative findings, type of conversion (reactive vs strategic), intra-operative and postoperative complications, readmission, reoperation, operative time (defined as time from first incision to closure of last incision), length of hospital stay (same day discharges coded as 0 days), estimated blood loss, and type of surgeon. Whether or not the surgeon

entered the endometrial cavity during surgery could not be reliably determined from the clinical record. Conversion was defined according to the recent consensus definition.[12]

Intraoperative complications included injuries to the urinary tract, nerves, vessels, or bowel; estimated blood loss of more than 1000 mL; and major anesthesia-related issues. Postoperative complications were ranked according to the Clavien-Dindo classification system and included injuries to the urinary tract, nerves, vessels, or bowel diagnosed postoperatively, as well as hemorrhage requiring blood transfusion, pulmonary embolus, deep vein thrombosis, infection, fever, and other mild complications requiring treatment.

Types of surgeons included general and specialized gynecologists. The specialized gynecologists, defined as having completed fellowship training, were further subdivided into subspecialty: reproductive endocrinology and infertility (REI), oncology, and minimally invasive gynecologic surgery (MIGS). Instead of preoperative ultrasound measurements and/or clinical examination information, operative findings were used to account for the number and size of myomas, assuming that the surgeons had roughly this information before starting the procedure.

Statistical analyses were performed using SPSS version 20 for Windows (IBM, Armonk, NY). Data were summarized, and extreme values were verified to be correct. The AM procedures were compared with LM, and the converted LM cases were compared with nonconverted cases. To assess the significance of individual parameters, univariate logistic regression analysis was performed. For descriptive data with an empty category, the chi square or Fisher's exact test was used as appropriate. To investigate the combination of predictors for the route of myomectomy, multiple regression analysis was performed. A p-value <.05 was considered significant for all variables.

Results

We identified a total of 966 patients who underwent AM or LM between 2009 and 2012. These included 235 AMs (24.33%) and 731 LMs (75.67%), of which 343 cases (46.92%) were robot-assisted. The decision was made to treat the conventional laparoscopic cases and the robot-assisted laparoscopic cases as a single category, defined as LM. Overall, baseline characteristics were similar in these two subgroups (data not shown). One notable difference in perioperative outcomes was the weight of the removed myomas; specimen weight was significantly greater in the conventional laparoscopic group than in the robot-assisted group (mean grams, 396.87 vs 217.05; p<.001).

Baseline and operative characteristics of the LM and AM groups are displayed in Table 9.1. The demographic characteristics did not differ significantly between the two groups. With regard to the indications for myomectomy, the AM group had higher rates of menorrhagia (59.57% vs 50.71%; p=.037) and infertility (19.57% vs 14.35%; p=.021), whereas the incidence of pelvic pain was higher in the LM group (66.90% vs 58.59%; p=.004). Regarding operative characteristics, patients who underwent AM had more myomas removed with greater specimen weights (mean number, 12.60±14.80 vs 3.54±4.10, p<.001; mean weight, 592.75±884 vs. 263.4±286.2, p<.001). In addition, AM patients experienced greater intraoperative blood loss (mean, 267.16±274.04 mL vs 181.54±342.02 mL; p=.002) and had a longer length of hospital stay (mean, 2.15±1.1 days vs 0.581.0 days; p<.001).

Regarding the location of the myomas treated, submucosal myomas and subserosal myomas were encountered with equal frequency in the two groups. Significantly more women with intramural myomas underwent LM compared with AM (62.7% vs 53.8%; p=.004).

A total of 28 surgeons performed procedures on patients of the cohort, of whom 17 had completed a fellowship. Gynecologists specializing in REI performed 89.3% of AMs and 54.8% of LMs, whereas those specializing in MIGS performed 42.87% of LMs (Table 9.1). General gynecologists performed 7.9% of all cases. Specific for LM, 98.5% of the cases were performed by a gynecologist who had completed a fellowship.

Table 9.2 compares characteristics of the LM cases complicated by conversion and those of cases without conversion. Eight LM cases (including 1 robotic case) were converted to an open procedure (1.09%). In each instance, this was a reactive conversion in response to an adverse event. In one case, subsequent abdominal hysterectomy was performed owing to major bleeding. The other 7 cases were converted to an AM because of excessive blood loss (n=2), prolonged operating time (n=1), large number or size of myomas to be removed (n=3), and a tear of the ileum (n=1). Intraoperative blood transfusion was necessary in three of those cases. Five of the converted cases were performed by MIGS specialists in minimally invasive gynecology, two cases were performed by REI specialists, and one case was performed by a general gynecologist.

There were no significant differences in baseline characteristics and the indication for myomectomy between the conversion group and the nonconverted LM group (Table 9.2). In terms of surgical outcomes, converted cases were associated with greater blood loss (mean, 1381.25±1645.85 mL vs 167.95±273.61 mL; p=.001) and a longer hospital stay (mean, 3.13±2.64 days vs 0.55±0.96 days; p=.001). The operative time was also longer in the converted cases, but the difference did not reach statistical significance (mean, 215±138.6 minutes vs 128.70±78.61 minutes; p=.232). The number and the weight of

Table 9.1: Baseline characteristics and surgical outcomes for laparoscopic and abdominal myomectomy cases

	Abdominal (n=235)	Laparoscopic (n=731)	Odds ratio (95% confidence interval)	p-value univariate	p-value multivariate
Age (years)	39.83±5.83	40.33±7.28	1.044 (0.998; 1.091)	--	.060
BMI (kg/m²)	27.50±6.12	26.75±5.84	0.999 (0.954; 1.046)	--	.970
Race					
White	103 (46.39)	411 (59.30)	1	--	.
Afro-Americans	88 (39.64)	162 (23.38)	0.820 (0.432; 1.558)		.545
Others	31 (13.97)	120 (17.32)	0.580 (0.285; 1.181)		.134
Prior laparotomy	68 (28.5)	154 (21.5)	0.737 (0.372; 1.460)	--	.381
Prior laparoscopy	20 (8.5)	109 (15.2)	1.928 (0.793; 4.687)	--	.147
Indication myomectomy					
Pressure/pain	135 (58.69)	471 (66.90)	2.473 (1.327; 4.607)	--	.004
Menorrhagia	137 (59.57)	357 (50.71)	0.507 (0.268; 0.959)		.037
Urologic/bowel problems	54 (23.48)	209 (29.69)	1.249 (0.653; 2.388)		.502
Infertility	45 (19.57)	101 (14.35)	0.415 (0.196; 0.878)		.021
Type of fibroids					
Submucosal	66 (36.3)	131 (20.9)	0.680 (0.365; 1.268)	--	.225
Intra/transmural	98 (53.8)	394 (62.7)	2.425 (1.376; 4.272)		.002
Subseroasal/pedunculated	125 (68.7)	373 (59.4)	1.436 (0.780; 2.644)		.245

	Abdominal (n=235)	Laparoscopic (n=731)	Odds ratio (95% confidence interval)	p-value univariate	p-value multivariate
Fibroids					
Number	12.60±14.80	3.54±4.10	0.845 (0.804; 0.888)	--	<.001
Weight (gram)	592.75±884	263.4±286.20	0.997 (0.996; 0.998)		<.001
EBL (mL)	267.16±274.04	181.54±342.02	0.999 (0.999;1.000)	.002	--
Length of stay (days)	2.15±1.10	0.58±1.00	4.439 (3.592;5.485)	<.001	--
Mode of myomectomy					
Abdominal	235 (100)	--	--	--	--
Laparoscopic	--	388 (53.08)			
Robotic	--	343 (46.92)			
Surgeon type					
MIGS	0	313 (42.87)	--	<.001	--
REI	208 (89.27)	400 (54.80)			
General gyn	15 (6.44)	11 (1.50)			
Oncology	10 (4.29)	6 (0.82)			

Data presented as mean (±SD) or as n (%).
Dependent variable for univariate and multivariate regression = laparoscopic myomectomy.

Table 9.2: Baseline characteristics and surgical outcomes for the laparoscopic myomectomy cases and the converted cases

	Non converted laparoscopic cases (n=722)	Converted cases (n=8)	Odds ratio (95% confidence interval)	p-value
Age (years)	40.33±7.30	40.88±5.08	1.010 (0.919; 1.110)	.832
BMI (kg/m^2)	26.78±5.85	23.23±1.94	0.853 (0.671; 1.085)	.195
Race*				
White	407 (59.33)	4 (57.14)	--	.320
Afro-Americans	159 (23.18)	3 (42.86)		
Others	120 (17.49)	0		
Prior laparotomy	151 (21.33)	3 (37.50)	2.213 (0.523; 9.336)	.280
Prior laparoscopy*	109 (15.40)	0	--	.373
Indication myomectomy				
Pressure/pain	464 (66.67)	7 (87.5)	0.188 (0.19; 1.815)	.149
Menorrhagia	353 (50.72)	4 (50.0)	0.790 (0.184; 3.389)	.751
Urologic/bowel	208 (29.89)	1 (12.50)	3.893 (4.69; 32.316)	.208
Infertility	100 (44.25)	1 (12.50)	0.624 (0.061; 6.404)	.691
Suspicion of malignancy*	4 (0.57)	0	--	1.000
Type of fibroids*				
Submucosal	131 (21.12)	0	--	.215
Intra/transmural	389 (62.74)	5 (62.5)	0.990 (0.234;4.180)	.989
Subseroasal/pedunculated	368 (59.35)	5 (62.5)	1.141 (0.270;4.819)	.857
Fibroids				
Number	3.48±3.84	9.75±12.59	1.117 (1.039; 1.201)	.003
Weight (gram)	259.25±281.56	667.79±448.67	1.002 (1.000; 1.003)	.015
Converted cases of >500g	--	4 (4.16)	8.551 (1.883; 38.822)	.005
EBL (mL)	167.95±273.61	1381.25±1645.85	1.002 (1.001; 1.002)	<.001
Length of stay (days)	0.55±0.96	3.13±2.64	1.732 (1.307; 2.296)	<.001
Mode of myomectomy				
Laparoscopic	381 (52.77)	7 (87.50)	1	.086
Robotic	342 (47.37)	1 (12.50)	0.159 (0.19; 1.300)	.086
Surgeon type*				
MIGS	308 (42.66)	5 (62.5)	--	.096
REI	398 (55.12)	2 (25.0)		
General gyn	10 (1.39)	1 (12.5)		
Oncology	6 (0.83)	0		
OR time (min)	128.70±78.61	215±138.6	1.005 (0.998; 1.011)	.197

Data presented as mean (±SD) or as n (%).
Dependent variable for univariate regression = conversion.
* Chi square/Fisher exact performed, due to empty categories.

the removed myomas were associated with an increased risk of conversion (mean number of myomas removed: 9.75±12.59 in the converted subgroup vs 3.48±3.84 in the non-converted group; p=.003; mean specimen weight: 667.79±448.67 g vs 259.27±281.55 g; p=.015), especially when the specimen weight exceeded 500 grams, (conversion risk, 4.16% vs 0.47%; OR=8.551; p=.005).

The converted LM cases and AM cases are compared in Table 9.3. There were no significant between-group differences in baseline characteristics or indications for myomectomy. Similarly, no differences were found in the number of removed myomas or specimen weight (mean number of myomas removed: 9.75±12.59 vs 12.60±14.80; p=.694; mean specimen weight: 667.79±448.67 g vs 592.75±884 g; p=.549). The converted LM group had significantly greater intraoperative blood loss (mean, 1381.25±1645.85 mL vs 267.16±274.04 mL; p<.001) and longer postoperative hospital stay (mean, 3.13±2.64 days vs 2.15±1.10 days; p=.036).

Table 9.3: Baseline characteristics and surgical outcomes for the abdominal myomectomy cases and the converted cases

	Abdominal cases (n=235)	Converted cases (n=8)	Odds ratio (95% confidence interval)	p-value
Age (years)	39.83±5.83	40.88±5.08	1.032 (0.913; 1.166)	.617
BMI (kg/m^2)	27.50±6.12	23.23±1.94	0.829 (0.654; 1.051)	.122
Race*				
White	103 (46.39)	4 (57.14)	--	.559
Afro-Americans	88 (39.64)	3 (42.86)		
Others	31 (13.97)	0		
Prior laparotomy	68 (28.5)	3 (37.50)	1.474 (0.343; 6.338)	.302
Prior laparoscopy*	20 (8.5)	0	--	1.000
Indication myomectomy				
Pressure/pain	135 (58.69)	7 (87.5)	5.900 (0.614; 56.645)	.124
Menorrhagia	137 (59.57)	4 (50.0)	0.883 (.207; 3.772)	.867
Urologic/bowel	54 (23.48)	1 (12.50)	0.325 (0.38; 2.763)	.303
Infertility	45 (19.57)	1 (12.50)	1.051 (0.109; 10.169)	.965
Suspicion of malignancy*	4 (1.74)	0	--	1.000
Type of fibroids				
Submucosal*	66 (36.3)	0	--	.052
Intra/transmural	98 (53.8)	5 (62.5)	1.429 (0.332; 6.156)	.632
Subserosal/pedunculated	125 (68.7)	5 (62.5)	0.760 (0.176; 3.290)	.714
Fibroids				
Number	12.60±14.80	9.75±12.59	0.988 (0.931; 1.049)	.694
Weight (gram)	592.75±884	667.79±448.67	1.00 (0.99; 1.002)	.549
EBL (mL)	267.16±274.04	1381.25±1645.85	1.002 (1.001; 1.003)	.001
Length of stay (days)	2.15±1.10	3.13±2.64	1.459 (1.025; 2.075)	.036
Surgeon type*				
MIGS	0	5 (62.5)	--	<.001
REI	208 (89.27)	2 (25.0)		
General gyn	15 (6.44)	1 (12.5)		
Oncology	10 (4.29)	0		

Data presented as mean (±SD) or as n (%).
Dependent variable for univariate regression = conversion.
* Chi square/Fisher exact performed, due to empty categories.

Discussion

To our knowledge, this retrospective study is the largest cohort of patients undergoing LM analyzed to date, with 98.5% of the laparoscopic cases performed by a gynecologist who had completed a fellowship. We found that risk of conversion at time of LM was low (1.09%) and in line with recent reports.[9;15;16] In addition, our data show that converted cases were associated with more intraoperative blood loss and a longer hospital stay compared with LM or planned AM.

The low incidence of conversion at the time of LM in our cohort may be attributable to surgeon experience (with 17 of 28 surgeons having completed a fellowship, performing 98.5% of the LM cases), as well as appropriate patient selection for this complex procedure.[7] Various selection criteria for LM have been proposed in previous studies based on the size and number of myomas, location of myomas, and surgical history of the patient.[7;9] In addition, infertility as indication for surgery has been a consideration when choosing the mode of myomectomy.[17] With technical advances in minimally invasive surgery, increasingly complex cases are being considered for the laparoscopic approach.[16] Indeed, the majority of the LM cases at our hospital are now managed in a minimally invasive fashion. Recent studies have suggested that after surgeons overcome the learning curve of LM, limiting factors may disappear provided the availability of optimal instrumentation, a trained and dedicated operating room team, and an experienced surgeon who feels at ease with the case.[9;14;16]

Regarding the risk factors for conversion during LM, the number of removed myomas and their weight were associated with conversion in our cohort. The number of myomas removed varied widely in the converted group, ranging from one up to 31 myomas. Therefore, we could not define a clear cutoff, in contrast to a previous study, where attempted removal of more than four myomas was associated with a greater risk of conversion.[7] We also noted that specimen weight of more than 500 grams, corresponding approximately to a uterus of 16 weeks gestation was associated with a greater risk of conversion (4.16% vs 0.47%; OR=8.551; p=.005).[18;19] This finding is in accordance with several other studies of LM.[7;9] Similarly, for cases of laparoscopic hysterectomy, a uterus weighing more than 500 gram was also found to be a predictor for conversion.[20] This may be clinically relevant, given that estimated myoma volume can be calculated preoperatively based on imaging findings.[21] For patients with a preoperative estimated myoma volume of more than 500 gram, we suggest that surgeons should consider the case carefully and counsel the patient about the increased risk of conversion.[9] In this respect, in cases of myomas weighing more than 500 grams, low-volume providers might consider referral to a specialized center.

Of note, minimally invasive gynecologic surgery has been confronted recently with a complex problem regarding the use of power morcellation during laparoscopic surgeries, and this might influence the general approach to LM. We have generally recommended the use of contained tissue extraction and have demonstrated the feasibility of this approach in recent publications.[22-26]

Limitations of this study include its retrospective design and inherent propensity for misclassification, although the latter is presumed to be nondifferential in nature. In addition, the missing values seen in retrospective studies could potentially affect the results of our analysis. Moreover, our findings are based on a single outcome (risk of conversion) and did not include such outcomes as pregnancy rate or patient satisfaction. We combined the robotic and the conventional laparoscopic cases because of the small number of converted cases, precluding more detailed analysis of these groups. Strengths of the study include the large number of patients included and the widely varying case mix.

In conclusion, LM is a safe and effective minimally invasive option for the removal of uterine myomas. A minimally invasive approach to myomectomy confers many benefits to patients compared with AM. Our data suggest however that myomas weighing more than 500 grams predict potential surgical difficulties and a significantly greater risk of conversion. Therefore, in an effort to optimize patient outcomes, it may be prudent to evaluate estimated myoma number and size pre-operatively, and to take this information into consideration during operative planning.

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Chapter 10

Reintervention risk and quality of life outcomes after uterine-sparing interventions for fibroids: a systematic review and meta-analysis

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Abstract

Objectives: To compare uterine-sparing treatment options for fibroids in terms of reintervention risk and quality of life.

Design: Systematic review and meta-analysis according to PRISMA guidelines.

Setting: Not applicable.

Patients: Women with uterine fibroids undergoing a uterine-sparing intervention.

Interventions: Not applicable.

Main outcome measures: 1) Reintervention risk after uterine-sparing treatment for fibroids after 12, 36 and 60 months; and 2) quality of life outcomes, based on validated questionnaires. Two separate analyses were performed for the procedures that used an abdominal approach (myomectomy, uterine artery embolization [UAE], artery ligation, high-intensity focused ultrasound [HIFU], laparoscopic radiofrequency ablation [RFA]) and for the procedures managing intracavitary fibroids (hysteroscopic approach, including hysteroscopic myomectomy and hysteroscopic RFA).

Results: There were 85 articles included for analysis, representing 17,789 women. Stratified by treatment options, reintervention risk after 60 months was 12.2% (95% confidence interval 5.2–21.2%) for myomectomy, 14.4% (9.8–19.6%) for UAE, 53.9% (47.2–60.4%) for HIFU, and 7% (4.8–9.5%) for hysteroscopy. For the other treatment options, no studies were available at 60 months. For quality of life outcomes, symptoms improved after treatment for all options. The HIFU procedure had the least favorable outcomes.

Conclusions: Despite the substantial heterogeneity of the study population, this meta-analysis provides valuable information on relative treatment efficacy of various uterine-sparing interventions for fibroids, which is relevant when counseling patients in daily practice. Furthermore, this study demonstrates that long-term data, particularly for the newest uterine-sparing interventions, are urgently needed.

Introduction

Fibroids are the most common benign tumors of the female genital tract, with a symptomatic occurrence rate of 20–40% in reproductive-age women.[1] For women requiring surgical treatment but desiring uterine conservation, myomectomy has typically been the first choice for intervention. Yet technologic advances have led to a wider range of available options, depending on the location and number of fibroids, the indication for treatment, patient preference, and technologic facilities of hospitals. Uterine artery embolization (UAE) is one of the alternatives, and this well-studied technique has been used in many countries for more than three decades.[2] Other treatment options include, among others, radiofrequency ablation (RFA), (laparoscopic) ligation, and cryoablation. Advanced techniques, such as high-intensity focused ultrasound (HIFU), also have recently emerged, and are applicable without the need for surgical intervention.

Data regarding the feasibility of these uterine-sparing treatment options vary, and limited information exists on relative efficacy. Guidelines from the American College of Obstetricians and Gynecologists,[3] the National Institute for Health and Care Excellence (United Kingdom),[4] and the Society of Obstetricians and Gynecologists of Canada[5] on this topic state that patients should be counseled about the different available treatment options but do not define a preferred intervention. The objective of the present systematic review and meta-analysis was to evaluate the relative efficacy of the various uterine-sparing options for treating fibroids. We specifically aimed to compare the different techniques in terms of reintervention risk and quality of life.

Materials and methods

Eligibility criteria, information sources, search strategy

A systematic review was conducted following the PRISMA guidelines.[6] No study protocol was available. A literature search was set up in collaboration with a clinical librarian, and original articles were identified though Pubmed, Medline, Embase, and Web of Science. The exact search terms are presented in Supplemental Appendix 1 (Supplemental Appendices 1–4 are available online at www.fertstert.org). The literature search was restricted to studies published from January 2000 through February 2017. By selecting only recent studies, we aimed to provide an overview of current treatment options. We considered randomized controlled trials (RCT) and cohort studies (both noncomparative and comparative) only. Review articles, technical reports, animal studies, non-English studies, published abstracts without a full manuscript, and reports from meetings were excluded.

Studies eligible for inclusion were studies evaluating at least one of our primary outcomes: 1) surgical reintervention risk after uterine-sparing treatment; and 2) quality of life after treatment. In addition, studies had to have a minimum follow-up time of 12 months. We defined reintervention as any additional treatment needed at least one year after treatment owing to symptomatic recurrence of fibroids. Reinterventions directly related to procedure complications were excluded, and dilation and curettage was not considered to be reintervention. Because we aimed to study the reintervention risk after a first treatment for fibroids, studies were also excluded when all women in the cohort had an earlier history of intervention for fibroids. To reliably compare the quality of life outcomes, we limited our selection to studies using the Severity Symptom Score (SSS) or the Health-Related Quality of Life questionnaire (HRQL). Both have been validated for assessment of fibroid-related symptoms.[7] The SSS and HRQL are scored from 0 to 100. When symptoms improve, the SSS score decreases whereas the HRQL score increases.

Study selection

The first two authors (E.M.S. and F.H.M.P.T.) independently screened titles and abstracts for relevance. Potentially relevant studies were obtained in full text and assessed for inclusion. In case of disagreement, a third author (F.W.J.) was consulted. The references of the selected articles were cross-checked to identify other potentially relevant studies.

Data extraction

From the included studies, we extracted data regarding primary outcomes (reintervention risk and quality of life) and baseline characteristics. Variables of interest included study characteristics (study design, type(s) of treatment, country where the study was conducted, and potential source of funding) and patient characteristics (age, body mass index [BMI], and fibroid weight).

Data were pooled for meta-analysis for our primary outcomes at 12, 36 and 60 months after intervention. For the comparative studies included, each intervention group was assessed separately. Two separate analyses were performed for procedures approaching the fibroids through the abdomen (henceforth called abdominal approach) and for procedures managing intracavitary fibroids (henceforth called hysteroscopic approach). Additional subanalyses were performed to specifically evaluate the number of women undergoing hysterectomy after initial therapy.

Assessment of risk of bias

To assess the risk of bias for each study, the following criteria were employed: 1) inclusion of consecutive patients (if it was not stated that patients were consecutively included, risk of bias was assessed as unclear); 2) rate of patients that had infertility as indication for treatment, because it may influence or limit treatment choice (<10% of the study population with infertility indication was considered to indicate low risk of bias and >20% high risk); and 3) loss to follow-up rate (<10% loss to follow-up was considered to indicate low risk of bias and >20% high risk). The template of Review Manager (version 5.1) was used for data organization.

Data synthesis and statistical analysis

Descriptive characteristics were summarized with the use of SPSS version 23.0. Continuous data were presented as range and categoric data as frequency with percentage. Meta-analysis was performed with the use of Stata (version 14, Statacorp). The reintervention risk and the difference of the means of the quality of life scores were pooled in a random effects model, and 95% confidence intervals (95% CIs) were reported. In cases where only median and range were available, instead of the mean and standard deviation, data were transformed as described by Hozo et al.[8]

Results

Study and patient characteristics

The search strategy identified 3,250 unique articles. Full texts of more than 600 articles were reviewed because the reintervention risk was usually not a primary end point in studies and therefore not explicitly mentioned in the abstract.

As demonstrated in Supplemental Figure 1 (available online at www.fertstert.org), 85 original articles were deemed eligible for inclusion in this review. Eight of the studies were randomized controlled studies[9-16] and 77 were cohort studies.[17-93] Fourteen studies, of which six were RCTs, compared two different uterine-sparing treatment options (e.g. myomectomy vs. UAE).[9;10;12-15;21;35;59;60;64;75;84,93] These studies were therefore included in two main categories. Supplemental Appendix 2 (available online) provides a summary of the characteristics of the included studies.

Fifteen studies included at least in part the same cohort of patients.[9;10;12;15;32;35;42;59;63;69;72;77;94-96] Efforts were made to ensure that data from each patient was not included more than once.

Two studies were eventually excluded because we could not correct for the overlapping study period.[95;97]

Of the included studies, 33 originated from Europe (38.8%), 23 from North America (27.0%), 22 from Asia (25.9%), four from Africa (4.7%), two from Australia (2.4%) and one from Latin America (1.2%). In 29 studies (34.1%), disclosures regarding funding were reported: in 14 studies, research had been funded by a medical device company (Biocompatibles, Biosphere Medical, Boston Scientific, Gynesonics, Halt Medical, and Insightec); the other 15 studies were funded by governmental funds, research institutes, and charity organizations.

Data regarding ten treatment options was identified: abdominal, laparoscopic or robotic myomectomy, hysteroscopic myomectomy, UAE, (laparoscopic) ligation, HIFU, laparoscopic and hysteroscopic RFA, percutaneous microwave ablation, and cryoablation. An eleventh treatment option, laparoscopic uterine artery occlusion, was described in studies,[98-100] but none of those studies met our inclusion criteria. For the analysis, the data of abdominal, laparoscopic, and robotic myomectomy were combined (henceforth called myomectomy), as were the data of laparoscopic RFA and percutaneous microwave ablation, both thermal ablations. The abdominal approach included six different interventions: myomectomy, UAE, artery ligation, HIFU, laparoscopic RFA, and cryoablation. The hysteroscopic approach consisted of hysteroscopic myomectomy and hysteroscopic RFA.

Baseline characteristics of the study population are summarized in Table 10.1. The total study population included 17,789 women. A total of 15,348 women (87.8%) had undergone an abdominal approach and 1,912 (12.2%) a hysteroscopic approach. The UAE group had the largest study population (8,244), followed by myomectomy (5,114) and hysteroscopic myomectomy (1,741). For the laparoscopic cryoablation and artery ligation procedures, one study was available for each treatment option.

The mean ages of the studied populations ranged from 29.3 to 47.9 years, the mean BMIs from 21.2 to 56.6 kg/m^2, and the mean fibroid weights from 18.8 to 538.5 grams. Because only means were available from every individual study, it was not possible to calculate if the outcome measures of these baseline characteristics were statistically different between the different treatment options.

Risk of bias of the included studies

A summary of risk of bias for the individual studies is depicted in Supplemental Appendix 3 (available online). In the myomectomy group and the hysteroscopic myomectomy group, none of the studies excluded infertility as indication of treatment. For the other treatment options, approximately one-half of the studies explicitly mentioned excluding infertility.

Table 10.1: Baseline characteristics

	Number of studies or substudies	Number of patients	Age (year)	Number of studies or substudies	BMI (kg/m^2)	Number of studies or substudies	Fibroid weight (grams)	Number of studies or substudies
Overall	96	17,489	29.3–47.9	81	21.2–56.6	24	18.8–538.5	32
Abdominal approach								
Myomectomy	20	5114	29.3–43.5	15	21.2–27.5	7	--	--
UAE	40	8244	32.3–47.0	34	23–28.4	5	59–538.5	12
Artery ligation	1	50	39.6	1	--	--	180.9	1
Laparoscopic RFA	8	652	40.0–43.6	8	22.7–30.5	5	76.8–95.0	2
(MR/US)-HIFU	17	1548	36.2–46.0	14	21.6–56.6	6	53.2–396.3	13
Laparoscopic cryoablation	1	20	46.9	1	27.6	1	75	1
TOTAL	87	15,348	29.3–47.0	74	21.2–56.6	24	53.2–538.5	29
Hysteroscopic approach								
Hysteroscopic myomectomy	6	1741	31.4–47.9	5	--	--	--	--
Hysteroscopic RFA	3	120	40.1–40.8	2	--	--	18.8–112.4	3
TOTAL	9	1912	31.4–47.9	7	--	--	18.8–112.4	3

Data are presented as range of the means (minimum-maximum).
UAE= uterine artery embolization; RFA=radiofrequency ablation.

For 'loss to follow-up', a high risk of bias was observed in all groups. This was mainly attributed to studies focusing on long-term quality of life questionnaires after treatment.

Primary outcomes

Additional figures of the data from this section are available in Supplemental Appendix 4 (available online).

Reintervention risk for the abdominal procedures

The reintervention risks for the six abdominal procedures are presented in Table 10.2. Almost all analyses demonstrated considerable statistical heterogeneity. At 12 months, the reintervention risk for these abdominal procedures varied from 0.3% (laparoscopic RFA, 95% CI 0–1.6%; I^2=0%, 6 studies) up to 15% (cryoablation, 1 study). At 36 months, the reintervention risk varied from 1.2% (myomectomy, 0–5.2%, 4 studies) to 34.7% (HIFU, 27.3–42.4%, 4 studies). At 60 months, reintervention risks were 12.2% (5.2–21.2%; I^2=95.2%; 10 studies) for myomectomy, 14.4% (9.8–19.6%; I^2=65.9%; 17 studies) for UAE, and 53.9% (47.2–60.4%; I^2=99.5%; 2 studies) for HIFU (Figure 10.1). For artery ligation, laparoscopic RFA, and cryoablation, no studies were available at 60 months.

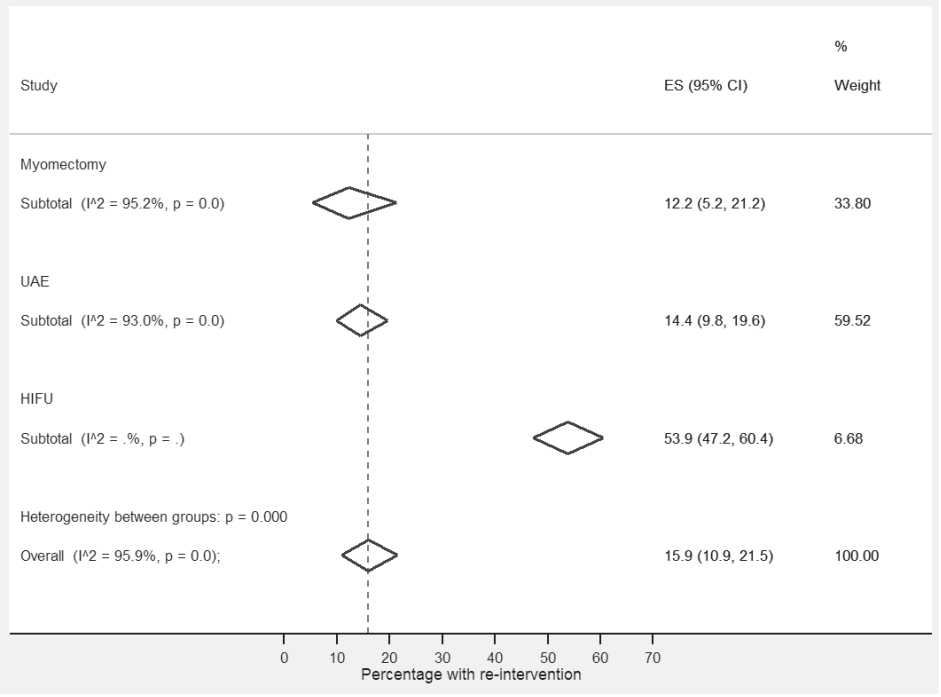

Figure 10.1: Reintervention risk 60 months after abdominal approach.

Table 10.2: Overall re-intervention risk at 12, 36 and 60 months

(%) [95% CI]	12 months	I^2	Nr of studies or substudies	36 months	I^2	Nr of studies or substudies	60 months	I^2	Nr of studies or substudies
Abdominal approach									
Myomectomy	1.1 [0.0;3.7]	89.9	8	1.2 [0;5.2]	65.9	4	12.2 [5.2;21.2]	95.2	10
UAE	3.6 [2.4;4.9]	61.9	26	7.4 [0.9;10.7]	--	3	14.4 [9.8;19.6]	65.9	17
Artery ligation	--	--	0	6	--	1	--	--	0
Laparoscopic RFA	0.3 [0.0;1.6]	0	6	10.4	--	1	--	--	0
HIFU	9.7 [4.0;17.3]	88.3	10	34.7 [27.3;42.4]	47.0	4	53.9 [47.2;60.4]	--	2
Cryoablation	15	--	1	--	--	0	--	--	0
TOTAL	**3.6 [2.5;4.8]**	**80.5**	**51**	**10.4 [4.6;18.1]**	**96.8**	**13**	**15.9 [10.9;21.5]**	**95.9**	**29**
Hysteroscopic approach									
Hysteroscopic myomectomy	6.6 [0.6;17.6]	94.0	4	3.2 [0.0;10.2]	--	3	7.0 [4.8;9.5]	--	2
Hysteroscopic RFA	11.1 [3.3;22.2]	--	3	--	--	0	--	--	0
TOTAL	**8.3 [2.7;16.0]**	**89.1**	**7**	**3.2 [0.0;10.2]**	**--**	**3**	**7.0 [4.8;9.5]**	**--**	**2**

Data are presented as percentages with 95% confidence interval [CI].
I^2 = study heterogeneity.
UAE = uterine artery embolization; RFA=radiofrequency ablation.

Subanalysis for abdominal procedures: hysterectomy as reintervention

A hysterectomy was performed 12 months after the primarily uterine-sparing abdominal intervention in 0.8% of the cases (95% CI 0.3–1.5%; I^2=66.8%; 44 studies). At 36 months, the reintervention risk for hysterectomy varied from 0.6% (myomectomy, 0–2.3%; I^2=60.2%; 4 studies) to 8.1% (laparoscopic RFA, 1 study). By 60 months, 7% (2.5–13.2%; I^2=90.6%; 8 studies) of the patients who had undergone myomectomy required a hysterectomy, compared with 9.4% after UAE (5.5–14.2%; I^2=93.6%; 15 studies). For the HIFU treatment, one study reported the reintervention risk at 60 months and noted that 8 of the 36 women (22.2%) required a hysterectomy.[59] For the other treatment options, no long-term data on hysterectomy reintervention rate were available.

Reintervention risk for hysteroscopic procedures

For the two hysteroscopic procedures, data demonstrated at 12 months a reintervention risk after hysteroscopic RFA of 11.1% (95% CI 3.3–22.2%), 3 studies), compared with 6.6% after hysteroscopic myomectomy (0.6–17.6%; I^2=94.0; 4 studies; Table 10.2). At 36 and 60 months, no data were available for hysteroscopic RFA.

Subanalysis for hysteroscopic procedures: hysterectomy as reintervention

For the reintervention risk for hysterectomy, 1.1% (95% CI 0–6.8%, 3 studies) of the patients in the hysteroscopic myomectomy group required a hysterectomy at 12 months, compared with 2% (0–5.9%, 3 studies) after hysteroscopic RFA. At 36 and 60 months, no data were available for hysteroscopic RFA.

Quality of life for abdominal procedures

For the abdominal procedures, the postoperative SSS and HRQL scores were reported in 18 and 11 studies, respectively. An overview of the outcomes is presented in Table 10.3. The mean difference of SSS between baseline and 12 months after treatment was -31.2 (95% CI -36.9–-25.5). Most mean differences of the treatment options ranged from -37 to -35, with the exception of the HIFU treatment option. The HIFU group had a mean difference of -24.5 (-90.8–-18.1; I^2=96.9%; 8 studies) and thus the least improvement of symptoms over time.

For HRQL, the mean difference in scores at 12 months was 36.1 (31.8–40.4; I^2=89.4%; 11 studies). Again, the HIFU group was associated with the least favorable outcomes, with a mean difference of 24.6 (13.4–35.8, 1 study). At 36 and 60 months, too few studies were available to pool data, but all studies showed improvement of symptoms over time or normalization of the scores after treatment.

Table 10.3: Quality of life at 12 months

(%) [95% CI]	12 months	I^2	Number of studies or substudies
Abdominal approach			
SSS scores			
Myomectomy	-37.6 [43.8;-31.4]	--	1
UAE	-35.8 [-40.6;-30.9]	82.5	4
Artery ligation	--	--	--
Laparoscopic RFA	-37 [-44.6;-29.4]	85.6	4
HIFU	-24.5 [-90.8;-18.1]	96.9	8
Laparoscopic cryoablation	-37.5 [-48.1;-26.9]	--	1
TOTAL	**-31.2 [-36.9;-25.5]**	**98.4**	**18**
HR-QL scores			
Myomectomy	39.9 [33.0;46.8]	--	1
UAE	38.9 [35.8;41.9]	35.9	3
Artery ligation	--	--	--
Laparoscopic RFA	35.1 [28.7;41.6]	79.4	5
HIFU	24.6 [13.4;35.8]	--	1
Laparoscopic cryoablation	41.3 [29.1;53.5]	--	1
TOTAL	**36.1 [31.8;40.4]**	**89.4**	**11**
Hysteroscopic approach			
SSS scores			
Hysteroscopic myomectomy	--		
Hysteroscopic RFA	-42.6 [-68.1;-17.2]	98.6	3
TOTAL	**-42.6 [-68.1;-17.2]**	**98.6**	**3**
HR-QL scores			
Hysteroscopy	--		
Hysteroscopic RFA	38.1 [22.9;53.4]	94.8	3
TOTAL	**38.1 [22.9;53.4]**	**94.8**	**3**

Data are presented as percentages with 95% confidence interval [CI].
I^2 = study heterogeneity.
UAE = uterine artery embolization; RFA=radiofrequency ablation.

Quality of life for hysteroscopic procedures

For hysteroscopic procedures, three studies of hysteroscopic RFA were analyzed (Table 10.3). All of those studies demonstrated improvement of symptoms after treatment. No data were available for quality of life after hysteroscopic myomectomy.

Discussion

Because limited evidence exists on the relative efficacy of the different uterine-sparing treatment options, choosing the best option for a patient might not always be evident. When counseling a patient about the different treatment options, long-term outcomes on reintervention risk and quality of life are, among others, important aspects to consider. In the present meta-analysis based on 85 studies, these two clinically relevant outcomes were evaluated for all available uterine-sparing treatment options for fibroids. For the treatment options with an abdominal approach (all types of myomectomy, UAE, HIFU, laparoscopic RFA, cryoablation, and artery ligation), we demonstrated that 60 months after initial therapy, myomectomy had a risk of reintervention of 12.2%, UAE 14.4%, and HIFU 54%. For the HIFU group, it is important to note that only a few studies were available on the long term. Despite the limited evidence, it is interesting to observe that the HIFU treatment option, which is one of the newest techniques, is currently associated with the least promising outcomes. The authors of the included studies suggested themselves that the high reintervention risk after HIFU might be the result of inadequate patient selection.[59;72;78] Defining the right patient population is indeed one of the key factors associated with success[2] HIFU treatment has been Food and Drug Administration (FDA) approved since 2004 for a selected patient population, and this treatment option seems attractive in terms of procedural morbidity.[78;101;102] However, the findings of this review show that this advanced technique still needs to be further evaluated, especially regarding its long-term outcomes. Obviously, this also applies to the other approaches, such as cryoablation, artery ligation, and laparoscopic RFA, that are currently lacking long-term outcomes data.

Looking specifically at myomectomy and UAE procedures, available evidence was more robust. It is important to note that confounding by indication, particularly infertility, could have influenced these reintervention risk data. Specifically for UAE, our reintervention risk was lower than in the two RCTs included in our analysis that compared UAE and surgery (myomectomy or hysterectomy) in women not desiring future pregnancy.[15;16] Those studies demonstrated after UAE a 5-year reintervention risk of 28.4–32%.[15;16] Both study groups also analyzed the costs associated with UAE compared with myomectomy or hysterectomy and concluded that the costs of UAE were substantially lower than after surgery at 12[15;103] and 24 months.[104] However at 60 months, the benefit of costs disappeared because of the increased reintervention risk.[15] As a result, studies have argued whether women undergoing embolization who were not interested in future pregnancy would not be better served by an initial definitive solution (e.g. hysterectomy).[104] On the other hand, it can also be reasoned that 70% of the women included in these studies have avoided a

more invasive procedure.[104] Although we did not perform a cost-effectiveness analysis, our findings demonstrated that <10% of the patients required a hysterectomy in the long term after UAE.

It would have been interesting in our analysis to correct for infertility as indication of treatment, but the available evidence did not allow it. Reintervention management can be expected to be different for women with future pregnancy desire compared with women without future pregnancy desire. For patients with fibroids and infertility, myomectomy is the criterion standard. Most other interventions remain a relative contraindication and have not yet been cleared by the FDA for this indication.[102;104] This was also reflected in our risk assessment of the included studies: only in the treatment group of myomectomy and hysteroscopic myomectomy were studies included that specifically enrolled patients with infertility as indication of treatment. Although successful pregnancies have been reported after embolization, it has also been associated with a higher risk of pregnancy and/or delivery complications (spontaneous abortion, malpresentation, postpartum hemorrhage, premature delivery)[105] and an increased risk of ovarian dysfunction.[106] For laparoscopic RFA and HIFU, evidence regarding pregnancy outcomes is currently poor. The safety and effectiveness of these treatments in women wishing to maintain their fertility has not been established.[107;108] For the hysteroscopic treatment options, available evidence was limited for the two procedures (hysteroscopic myomectomy and hysteroscopic RFA), especially in the long term. A systematic review has demonstrated the benefits of intracavitary fibroid removal in general for infertility treatment, but data on reintervention are currently lacking to formulate recommendations on the most favorable treatment option.[109]

Regarding quality of life after treatment (based on SSS and HRQL scores), all studies showed improvement of symptoms 12 months after therapy. Long-term outcomes were scarce for all categories although they were in line with the 12-month outcomes. Based on current evidence and with the most appropriate available questionnaires, we can conclude that in terms of quality of life, no difference was observed between the treatment options, except potentially for HIFU. That treatment option was associated in both questionnaires with the least favorable outcomes. Although the reason for this finding is unclear, it is important to realize that the necessity of reintervention probably affects quality of life and may lead to lower scores.[110] Furthermore, it is interesting to mention that one of the included RCTs evaluated quality of life in 22 patients after HIFU compared with placebo treatment.[11] They demonstrated similar symptoms reduction in the first 4 weeks, showing the potential strong impact of placebo therapy on symptom relief. However, at 12 weeks in that study, the symptoms of patients in the placebo group were significantly worse than in the treatment group.

The main limitation of the present systematic review and meta-analysis was the substantial heterogeneity observed. We are aware that patient characteristics (including age, menopause status, or indication for treatment) might influence the choice of procedure and the risk of reintervention. However, further subanalysis by patient characteristics was not possible, because most studies reported only a mean or overall percentage of their cohort, and such data presentation does not allow for further specific modifications. Because of potential confounding, we should be careful about comparing the outcomes of the different procedures with each other, and our data should not be interpreted as a comparative effectiveness analysis. Nevertheless, this meta-analysis provides insights into current reintervention risks based on a large study population. These findings can be directly applicable in daily practice for counseling patients that are often eligible for more than one treatment option. Another limitation that should be considered is that we did not evaluate the safety of the procedures (i.e., complications risk), costs, or subsequent pregnancy rates in patients desiring fertility preservation. These findings would have also been interesting to determine relative efficacy of the procedures and should be considered in future research. Strengths of this review include the description of a wide variety of treatment options with quantifiable outcomes. In addition, by focusing on reintervention risk, we evaluated only the recurrence of clinically symptomatic fibroids. We think that data on recurrence of fibroids according to periodic diagnostic follow-up may not be representative or relevant, because a proportion of patients remain asymptomatic. Moreover, a periodic follow-up could lead to unnecessary anxiety for patients and eventually extra unnecessary interventions and costs.

Over the past decades, many new uterine-sparing surgical treatments have been developed in attempts to minimize the invasiveness of the procedure and to improve women's quality of life. It is interesting to consider why some new techniques are being widely adopted while others, sometimes with promising results, never achieve widespread popularity. For example, the first publication on cryoablation dates from 1996,[111] but only one relevant article was found in our search after the year 2000.[39] In the present review almost 15% of the studies were directly sponsored by a medical devices company, and it must be considered that marketing and financial resources play a role in the success of an instrument. Sponsoring innovation is not necessarily unwarranted, but should not be ignored in terms of publication bias. Although almost all treatment options studied in this review have been approved by the FDA and appeared to be safe, it is important to keep evaluating the long-term outcomes, especially for more newly introduced treatment options. In contrast to the introduction of new drugs, techniques and de-vices may not be introduced before extensive evaluation of efficacy or safety, and the true impact of new technologies can be appreciated only over time. As a result, there is always a risk that

serious complications or suboptimal outcomes are being overlooked when the technique is not properly assessed.

Conclusion

Sixty months after initial therapy, a reintervention was necessary in 12.2% after myomectomy, in 7% after hysteroscopic myomectomy, and in 14.4% after UAE, although infertility as indication for treatment may have influenced outcomes. For HIFU, long-term results were not necessarily encouraging (54%), though based on limited evidence. For the other studied interventions, no long-term data were available at all. In terms of patient satisfaction, improvement of symptoms and quality of life was observed at 12 months after all approaches regardless of the technique applied. The HIFU treatment option showed the least improvement.

Despite the substantial heterogeneity of the study population, this meta-analysis provides valuable information on relative treatment efficacy of various uterine-sparing interventions for fibroids. Our results are important to consider when counseling patients in daily surgical practice. Furthermore, although most uterine-sparing treatment options for fibroids are FDA approved, long-term data regarding their efficacy are limited and therefore urgently needed.

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Chapter 11

Klinische les: Optimaliseren van postoperatief herstel thuis

Individueel ontslagbeleid en werkafspraken tussen huisarts en specialist

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Abstract

In the last decennia, the length of hospital stay of admitted patients has significantly decreased in all medical fields. As a result, postoperative recovery mainly takes place at home, inherently leading to new challenges. Here, two patients are being discussed for whom the postoperative period was substandard. To guarantee optimal quality of care in the home situation, the medical specialist and the general practitioner need to make the necessary arrangements. We would first of all recommend providing each discharged patient with specific, structured and individualised advices regarding postoperative recovery but also regarding alarm symptoms and logistics (e.g. who to call in case of emergency). Finally, we believe that, as (serious) complications are rare, it should be agreed on the fact that the responsible medical specialist is the coordinator of the postoperative period and the first contact point for postoperative patients.

Dames en heren,

De algemene ligduur van patiënten in Nederlandse ziekenhuizen is de laatste decennia gestaag gedaald.[1] Voor de groep geopereerde patiënten hebben verschillende factoren hieraan bijgedragen, onder andere de introductie en ontwikkeling van nieuwe chirurgische technieken als minimaal invasieve chirurgie, het toenemende aantal ingrepen in dagbehandeling en de beter ingerichte zorgprocessen.[1] Ook de toegenomen financiële doelmatigheid speelt een rol. Door de verkorte ligduur herstellen patiënten nu grotendeels thuis, maar om de hoogste kwaliteit van zorg te kunnen waarborgen zijn aanpassingen nodig. Dat het postoperatieve traject niet altijd optimaal is illustreren wij aan de hand van twee casussen.

Patiënt A, een 74-jarige vrouw, werd doorverwezen naar de polikliniek Gynaecologie wegens sinds 6 maanden bestaande zeurende pijn rechts onder in de buik. Ze had een BMI van 32 kg/m^2, was vitaal voor haar leeftijd en woonde zelfstandig thuis. Haar voorgeschiedenis vermeldde een laparoscopische sterilisatie en diverticulitis van het sigmoïd. Vanwege aanwijzingen voor een ruimte-innemend proces uitgaande van het rechter adnex verrichtten we een laparoscopische bilaterale adnexextirpatie. Om de adnexa via de subumbilicale incisie te verwijderen, werd deze incisie tot 5 cm verlengd. De ingreep verliep ongecompliceerd. Pathologisch onderzoek toonde een ovariumfibroom. Patiënte werd op de tweede dag na de operatie in goede klinische conditie naar huis ontslagen. Zij kreeg van de verpleegkundigen 'zoals gebruikelijk' zowel mondelinge als schriftelijke adviezen en instructies mee voor in de thuissituatie. Specifiek werd haar verteld op welke alarmsymptomen zij postoperatief moest letten, welk nummer zij moest bellen indien nodig en wanneer haar poliklinische controle zou plaatsvinden. De zaalarts stuurde de dag van haar ontslag een brief aan de huisarts waarin de operatie en het ongecompliceerde postoperatieve beloop werden beschreven.

In de nacht van de vijfde dag postoperatief nadat patiënte heftig moest niezen liep plotseling fors wondvocht en helderrood bloed uit de wond af bij de navel. Ongerust hierover belde patiënte 's nachts het nummer van de polikliniek dat haar was meegegeven. Zij kreeg echter het antwoordapparaat en besloot de volgende ochtend opnieuw telefonisch contact op te nemen. Zij werd doorverbonden met de zaalarts van de afdeling Gynaecologie die haar de keuze gaf de wond te laten beoordelen door de huisarts of op de afdeling. Hierop nam patiënte 's ochtends zelf contact op met de huisarts, die haar vanwege vermoeden van een fasciedehiscentie (platzbauch) meteen doorstuurde naar de afdeling Gynaecologie.

Hier werd een 4 cm lange fasciedehiscentie van de navelincisie vastgesteld waarbij de darmen à vue kwamen. Patiënte werd direct aangemeld voor een hersteloperatie. Het fasciedefect werd gesloten en patiënte herstelde hierna voorspoedig.

Bij poliklinische controle 6 weken later was patiënte klachtenvrij en werd bij de Valsalva-manoeuvre geen breuk gevoeld. Bij die nacontrole vertelde patiënte dat ze meteen geen goed gevoel had gehad over de wond en dat ze liever direct naar het ziekenhuis had willen komen. Volgens patiënte had de zaalarts gezegd dat ze 'eerst naar de huisarts moest gaan'.

Patiënt B, een 61-jarige vrouw met een blanco voorgeschiedenis, werd op de polikliniek Chirurgie gezien met sinds 3 maanden bestaande klachten van een asymptomatische zwelling ter plaatse van haar linker bil.

Bij lichamelijk onderzoek werd een wekedelenzwelling van 5–6 cm gepalpeerd, die loslag van de huid, maar vastzat aan de onderlaag. Voor nadere diagnostiek werd een echogram en een MRI-scan gemaakt, waarop een tumor in de M. gluteus maximus van 63 x 44 x 67 mm zichtbaar werd. Differentiaaldiagnostisch dachten we aan een myxoom, angiomyxoom of fibrosarcoom en we besloten de zwelling met marge te excideren. De ingreep verliep ongecompliceerd en patiënte werd de volgende dag ontslagen. Bij het ontslaggesprek kreeg ze mondeling uitleg over de wondverzorging en mondelinge en schriftelijke instructies ten aanzien van alarmsymptomen en postoperatieve adviezen. Pathologisch onderzoek toonde een marginaal verwijderd myxoom met indicatie voor follow-up.

Op de zestiende dag postoperatief nam patiënte telefonisch contact op met de afdeling Chirurgie omdat ze steeds ongeruster werd over het wondgebied. Ze zei dat de wond roder en pijnlijker was, maar dat zij geen koorts had. Zij werd daarop beoordeeld door de chirurg. Er was sprake van een geïnfecteerde wond, waarvoor 7 dagen flucloxacilline werd voorgeschreven. Er werden geen vervolgafspraken gemaakt voor de wond en patiënte werd geïnstrueerd terug te komen als de klachten toenamen. Tien dagen na dit contact bezocht patiënte haar huisarts omdat ze last had van haar knie. Op dat moment had de huisarts enkel een korte ontslagbrief ontvangen van de chirurg waarin vermeld werd dat de procedure ongecompliceerd was verlopen. Patiënte vertelde de huisarts spontaan over de wondinfectie en het antibioticumbeleid, waarop de huisarts de wond inspecteerde en een kleine, fluctuerende zwelling aan de rand van de wond met geel wondvocht aantrof. De huisarts dacht aan een abces en besloot een ontlastende incisie te verrichten. Hierbij kwamen wondvocht en bloed vrij en bleek de wond een stuk dieper dan de huisarts had verwacht. Hierop stuurde hij patiënte in naar de chirurg.

Bij inspectie zag de chirurg een wond met rustig aspect en een verse incisie die reikte tot 6.5 cm in de diepte. We besloten tot een wondbeleid van éénmaal daags spoelen met

aanvullend een antimicrobieel katoengaas geïmpregneerd met dialcylcarbamoylchloride. De wond werd regelmatig gecontroleerd op de wondpoli en het verdere beloop was zonder bijzonderheden.

Bij de laatste controle in het ziekenhuis gaf patiënte aan dat het voor haar onduidelijk was geweest met wie zij precies contact behoorde op te nemen toen de wondproblemen optraden. Bovendien had zij een algemene leefregel meegekregen waarin vermeld stond dat alleen in de eerste week postoperatief contact met de afdeling kon worden opgenomen.

Beschouwing

De afgelopen decennia wordt ziekenhuisbreed een kortere opnameduur waargenomen.[1] Een gevolg hiervan is dat geopereerde patiënten het grootste deel van het postoperatieve zorgtraject in hun eigen omgeving doorbrengen. Door het ontbreken van continue observatie door het behandelend team moet dit traject nauwlettend ingericht worden, zodat patiënten weten bij wie, wanneer en hoe zij aan de bel moeten trekken.

Ontslagbeleid

In veel ziekenhuizen wordt het ontslag gecoördineerd door verpleegkundigen die patiënten mondelinge en schriftelijke leefregels meegeven bij ontslag, zoals ook bij patiënt A en B het geval was. Het ontslagbeleid is in de praktijk echter weinig gestroomlijnd. Door gebrek aan wetenschappelijke onderbouwing zijn hersteladviezen vaak algemeen, weinig gestructureerd en onvoldoende geïndividualiseerd, waardoor patiënten onnodig lang herstellen.[2] Een voorbeeld van opties om het herstel te optimaliseren is het zogeheten 'Enhanced recovery after surgery' (ERAS)-programma, waarbij multidisciplinaire begeleiding en wetenschappelijke onderbouwde interventies vóór, tijdens en na de operatie plaatsvinden.[3] De eerste resultaten zijn veelbelovend en dergelijke initiatieven verdienen de komende jaren navolging.

Uit onderzoek blijkt echter dat de belangrijkste oorzaken van vermijdbare heropnames niet ziektegerelateerd zijn, maar te maken hebben met menselijke communicatie- en coördinatiefouten.[4] Een voorbeeld hiervan is het verkeerde telefoonnummer dat patiënt A meekreeg, waardoor zij tot de volgende ochtend moest wachten om iemand van de ziekenhuisafdeling te spreken.

Optimalisering van het ontslagbeleid is recent tot algemeen speerpunt voor verbetering benoemd in het LUMC. Dit speerpunt volgde uit de resultaten van de routinematige patiëntervaringenenquête, die sinds eind 2013 door meer dan 14.000 patiënten is

ingevuld.[5] Voor zowel de snijdende als niet-snijdende specialismen waren de grootste aandachtspunten bij het ontslagbeleid de controleafspraak en de uitleg over medicijnen en alarmsymptomen.

Aan de hand van de uitkomsten van deze enquête zijn in het LUMC diverse initiatieven ontwikkeld. Om de ontslaginformatie aan patiënten te structureren wordt bijvoorbeeld gebruikgemaakt van 'de drie P's': 'Pillen, Poli-afspraak en Paniek'. Op de afdeling Gynaecologie zijn folders ontwikkeld voor gepersonaliseerde adviezen na ontslag (Tabel 11.1). Naast de checklist voor ontslag en het overzicht van alarmsignalen, kunnen verpleegkundigen hierop aangeven welke adviezen – die momenteel alleen nog gebaseerd zijn op klinische ervaring in plaats van wetenschappelijk bewijs – van toepassing zijn voor de specifieke patiënte.

Table 11.1: Onderwerpen uit de gepersonaliseerde gynaecologiefolder

Checklist voor ontslag
• Ontslagmedicatie • Nacontrole op de poli/ afspraken voor uitslagen weefselonderzoek • Ontslag gesprek met arts en verpleegkundige • Opvang thuis
Algemene adviezen
• Bewegen* • Urineren/stoelgang • (Wond)pijn • Vloeien • Seksualiteit
Specifieke adviezen
• Bijvoorbeeld ten aanzien van hechtingen
Alarmsignalen
• Koorts >38,5^{0}C • Vaginaal bloedverlies dat sterkt toeneemt of sterk ruikt • Pijn ondanks de voorgeschreven pijnstilling • De genezing van de wond is verstoord • Overige zorgen die niet in de folder staan
Contactgegevens ziekenhuis

*** Voorbeeld van gepersonaliseerde informatie over bewegen**

Bewegen
Wij adviseren u een periode van rust te nemen van ongeveer:
- 2 weken
- 4 weken
- 6 weken

(Aankruisen wat van toepassing is voor patiënte).

Ontslaginstructies en leefregels dienen met zorg te worden samengesteld zodat duidelijk is dat patiënten bij problemen die gerelateerd zijn aan de behandeling, zich altijd kunnen richten tot de specialist en dat hier geen termijnen voor gelden, zoals wel gesuggereerd werd in de papieren die patiënt B ontving.

Coördinatie tussen eerste en tweede lijn

Naast gerichte leefregels en hersteladviezen, is het belangrijk te beseffen dat door de verkorte opnameduur huisartsen steeds meer betrokken worden bij patiënten die zich in het postoperatieve traject bevinden. Om die reden is het belangrijk dat de eerste en tweede lijn concrete werkafspraken met elkaar maken. In enkele regio's is daartoe al initiatief genomen.[6] Een goede samenwerking kan vertraging beperken en onnodige zorg zoals bij patiënt A en B vermijden.

Om deze samenwerking goed te laten verlopen is het zaak dat de huisarts tijdig geïnformeerd wordt over de opname en het ontslag. In de richtlijn 'Informatie-uitwisseling tussen huisarts en specialist bij verwijzingen' wordt dan ook aangegeven dat direct bij ontslag een voorlopige ontslagbrief verstuurd moet worden.[7] In de praktijk kan het echter voorkomen dat de ontslagbrief nog ontbreekt of niet volledig is, waardoor de huisarts met incomplete informatie moet werken.

In de casus van patiënt B was de huisarts niet geïnformeerd over de wondinfectie en de behandeling daarvan, maar kwam dit onderwerp spontaan ter sprake tijdens het consult omdat patiënte zich zorgen maakte. Als een geopereerde patiënt zich in de eerste weken van zijn of haar herstel bij de huisarts meldt en er twijfel bestaat over de oorsprong van de klacht, is het belangrijk dat er laagdrempelig overleg met of terugverwijzing naar de verantwoordelijke specialist plaatsvindt. De postoperatieve zorg blijft bij uitstek de verantwoordelijkheid van het ziekenhuis, en specialisten kunnen in de eerste weken juist de huisartsen hierin ontlasten.

Postoperatieve complicaties komen voornamelijk voor in de eerste 4–6 weken na ontslag, zoals ook gereflecteerd in de termijnen die door de vakgroepen zijn afgesproken voor het registreren van complicaties, respectievelijk 30 dagen na ontslag van de afdeling Chirugie,[8] en 6 weken bij de afdeling Gynaecologie.[9] Maar het kan natuurlijk altijd gebeuren dat klachten zich later manifesteren. Huisartsen zullen daarom ook langere tijd na de ingreep alert moeten blijven om bij aspecifieke klachten een postoperatieve complicatie te onderkennen. Het zal duidelijk moeten zijn dat de deur van de specialist altijd openstaat, zowel voor de patiënt als voor de huisarts.

Telefonische triage

Als geopereerde patiënten telefonisch contact opnemen vanwege klachten, wordt er veelal zonder observatie getrieerd. Dit gaat gepaard met het risico op een inschattingsfout. Zo werd patiënt A, na het uitspreken van haar verontrusting over de wond, zelf voor de keuze gesteld om bij de huisarts of de specialist langs te gaan. Gezien het over algemeen lage complicatierisico passen klachten vaak bij het gebruikelijke postoperatieve beloop. Men moet zich echter wel realiseren dat er, ondanks goede werkafspraken, altijd zeldzame of late complicaties kunnen optreden waar niet altijd op geanticipeerd kan worden. Wij willen er daarom voor pleiten dat medisch specialisten in de eerste weken na de ingreep de coördinerende rol blijven houden met betrekking tot het postoperatieve beleid. Voor iedere postoperatieve patiënt die telefonisch contact opneemt met het ziekenhuis is het belangrijk een duidelijk plan te maken waarbij de patiënt gezien wordt door de initieel behandelend specialist, naar de huisarts wordt verwezen of weet wanneer hij opnieuw moet bellen.

Dames en Heren, ontwikkelingen in de zorg resulteren in een verkorte ziekenhuisopnameduur voor het postoperatieve herstel, dat zich daardoor voornamelijk in de thuissituatie afspeelt. Om de voordelen van deze verkorte opnameduur optimaal te benutten is het zaak het postoperatieve traject goed in te richten en de samenwerking tussen eerste en tweede lijn te versterken. Dit geldt niet alleen voor de snijdende specialismen, maar is waarschijnlijk ook een belangrijke boodschap voor de niet- snijdende specialismen.

Het is essentieel dat patiënten heldere en gestructureerde adviezen meekrijgen over het herstel, maar daarbij ook worden voorgelicht over alarmsymptomen en logistieke aspecten. Ondanks gebrek aan direct medisch toezicht in de thuissituatie moet het voor zowel huisarts als patiënt duidelijk zijn dat er in de postoperatieve periode altijd en drempelloos contact kan worden opgenomen met de initieel behandelend specialist. In die postoperatieve periode zal de regierol bij de verantwoordelijke specialist moeten blijven liggen, om met name te voorkomen dat patiënten met zeldzame complicaties tussen de wal en het schip vallen. Het is belangrijk dat medisch specialisten en huisartsen hierover heldere werkafspraken maken.

Leerpunten

- Omdat geopereerde patiënten tegenwoordig grotendeels thuis herstellen, is het essentieel het postoperatieve traject voor elk specialisme goed in te richten, zodat de voordelen van de verkorte opnameduur tot hun recht komen.
- Naast gericht hersteladviezen, is het belangrijk patiënten bij ontslag voor te lichten over alarmsymptomen en logistieke aspecten om onnodige vertragingen tegengaan.
- In de eerste weken na een operatie ligt de regierol bij de verantwoordelijke specialist; voor patiënt en huisarts moet duidelijk zijn dat zij dan altijd en drempelloos contact kunnen opnemen met deze specialist.
- Het is belangrijk is dat huisartsen en medische specialisten in de regio duidelijke werkafspraken maken over het postoperatieve traject van hun patiënten.

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Chapter 12

Medical malpractice claims in laparoscopic gynecologic surgery: a Dutch overview of 20 years

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Abstract

Background: The success of newly introduced surgical techniques is generally primarily assessed by surgical outcome measures. However, data on medical liability should concomitantly be used to evaluate provided care as they give a unique insight into substandard care from patient's point of view. The aim of this study was to analyze the number and type of medical claims after laparoscopic gynecologic procedures since the introduction of advanced laparoscopy two decades ago. Secondly, our objective was to identify trends and/or risk factors associated with these claims.

Methods: To identify the claims, we searched the databases of the two largest medical liability mutual insurance companies in the Netherlands (MediRisk and Centramed), covering together 96% of the Dutch hospitals. All claims related to laparoscopic gynecologic surgery and filed between 1993 and 2015 were included.

Results: A total of 133 claims met our inclusion criteria, of which 54 were accepted claims (41%) and 79 rejected (59%). The number of claims remained relatively constant over time. The majority of claims were filed for visceral and/or vascular injuries (82%), specifically to the bowel (40%) and ureters (20%). More than one-third of the injuries were entry related (38%) and 77% of the claims were filed after non-advanced procedures. A delay in diagnosing injuries was the primary reason for financial compensation (33%). The median sum paid to patients was €12,000 (500–848,689). In 90 claims, an attorney was defending the patient (83% for the accepted claims; 57% for the rejected claims).

Conclusion: The number of claims remained relatively constant during the study period. Most claims were provoked by bowel and ureter injuries. Delay in recognizing injuries was the most encountered reason for granting financial compensation. Entering the abdominal cavity during laparoscopy continues to be a potential dangerous step. As a result, gynecologists are recommended to thoroughly counsel patients undergoing any laparoscopic procedure, even regarding the risk of entry-related injuries.

Introduction

Safely introducing new technologies in the surgical field is challenging, particularly for highly advanced procedures. In contrast to the introduction of new drugs, (surgical) techniques and devices may not be introduced prior to extensive evaluation and their true impact can often only be appreciated over time.[1] Consequently, recent reports and studies from different medical fields have recommended systematic evaluations of efficacy and safety of every newly introduced (surgical) technique or instrument.[1;2;3] The success of new technology is generally primarily assessed by clinical outcome measures. In an era where Value-Based Health Care is being broadly implemented, other source of information should also be concomitantly used to evaluate provided care. One interesting and complementary source of information is data on medical liability.[4] Even though litigation climate varies among countries and not every claim is the consequence of an adverse event, these data provide a unique insight into incidents judged by patients as substandard care.[5]

Over the past two decades, laparoscopic surgery has been rapidly implemented in many countries.[6] Although the minimally invasive technique is still advancing, its introduction has definitely changed our daily surgical practice. Minimally invasive surgery has even been described as the most important revolution in surgical technique since the early 1900s.[7] In the field of gynecology, advanced laparoscopic surgery has been widely introduced two decades ago. Understanding the reasons for filing claims, especially in new (surgical) fields, should be part of the evaluation process to improve care. As a result, we aimed in this present study to analyze the medical liability claims of laparoscopic gynecologic procedures in the Netherlands since the broad introduction of (advanced) laparoscopy two decades ago. Secondly, our objective was to identify trends and/or risk factors associated with these claims.

Materials and methods

Selection criteria

To identify the medical claims of laparoscopic gynecologic surgery, we searched the databases of the two largest medical liability mutual insurance companies in the Netherlands (MediRisk and Centramed). The search terms used were 'gynecology' and 'laparoscopy' and all claims concerning laparoscopic gynecologic surgery were included up to 1st of January 2016. Claims were available from 1993 for MediRisk and 1995 for Centramed, the founding years of the companies. The study was exempted from Institutional Review Board approval.

MediRisk and Centramed currently cover together 87 of the 91 Dutch hospitals (95.6%). The insured hospitals are teaching and non-teaching hospitals and Centramed specifically insures six of the eight Dutch academic hospitals.

To evaluate the impact of laparoscopic gynecological surgery, we exclusively included claims related to injuries and/or technological failures. We excluded claims regarding unwanted pregnancies after failed laparoscopic sterilization and claims concerning intra-uterine procedures (e.g. hysteroscopy and intra-uterine device placement).

Both claims of accepted and rejected cases were included. An accepted case signifies that the medical insurance company recognizes that the given care was suboptimal and that the adverse event could have been avoided. These patients are being financially compensated for the caused damage. A rejected case means that, although an adverse event may have occurred, no medical malpractice was observed. As such, no pay-outs were granted for those cases. Also, both open and closed claims were included in the present study. The 'open claims' were only included if the verdict on liability was available when chart review was performed (October 2016).

Data extraction

The medical and legal charts of all selected claims were reviewed at the insurance company offices. The following data were extracted: (1) description of the incident including the moment the incidence was discovered, (2) legal information (liability, the presence of an attorney, time frame, costs, and pay-outs), (3) patient characteristics [age and BMI (kg/m^2) at initial procedure, previous surgeries, health care-related job, type of hospital (teaching, non-teaching)], and (4) surgical procedures (classified according to the European Society for Gynecological Endoscopy (ESGE)[8] and complications. Complications were defined following the internationally recognized classification of the Dutch Society of Obstetrics and Gynecology (NVOG).[8] Each complication was further subcategorized into four categories: (A) temporary disability, no re-operation required; (B) disability resolved after re-operation; (C) permanent disability; and (D) death. Detailed information on the ESGE classification for laparoscopic procedures and the NVOG classification for complications is available in Appendix 12.1 (Table S12.1 and Table S12.2).

Statistics

Data were analyzed using SPSS version 23 for Windows. Collected data were summarized and outliers were reviewed. Continuous data were presented as median with minimum and maximum and categorical data as frequency and percentages.

Results

Claim selection

Over the study period, 328 claims were identified (Appendix 12.1, Figure S12.1). A total of 146 claims (44.5%) did not meet our inclusion criteria and were excluded. In addition, 49 claims (15%) were not available as their files had been destroyed or could not be found in the archives anymore (29 for MediRisk and 20 for Centramed). A total of 133 claims were eventually included in our study (119 from MediRisk and 14 from Centramed).

Of these 133 claims, 79 were rejected by the medical insurance company (59.3%) and 54 were accepted (40.6%), of which 20 with an amicable settlement. A total of sixteen claims were still open at the time of our study but as their verdicts were known, they were included in the analysis. These claims had not been closed yet, as for the rejected claims (n=11) an appeal had been made and for the accepted claims (n=5) the amount of pay-outs was still being negotiated.

Patient and surgical characteristics

Table 12.1 depicts the baseline characteristics of the women filing a claim and their indication for surgery. Twenty-one of the women filing a claim (21.6%) were working themselves in the medical sector. During the study period, 63 of the 87 hospitals (72.4%) had at least one claim and the number of claims per hospital varied, with a maximum of six claims. Slightly more claims were filed by patients treated in teaching hospitals compared to the non-teaching hospitals (55.8 vs. 44.2%).

Figure 12.1 presents an overview of the claims stratified by type of surgery. Adnexal surgery was associated with the highest number of claims (33.8%), followed by laparoscopic hysterectomy (LH) (19.5%), diagnostic laparoscopy (18.8%), and laparoscopic sterilization (15.8%). The other procedures (12%) included adhesiolysis, ectopic pregnancy surgery, laparoscopic removal of an intra-uterine device in the abdomen, and laparoscopic sacrocolpopexy. Based on the classification of the ESGE9, 77% of the filed claims were non-advanced procedures (levels 1 and 2).

Malpractices

Figure 12.2 demonstrates the total number of claims per year. On average, six claims were filed per year. The highest incidence of claims was observed in 2007 (15 claims). Our data showed that 91.7% of the claims related to LH were filed in the last 10 years (from 2005).

Table 12.1: Baseline characteristics of women filing a claim

	Total (n=133)	Accepted claims (n=54)	Rejected claims (n=79)
Patient characteristics			
Age (years) (n=133)	41 (15–77)	41 (25–68)	41 (15–77)
BMI (kg/m^2) (n=82)	25.0 (18.0–88.2)	24.9 (18.0–44.1)	25.7 (18.3–88.2)
ASA classification (n=60)			
ASA 1	38 (63.3)	19 (70.4)	19 (31.7)
ASA 2	21 (35)	8 (29.6)	13 (21.7)
ASA 3 and 4	1 (1.7)	0	1 (1.6)
Previous surgery (n=115)			
Laparotomy	46 (40.0)	23 (62.2)	23 (57.5)
Laparoscopy	31 (27.0)	14 (37.8)	17 (42.5)
Job (n=97)			
Health care job	21 (21.6)	7 (15.9)	14 (26.4)
Parity (n=118)			
0	30 (25.4)	13 (26.5)	16 (23.5)
1	20 (16.9)	6 (12.2)	14 (20.6)
>1	68 (57.7)	30 (61.3)	38 (55.9)
Number of claims from (n=129)			
Teaching hospitals (27)	72 (55.8)	29 (55.8)	42 (55.3)
Non-teaching hospitals (36)	57 (44.2)	23 (44.2)	34 (44.7)
Type of surgery and main indication			
LH	26 (19.5)	11 (20.4)	15 (19.0)
Fibroids	17 (65.4)	7 (63.6)	10 (66.7)
Heavy menstrual bleeding	5 (19.2)	2 (18.2)	3 (20.0)
Malignancy	3 (11.6)	1 (9.1)	2 (13.3)
Endometriosis	1 (3.8)	1 (9.1)	0
Adnexal surgery (salpingectomy or cystectomy)	45 (33.8)	23 (42.6)	22 (27.8)
Cyst(s)	36 (53.5)	19	17 (77.4)
Adhesions	3 (4.3)	2	1 (4.5)
Suspected ovarian torsion	1 (4.3)	0	1 (4.5)
Suspected malignancy	1 (4.3)	0	1 (4.5)
Unknown	3 (13)	1	2 (9.1)
Diagnostic laparoscopy	25 (18.8)	9 (16.7)	16 (20.3)
Adhesions/chronic pain/	14 (57.7)	6 (75)	8 (50.0)
Infertility	7 (26.9)	3 (25)	4 (25.0)
Heavy menstrual bleeding	1	0	1 (6.3)
Acute abdominal pain	2 (7.6)	0	2 (12.3)
Staging ovarian tumour	1 (3.8)	0	1 (6.3)
Laparoscopic sterilization	21 (15.8)	6 (11.1)	15 (19.0)
Clips	7 (30.0)	2 (33.3)	5 (33.3)
Tuba cleavage	11 (52.4)	2 (33.3)	9 (60.0)
Unknown	1 (4.9)	1 (1.7)	0
Sterilization not performed	2 (5.7)	1 (1.7)	1 (6.7)
Other procedures	16 (12.0)	5 (9.3)	11 (13.9)
Adhesiolysis	5 (38.9)	4 (83.3)	1 (9.0)
Ectopic pregnancy surgery	4 (22.2)	1 (16.7)	3 (27.3)
IUD removal in abdomen	2 (11.1)	0	2 (18.2)
Laparoscopic sacrocolpopexy	5 (27.8)	0	5 (45.5)

ASA, American Society of Anesthesia; LH, laparoscopic hysterectomy; IUD, intra-uterine device.
Data are expressed as median (minimum-maximum) or as frequency (%).

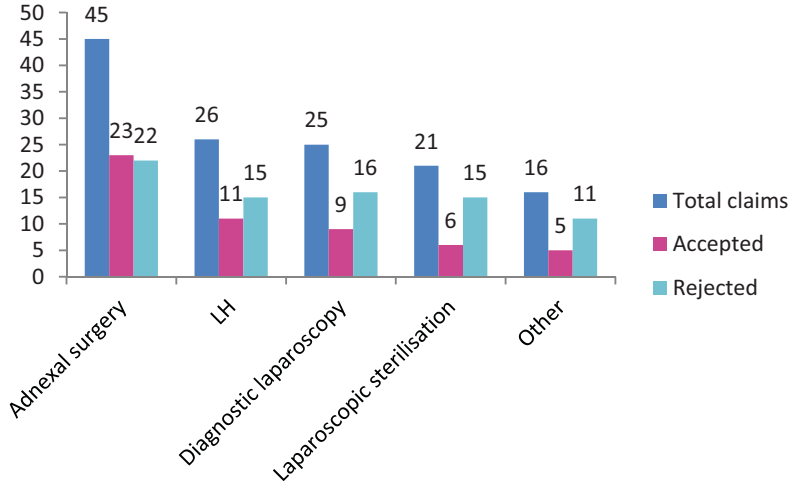

Figure 12.1: Claims per type of surgery.
LH, laparoscopic hysterectomy; other procedures include adhesiolysis, ectopic pregnancy surgery, laparoscopic removal of an intra-uterine device in the abdomen and laparoscopic sacrocolpopexy.

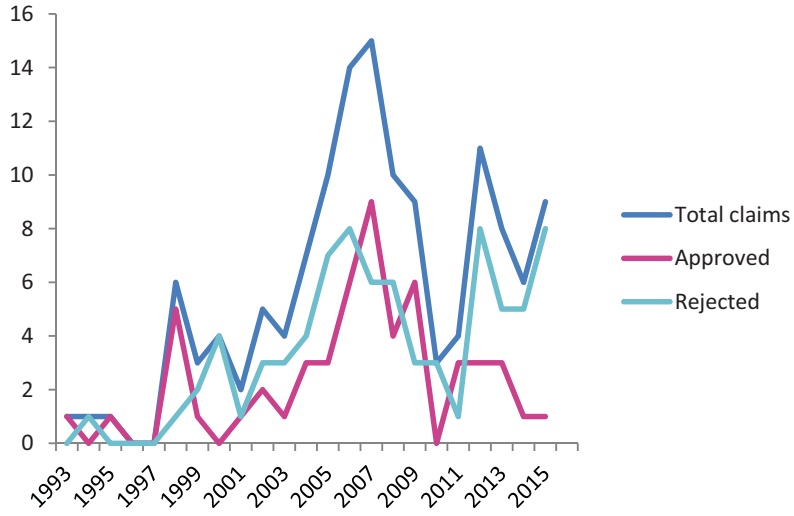

Figure 12.2: Overview of claims over study period.

No other specific trends were observed when stratifying the claims by type of procedure or type of injury (data not shown).

As can be observed in Table 12.2, 81.9% of the claims were filed for visceral and/or vascular injuries, and specifically 39.8% for bowel and 19.5% for ureter injuries. The bowel injuries were not related to a specific laparoscopic procedure, whereas 92% of the ureter injuries

Table 12.2: Overview of the main type of claims and their severity

	Total (n=133)	Accepted claims (n=54)	Rejected claims (n=79)
Type of injury			
Injuries	109 patients (81.9), 111 injuries	42 patients (75.9), 43 injuries	67 patients (78.5), 68 injuries
Bowel	53* (39.8)	18* (33.3)	35 (44.3)
Ureter	26* (19.5)	13 (24)	13* (16.5)
Bladder	13* (9.7)	4* (7.4)	9* (11.4)
Vessel/hemorrhage	15 (11.3)	5 (9.3)	10 (12.7)
Stomach	1 (0.75)	1 (1.9)	0
Nerve	3 (2.2)	2 (3.7)	1 (1.3)
Chemical peritonitis	3 (2.2)	2 (3.7)	1 (1.3)
Wound dehiscence	4 (3.0)	1 (1.9)	3 (3.8)
Pulmonary embolism	1 (0.8)	0	1 (1.3)
Other	16 (12)	9 (16.6)	7 (8.9)
Unnecessary conversion	1	1	0
Skin burned	1	1	0
Foreign body	4	3	1
Failed procedure	4	0	4
Wrong procedure	4	4	0
Missed diagnose	1	0	1
Persistent symptoms	1	0	1
Cause of injury			
Laparoscopic entry-related	51 (38.3)	19 (35.2)	32 (40.5)
Thermal injury	12 (9.0)	5 (9.3)	7 (8.9)
Technical failure	7 (5.3)	6 (11.1)	1 (1.3)
No iatrogenic injuries	18 (13.5)	7 (13.0)	11 (13.9)
Unspecified	44 (33.1)	17 (31.5)	27 (34.2)
Severity of injury			
(A) Conservative treatment	19 (14.3)	10 (18.5)	9 (11.4)
(B) Re-intervention necessary	95 (71.4)	35 (64.8)	60 (75.9)
(C) Permanent disability	15 (11.3)	8 (14.8)	7 (8.9)
(D) Death	4 (3.0)	1 (1.9)	3 (3.8)
Moment discovered			
(1) Intra-operatively	26 (19.5)	14 (25.9)	12 (15.2)
(2) Postoperatively	40 (30.1)	14 (24.1)	26 (32.9)
(3) After discharge	67 (50.4)	26 (48.1)	41 (51.0)

* Two patients had two injuries.
Data are expressed as frequency (%).

occurred during LH or adnexal surgery. In 51 claims (38.3%), including 19 accepted claims, the introduction of the needle and/or trocar caused the injury. It was not always explicitly mentioned in the medical files that the adverse events were entry related, but when evident we classified them into this group (e.g., diagnostic laparoscopy with artery iliac injury). The entry-related incidents caused in total 35 bowel injuries, nine vessel injuries, six bladder

injuries, and one stomach injury (in a patient without nasogastric intubation). Twelve claims (9%), including five accepted ones, were filed for thermal injuries [bowel (n=5), ureter (n 6), and nerve (n=1)]. These injuries were all discovered postoperatively and re-operation was required in all cases. Technical failure played a role in six cases (4.5%), of which all claims were approved. These technical failures were related to the inappropriate use of instruments (n=1) and of laparoscopic monitor (n=1). In the other four cases, surgical items were accidentally retained into the abdomen (needle (n=2), sheath of instrument (n=1), and gauze after conversion (n=1)).

Concerning the severity of the injuries, 104 patients (78.2%) had to be re-operated at least once (including seven patients from category C and two from category D) and 84 of these patients had a laparotomy during re-operation (80.8%) (Table 12.2). In four patients, the adverse event resulted in death (3%). Three of these claims were rejected as no malpractice was observed. The first patient had a massive pulmonary embolism, the second one a massive hemorrhage during surgery for an initially suspected torsion of the ovary that appeared to be a sarcoma, and the third one died as a result of a sepsis after bowel injury diagnosed postoperatively. The fourth patient, whose case was accepted, died postoperatively as a result of sepsis after missed ureter injury. Her case was accepted because of delay in diagnosing the injury (exact time frame unclear). In 15 patients (11.3%), permanent disabilities occurred, including total loss of kidney function and nephrectomy after missed ureter injury, paralysis due to plexus lesions after malpositioning during surgery, or permanent stoma after bowel perforation. Half of all the injuries were discovered after discharge (50%). Specifically for the accepted claims, 89.5 and 91.7% of the bowel and ureter injuries, respectively, were missed intra-operatively. Almost all these patients had to be re-operated (94.7% of the bowel injuries and all ureter injuries).

Legal information

The principle reason for approving a claim is depicted in Table 12.3: 18 claims (33.3%) were related to a delay in diagnosing the injury (postoperatively), 14 claims (25.9%) to negligence during surgery (operative skills, malpositioning during surgery, or wrong surgery), 11 claims (20.4%) to the consequences of the injury itself, and five claims (9.3%) to an incomplete informed consent. A wrong indication or an incomplete medical file played a role in 2 (3.7%) and 3 (5.6%) claims, respectively. In one claim (1.9%) the reason was unclear.

Regarding the costs of the closed claims, the median total cost of the rejected claims was €374 (0–18,094) and €14,569 (500–897,282) for the approved claims (Table 12.4). The

Table 12.3: Main reason for accepting a claim

	Accepted claims (n=54)
Delayed/missed diagnose or complication	18 (33.3)
Negligence during surgery	14 (25.9)
During operation	8
Malpositioning during surgery	2
Wrong surgery	4
Consequences of the event itself	11 (20.4)
Incomplete informed consent	5 (9.3)
Indication for surgery	2 (3.7)
Incomplete medical file	3 (5.6)
Unknown	1 (1.9)

Data are expressed as frequency (%).

Table 12.4: Financial and time overview of closed claims

	Total claims (n=133)	Accepted claims (n=54)	Rejected claims (n=79)
Legal information (all claims, n=133)			
Representative of interests	90 (67.6)	45 (83.3)	45 (57.0)
Civil procedure	14 (32.6)	6 (11.1)	8 (10.6)
Finances (in €) (closed claims, n=125)			
Total sum	1,560 (0–897,282)	14,569 (500–897,282)	374 (0–18,093.8)
Sum paid directly to patients	--	12,000 (500–848,689)	--
Timeframe (days) (closed claims, n=125)			
Incident to filing a claim	231 (5–2,192)	218 (5–1,999)	239 (12–2,192)
Filing a claim to closure	661 (104–4,064)	1219 (141–3,960)	516 (104–4,064)

Data are expressed as median (minimum-maximum) or as frequency (%).

total cost included all expenses made by the insurance companies, including the costs of, e.g., medical experts and attorneys as well as the direct financial compensation for the patients. The median sum directly paid to the patients and their attorneys was €12,000 (500–848,689). The highest pay-out was given to a woman who had a bowel injury after diagnostic laparoscopy because of chronic abdominal pain. Her claim was approved as the patient was not properly counseled about the risks and the choice for laparoscopic approach was disputed because of her medical history (history of perforated appendix complicated by an adhesion ileus).

An attorney was defending the patient in 90 claims (67.6%). For the accepted claims, 83.3% had an attorney compared to 57% for the rejected claims. Patients who were represented by an expert were 2.6 times (95% confidence interval 1.4–4.9) as likely as those without to receive financial compensation for their filed claims. The median time frame between the incident and the moment the patient filed a claim was 231 days (5–2,192). From the moment the first complaint letter was sent out, it took a median period of 516 days (104–4,064) to close the case for the rejected claims and 1,219 days (141–3,960) for the approved claims.

Discussion

In an era where Value-Based Health Care is being broadly implemented, it is important not to focus only on surgical outcome measures to evaluate provided care but also to assess patient experience and outcome. In this line, data on medical claims provide a unique additional insight into incidents judged by patients as being substandard. Understanding the reasons for filing claims and sharing the data can be of added value for all practicing physicians.

Between 1993 and 2015, 133 claims were filed in the Netherlands after laparoscopic gynecologic procedures (six claims per year on average). The claims were relatively equally distributed over time, except for two unexplained peaks in 2007 and 2012. Both insurance companies reported observing similar trends in other medical fields in those years without being able to further explain it. Although our data do not seem to show a specific trend over time, conclusions are difficult to draw as the total number of procedures performed over the study period is unknown. However, to put the numbers in perspective, a study by Twijnstra et al. demonstrated that in 2007, 16,863 laparoscopic gynecological procedures were performed in the Netherlands (response rate 80%),[9] while 15 claims were filed (0.09%). Furthermore, studies evaluating the implementation of laparoscopic gynecologic surgery demonstrated a significant increase in the number of laparoscopic procedures from 2002, 2007, and 2012, and this was specifically the case for advanced surgeries (levels 3 and 4).[6;9;10] From our medical claim data, no such trend was observed and therefore it seems that the wide expansion of laparoscopic surgery was not associated with an increase in medical claims. In the same line, it would be interesting to further study the relation between surgical experience and the number of claims. More than two decades of experience with advanced laparoscopic surgery does not seem to guarantee a decrease in the number of claims. But again, this should be stated with caution as the overall number of procedures performed in the study period has been increasing.

In 41% of the studied claims, financial compensation was granted. Compared to other (non-European) countries, the Netherlands has a high rejection rate and relatively low payments, but also a low threshold for filing a claim as not handled through a jury trial.[11] Similar to other European systems, financial compensation is in the Netherlands only granted if the event has been judged as being the consequence of medical negligence, i.e., that it could have been avoided. As a result, claims filed for severe consequences do not necessarily result in financial compensation. This was reflected in our study by the three cases of deceased patients whose families did not receive any financial compensation as the adverse events were judged as inherent risks related to the procedures.

Most claims in our study were provoked by injuries to the bowel and ureter. Bowel and ureter injuries are rare but are known to have a high morbidity, especially if diagnosed with substantial delay (e.g., thermal injuries).[12-14] Overall, delay in diagnosing complications was the most reported reason for granting financial compensation (33%). This was in line with another claim study in general surgery that demonstrated that 26% of their 294 studied claims were related to delayed, wrong, or missed diagnosis.[4] In our study, patients with postoperative delayed diagnosis had often sought medical care (sometimes more than once) but because of the often unspecific symptom presentation of ureter and/or bowel injuries, injuries were not always (directly) recognized. Furthermore, it is important to realize that as the length of hospital stay after laparoscopic procedures is decreasing, most of these complications will only become manifest when patients are already at home. As a result, patients should receive sufficient instructions regarding the postoperative period and should be taken seriously when seeking care.

Patients with (unspecific) symptoms, even a long time after surgery, need close monitoring until the diagnosis becomes clear or symptoms disappear.[13;15;16]

A total of 51 claims (38%) were entry related. Wind et al. demonstrated in their study that one-fifth of all laparoscopy-related claims in surgery were entry-related complications.[17] Although specific risk factors, such as high BMI and previous procedures, have been associated with an increased risk of entry-related complications, needle and/or trocar insertion remains, in all patients and during all type of procedures, still one of the most hazardous steps in laparoscopy.[17]

In the present study, 77% of the claims concerned non-advanced procedures (levels 1 and 2). It is important to realize that the denominators of the different procedures are unknown and therefore this finding does not imply that the incidences are necessarily higher for non-advanced laparoscopic procedures. Yet, it can be hypothesized that when an adverse event occurs in non-advanced procedures, it might be more difficult for a patient to accept

it, as less expected. As a result, a detailed preoperative counseling is mandatory, even for routine procedures.[18] In the Netherlands, there are currently no government-mandated forms that must be used during counseling. It is the responsibility of the surgeons to adequately counsel their patients. It is self-evident that an incomplete informed consent weakens legal defense.[5] This was observed in our study in five cases (9.3%), where financial compensation was primarily granted because of incomplete informed consent. Furthermore, we want to emphasize that it is important that residents are also aware of the possible impact of incomplete counseling. A slightly higher number of claims were filed by women treated in teaching hospitals and it cannot be excluded that the inexperience of residents in counseling but also regarding surgical skills did influence these results. Another interesting finding in our study was that 20% of the claims were filed by women working in the medical sector themselves. A potential explanation is that they have more medical knowledge and might, as a result, be more critical regarding the incident. Finally, 85% of the approved claims had an attorney, compared to 57% for the rejected claims (relative risk 2.6). Although bias by severity may have occurred, it seems that patients being represented by an expert have a higher chance of being financially compensated.

Strengths and limitations

One of the limitations of this study was that 49 files (15%) of claims potentially meeting our inclusion criteria were destroyed. It is unclear though if all these claims would have been included in our study anyway: from our initial search, 146 (44%) did not meet our inclusion criteria either. Secondly, the data of the present study are based on the Dutch litigation system. Although the different European countries have overall similar liability laws, we are aware that our data might not be applicable to every country. Despite this limitation, we believe that our results provide an interesting overview of cases judged by patients as substandard care. Furthermore, this study was not conducted to provide an incidence number of adverse events, but rather to evaluate the type of filed claims. Finally, the largest proportion of claims originated from MediRisk. All claims from MediRisk insured hospitals are directly sent to the insurance company, whereas Centramed only gets involved when hospitals pay a starting fee. As a result, many claims from Centramed hospitals are handled in the initial hospital and these data were not available to us. Strengths of this work included the long study period and the fact that it provides a national overview (96% of the Dutch hospitals).

Conclusion

Over the study period of more than 20 years, the number of claims remained relatively constant. Most claims were provoked by injuries to the bowel and ureters and most claims were filed after non-advanced laparoscopic procedures (77%). Entry-related complications accounted for 38% of the claims and delay in diagnosing injuries was the primary reason for granting financial compensation. Based on our findings, gynecologists are recommended to closely monitor their patients in the postoperative period and to give them specific instructions for the first weeks at home. Secondly, it is important to realize that entering the abdominal cavity during laparoscopy is still a potential dangerous first step. Therefore, for any type of laparoscopic procedure, doctors should take time to thoroughly counsel their patients, even regarding the risk of entry-related injuries.

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Appendix 12.1

Table S12.1: ESGE classification of laparoscopic procedures

1st level -- Basic level
Diagnostic laparoscopy
Sterilization
Needle aspiration of simple cysts
Ovarian biopsy
2nd level -- Intermediate level
Salpingostomies for ectopic pregnancy
Salpingo-oophorectomies
Ovarian cystectomies
Adhesiolysis
Treatment of mild or moderate endometriosis-salpingostomy and salpingo-ovariolysis
3dr level -- Advance level
Hysterectomy
Myomectomy
Treatment of incontinence
Surgery for severe endometriosis
Extensive adhesiolysis including bowel and ureter
Repair of simple intestinal or bladder injuries
4th level -- Procedures under evaluation or practiced in specialized centers
Pelvic floor defects
Oncology procedures: lymphadenectomy, radical hysterectomy and axiolloscopy
Rectovaginal nodules
Others

Table S12.2: Complication classification according to the NVOG

Main category	Complication
Infection	Local Organ Systemic
Injury	Vascular Bowel Bladder Ureter Other
Wound dehiscence	--
Hemorrhage	> 1000 mL Post-operative bleeding
Thrombo-embolism	--
Dysfunction	Urinary retention Incontinence Ileus Liver Kidney
Systemic	Medication error Adverse drug event Other
Technical	Failed procedure Retained foreign body
Reactive conversion	--
Other	--

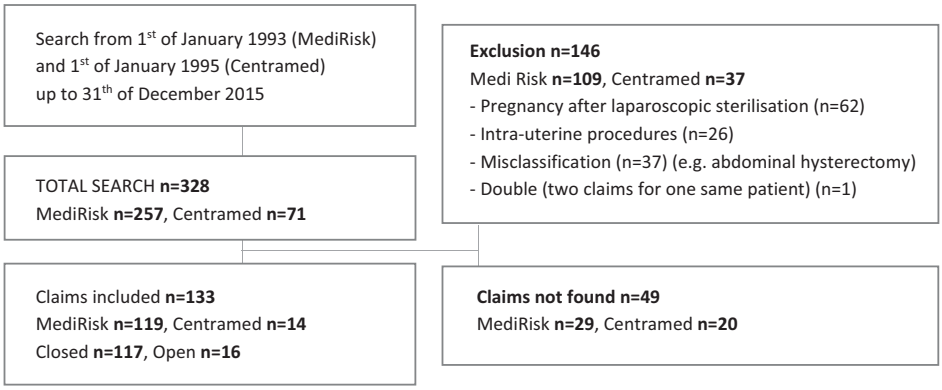
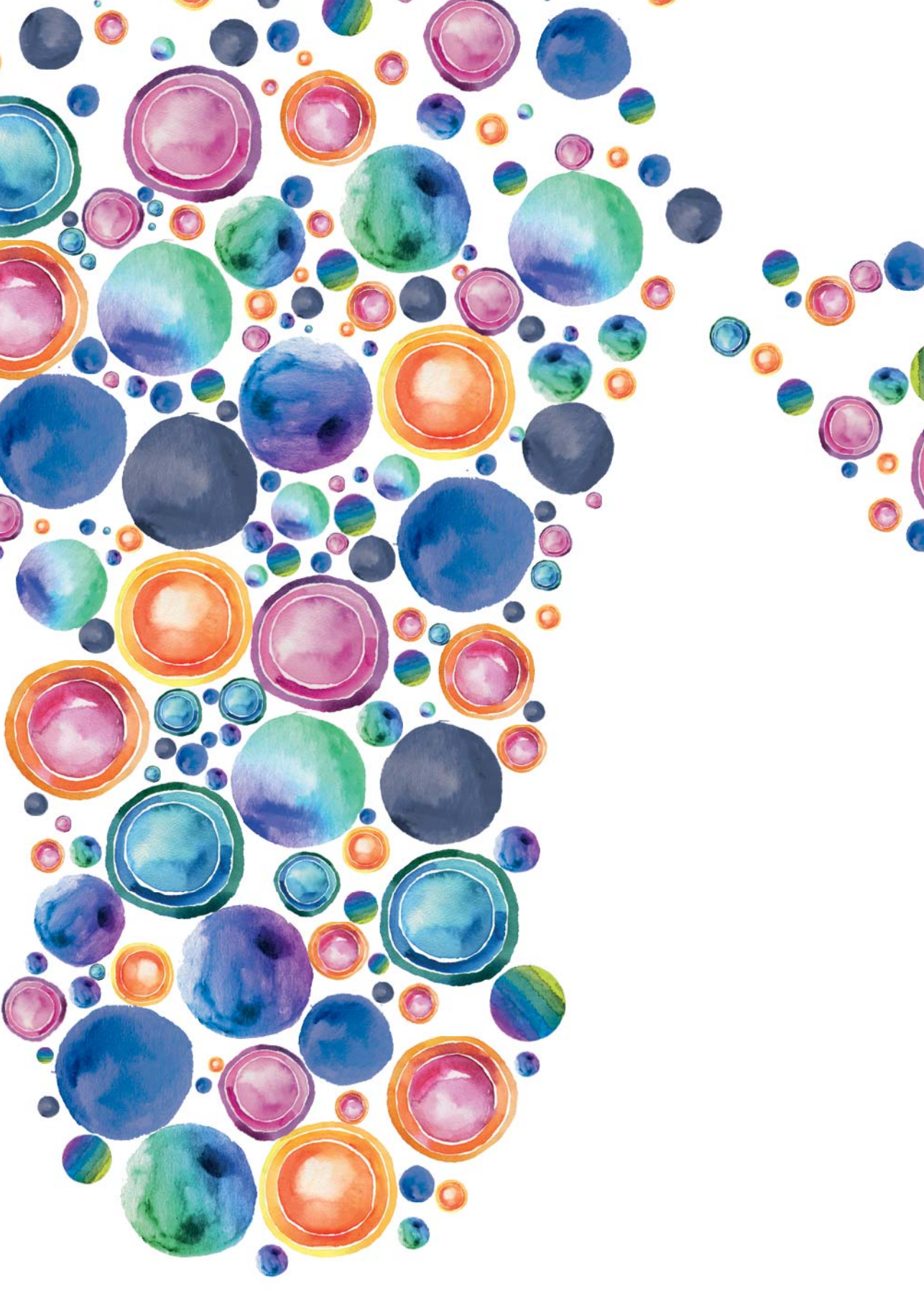


Figure S12.1: Flow-chart of selected claims.



Chapter 13

General discussion

The implementation of minimally invasive surgery (MIS) in general and of laparoscopic hysterectomy (LH) in particular, has been accelerated in the field of gynecology over the past 30 years.[1-3] As this new surgical technique was introduced so rapidly, surgeons may have developed their own authority based management, which most probably resulted in medical practice variations amongst hospitals and/or surgeons. In a time period of increasing transparency and strive for standardization, this thesis aimed to formulate best practices for clinical topics of LH and laparoscopic myomectomy (LM) that were associated with limited scientific support.

To start, a guideline for LH was developed to standardize this procedure. Chapter 2 summarizes the clinical recommendations of the guideline. A considerable finding was the fact that with the use of the GRADE method the quality of available evidence was frequently graded as *low* or *very low*. Of the more than 60 outcomes studied in the guideline, it appeared that for 38 of them (63%), the quality of the evidence was very low. Inherently, this opens the debate regarding the added value and relevance of the formulated recommendations.

Implication of a guideline associated with low quality of evidence

Firstly, to understand how the evidence was graded, background information on the GRADE method is essential. The GRADE approach was developed at the beginning of the 21st century by the group that had also introduced the term *evidence-based medicine* twenty years earlier.[4] This GRADE tool is meant to systematically evaluate the quality of evidence. It differes from previous methods as it assesses the strength of the evidence for defined outcomes, rather than for individual studies.[4] For each outcome, the GRADE method suggests to systematically grade five domains, which then generates a final level of evidence (high, moderate, low and very low quality of evidence). Although this method is internationally one of the most recognized tools in medicine, it is important to realize that it was originally developed by physicians of internal medicine. This is particularly relevant to consider when looking at the definitions set by the GRADE working group regarding the level of evidence. Indeed, high quality of evidence is defined as 'it is unlikely that further research will have an effect on the outcome'. For research with medication for example, this definition seems plausible, as for the same group of people further research will most probably not provide new insights. Yet, for research with surgical techniques, this definition seems less appropriate since techniques, technologies and the experience of surgeons keep evolving. For instance, one of the first randomized controlled trials (RCTs) comparing LH to abdominal hysterectomy did not demonstrate relevant significant advantages in favor

of LH.[5] In contrast, LH was associated with a prolonged operative time and an increased risk of complications, particularly to the urinary tract.[5] Yet with the further development of the laparoscopic technique and the increasing experience of the surgeons, it became clear that the laparoscopic approach was superior to the abdominal one.[6] From a GRADE point of view, many outcomes in this first trial would have most probably been classified as *high quality*, signifying that it is unlikely that further research will have an effect on the outcome. Thus, to avoid negatively interfering with the further development of a surgical technique, it is essential to interpret the results of the GRADE method in the right context.

Another limitation of the GRADE approach is that it is primarily designed for RCTs. When non-RCTs are included in the framework, the level of evidence is immediately downgraded, leading to an overall *low* or *very-low* quality of evidence. Since the introduction of evidence-based medicine, RCTs have been considered as the highest and most reliable study design. Although RCTs do indeed have advantages (e.g. the elimination of confounders), RCTs are for certain outcomes not always appropriate. For example, for rare complications, RCTs are often underpowered and large cohort analyses are much more relevant, provided that potential bias is taken into account. In **chapter 3** we observed this as well: RCTs alone did not demonstrate a difference between LH and VH for the risk of vaginal cuff dehiscence, that was only found in the overall analysis. In general, in our opinion, doctors but also clinical researchers and guideline-developers should more structurally incorporate the outcomes from large databases and should for this purpose take advantages of the increasing possibilities of information technology (IT) and big data. In the same line, the GRADE method, but also the Cochrane group, should consider cohort analyses from (national) large well-designed databases as a valid research tool, rather than focusing on RCTs only. Therefore, an adapted GRADE tool should be developed for the evaluation of surgical innovation.

The above points of criticism towards the GRADE method have been raised previously.[7] The GRADE working group has replied to this criticism by stating that their proposed method should be considered as a framework to get systematically insight into the quality of the available evidence, and that the process of translating this evidence into recommendations should be an open discussion. The GRADE working group stated that 'different expert panels may come up with somewhat different strength of recommendations based on the same body of evidence given variation in their clinical and socioeconomic settings and population of interest, and valued judgments'.[8] The level of evidence is thus not the same as the strength of the recommendation.[8] This idea is underlined in this thesis when looking firstly at the policy regarding the standard use of a cystoscopy after LH. The guideline of the American Association of Gynecologic Laparoscopists (AAGL)[9] recommends

considering routine cystoscopy after every LH while in the Netherlands, based on the same literature, we advise selective use (**chapter 2** and **chapter 5**). A second example is observed in **chapter 4**, where it was demonstrated that, although the LESS technique for hysterectomy is feasible, safe and equally effective compared to the conventional laparoscopic approach, it has no clinically relevant advantages. Yet, in certain parts of the world, mainly in Asia, the laproendoscopic single site surgery (LESS) technique has been widely implemented. In certain Asian hospitals, up to 80% of the laparoscopic surgery is done in this fashion.[10] These examples also demonstrate that evidence-based medicine is not as objective as we always claim and hope it is.

Despite the understanding of the origin of the *low* quality of evidence and the interpretation of these results, concerns were raised during the development of the guideline of LH (**chapter 2**) regarding the medico-legal impact of such a document. Although this guideline might indeed be used for liability issues, it is in our opinion a strength to have an 'official' document issued from our national medical society where the minimal requirements for LH are summarized. Furthermore, from medico-legal point of view, it can be assumed that if no Dutch documents are available, experts in court will most probably base their verdicts on other (European) guidelines or available literature. In Germany, France and Denmark similar guidelines have already been developed, again based on the same literature.[11;12;13] Yet, as discussed previously, the strength of the recommendations and the considered topics may vary according to the settings. As a result, we believe that it is a must to have a guideline tailored to the Dutch practice.

Besides the medico-legal aspects, a national guideline for LH is of additional value for the professionals (e.g. the gynecologists) as it provides an overview of the best practices for the procedure at issue. With the additional research performed thereafter in this thesis, most actual topics of LH have been covered and standardized. However, the job is not finished: as the LH technique keeps evolving, new clinical challenges will most certainly be faced. Surgical innovation is a dynamic process and therefore it is essential, for the surgical field in general, to keep evaluating the outcomes of surgical procedures.

Implementation of a new surgical technique

As already mentioned in the introduction, implementing surgical innovations is one of the most complex dilemmas in medicine. In **chapter 10**, we studied the newly-introduced uterine-sparing techniques for fibroid treatment and demonstrated that, compared to the conventional approaches such as myomectomy and embolization, the re-intervention risk after High Intensity Focused Ultrasound (HIFU) was associated with the least promising

results. Also, for most recent introduced uterine-sparing techniques such as Radio-frequency Ablation (RFA), we observed that long-term data were lacking. It is important to realize that most techniques described in **chapter 10** were FDA approved and were, despite the lack of evidence, not limited to clinical trials anymore. As a result, systematic data collection remains essential and long-term data are urgently needed.

In the same line, the power morcellator is one of the instruments that was rapidly introduced and of which an important limitation was overlooked, partly because of lack of long-term surveillance. It seems that for this specific example, history is repeating itself. Indeed, after the press release of the Food and Drug Administration (FDA) in 2014,[14] gynecologists and medical device industries have sought to develop techniques to reduce the risk of potential spread while conserving the benefits associated with the laparoscopic approach. Contained tissue extraction has been suggested as solution and in many clinics this technique with a bag has been rapidly adopted. However, these bags are being introduced off-label and again without proper systematic evaluation prior to implementation. In addition, in the Netherlands at least, no national registration system is currently in place which will allow for data analyses over time. Yet, it is absolutely necessary to collect (national) data as it is questionable if this contained tissue extraction technique is for example for myomectomy safe from oncological point of view, as we discussed in **chapter 8**. Even during abdominal myomectomy without morcellation, micro-spillage of tissue was observed in the abdomen. Although the clinical relevance of tissue dissemination at this level is unclear, it cannot be concluded that it is harmless.

Ideally, the outcome measures of all (laparoscopic) surgical procedures in the Netherlands should be registered in a similar way as done in the Scandinavian countries or by the Dutch Institute for Clinical Auditing (DICA). An argument in favor of such large registration system was underlined in **chapter 9**, where we observed that for laparoscopic myomectomy (LM) of more than 500 grams, conversion risk significantly increased. These conclusions were based on data from a large center in the United States. Looking at the number of myomectomies performed yearly in the Netherlands, such conclusions could have only been drawn by collaborating between hospitals. A national registration system will give us more insight into our general performance and will allow us to make the necessary improvements. The DICA has already proven that their yearly audits significantly improve quality of care.[15] For the field of benign gynecology in the Netherlands, the current system in place does not result in structural data collection, in the first place as data collection is not done automatically and is not mandatory. A first step was made in April 2017 though, when the Dutch government passed a law obliging all medical implants to be registered in a national system.[16] Yet, an additional crucial step for a successful registration is in our

opinion, a simple and user-friendly system. We therefore plea for a high-tech registration system supported by professional ICT resources, even though this is a financial investment.

Evidence-based medicine: measuring outcome

Besides appropriate data collection, adequate interpretation and evaluation is as essential. In all medical fields, standards to determine as objectively as possible the benefits of provided care have been proposed according to the principles of evidence-based medicine. It is almost needless to state that this evidence-based approach has made the medical field progress to unprecedented levels. When looking at history, it is interesting to realize that the term evidence-based was only introduced for the first time 30 years ago. The evidence-based principle was an answer to the wide practice variations observed in health care at that time and a manner to use current evidence in making decisions about the care of individual patients.[17] Evidence-based has become since then the watchword in all medical fields as it has been further embedded in medicine over the past decades. However, evidence-based medicine also has its drawbacks, of which we should be aware when evaluating the provided care.

In 2014 Greenhalgh et al. published the first article denunciated the unintended consequences of evidence-based medicine.[18] In 2017, in the Netherlands, the Council for Public Health and Society (*Raad van Volksgezondheid*) came up with a report on the same topic.[19] In those two publications, it was criticized that evidence-based medicine has become nowadays an authority on its own and that, consequently, doctors are often afraid to handle outside the established guidelines. This also results in the fact that the wishes of the patients are often regarded as secondary. Yet, it is important to realize that guidelines are often an over-standardization of care and are not applicable to every individual patient. Another major point of criticism of the evidence-based methodology is that it is primarily driven by statistics and p-values. As a result, there is a tendency to choose numerical outcomes measures such as blood loss, operative time and hospital stay when determining the treatment with the most benefits. This was also the case in **chapter 3** and **chapter 4**. Though, statistical differences in surgical outcomes are not necessarily clinically relevant and of (direct) influence for the patients. While for example from a statistical point of view a difference in blood loss of 50 mL can be relevant, it will probably go unnoticed for the patient. In contrast, a post-operative anemia or the need of a blood transfusion is much more relevant for daily clinical practice.

According to the Dutch report on evidence-based medicine, evidence should be individualized by applying the available evidence in the right context, i.e. *context-based*

medicine. Not only standards should be considered when deciding upon a treatment option but factors related to the patient, the doctor and their environment deserve as much attention. An example of *context-based medicine* was described in **chapter 6**, where we observed that the guideline regarding urinary catheter management after LH was not in line with the opinion of the working floor, i.e. the nurses. A total of 78% of the Dutch hospitals removed the urinary catheter one day after surgery, while 90% of the surveyed nurses believed that direct catheter removed was feasible and 78% would recommend it to a family member or friend. Evidence-based medicine should definitely not be abandoned but other aspects should be additionally considered, even though the statistical support might be less evident. All in all, doctors, nurses and patients should have a more critical approach towards the evidence provided from statistics. Additionally, more attention should be drawn towards relevant outcomes.

In 2006, the concept of *Value-Based Health Care* (VBHC) was introduced by Michael Porter and Elizabeth Olmsted Teisberg.[20] This theory proposes to evaluate medical treatment options based on patient reported outcome measures (PROMs). In that context, we evaluated in **chapter 10** the re-intervention risk after initial therapy and the long-term quality of life of different uterine-sparing techniques, two outcomes that seemed from a patient point of view relevant. Similarly, in **chapter 12**, we evaluated the medical claims filed by patients undergoing a laparoscopic gynecologic procedure. Although we did not directly assess the PROMs, evaluating the claims allowed us to get insight into care judged by patients as being substandard. Understanding the reasons for filing a claim can concomitantly help to improve the quality of care. Also, in **chapter 11**, suggestions were formulated to optimize the postoperative period at home after a minimally invasive procedure. A well-organized postoperative period can be of great value for the patients and also from a financial point of view. In addition, to assure an optimal postoperative recovery and increase patient satisfaction, every aspect of the process should be carefully evaluated. With this in mind, we researched in **chapter 7** the best moment to remove the urinary catheter after LH. Based on the findings of our RCT, immediate catheter removal was recommended as (new) standard practice after LH. Changing catheter policy after LH at a national level may seem a detail in the entire postoperative care process, though it can be of great influence for a patient and her recovery. Although VBHC also has its drawbacks, this concept has given new dimensions to the evaluation of health care and has accelerated the implementation of patient-oriented care.

From the perspectives of VBHC, the financial aspect also plays a crucial role when evaluating the provided care. VBHC aims to maximize patient outcomes for every euro spent. Determining the costs in health care is a complex subject as it is difficult to give

health a financial value. Additionally, data of the actual treatment costs are often not available due to a lack of transparency and differences in agreed prizes between the different hospitals and the health insurance companies. In the discussion comparing VH to TLH (chapter 3), the cost-effectiveness of the procedures is often being brought up as an argument in favor of VH. However, for the Netherlands, no financial data are available on the exact difference between the two surgical approaches. Similarly, in chapter 4, where LESS hysterectomy was compared to conventional LH, data on cost effectiveness were not available either. Although complex political issues might be of influence, additional insights into health care finances in general is absolutely necessary to strengthen the debate regarding the quality of care and even help deciding upon the best treatment.

Conclusion

With this research, we attempted to evaluate clinically relevant aspects of MIS in gynecology and to formulate best practices. For LH, different relevant surgical topics have been covered including an evaluation of the different minimally invasive surgical techniques, the utility of cystoscopy and the best moment to remove the urinary catheter after surgery. These best practices should all together lead to a uniform implementation of LH in the Netherlands. For LM, different topics were evaluated as well, including the potential risks associated with contained tissue extraction and the relative efficacy of LM compared to other uterine-sparing treatment options for fibroids.

Finally, different aspects of MIS were evaluated from patient's perspectives. Outcomes related to patient experience will in our opinion become increasingly important in healthcare in the future. As the MIS technique keeps evolving, we will most certainly face new clinical challenges in the field of gynecology. It is therefore essential to continue monitoring at a national level our procedures based on relevant outcomes only.

Future perspectives

Standardization of care has been proven beneficial from a quality point of view but also for cost reduction. With the development of the guideline for LH a first step towards standardization is made in the field of MIS. With the continuous development of new technology, we would recommend writing similar documents for other surgical procedures, such as LM but also vaginal or abdominal hysterectomy. In addition, an efficient, critical and systematic evaluation of the provided care should take place on a regular basis at a national and local level. In this context, we cannot longer ignore the urgency to systematically collect data for the entire country. Measurement brings knowledge and with the increasing development of information technology (IT), data are easily available. Cohort analyses from large national uniform registration systems should be, at least for surgical innovations, considered as high quality research.

Over the past decades, the introduction of a couple of innovations and techniques in the field of MIS has been inadequate as certain negative outcomes were overlooked. Although not every risk can be anticipated, the introduction of new technology should be more controlled than it has been so far. For a small country as the Netherlands, we would recommend coordinating the implementation of surgical innovations at a national level. Rather than having individual hospitals introducing these new technologies by themselves, expertise should be combined. For this national coordination, we would suggest creating an independent board of experts, who would formulate recommendations regarding the implementation of new technique or technology and perform a PRI that can be shared among hospitals. Meanwhile, surgeons should only be allowed to introduce the innovation in their hospitals in the context of the terms set at national level. One of the main criteria should be that early adopters have the obligation to track outcomes, including outcome measures taking patient's perspectives into consideration. We are aware that creating such a national collaboration is challenging. Yet, we believe that centralizing the introduction of surgical innovations is worth the effort and investment. Unsafe practice will probably be detected earlier and might in the future prevent emotionally driven media attention as we have seen in the past.

In all fields of medicine, challenging clinical topics will always be encountered. To address these issues, the evidence-based approach should remain. However, evidence-based medicine also has limitations that need to be recognized. Specifically for the GRADE assessment, a new system for evaluating the level of evidence of surgical procedures should be developed, and in this new model, we advise a different approach towards the position of cohort studies in relation to randomized controlled trials, since RCTs are not always the best way to answer research questions.

For the practicing doctors, it is important to be continuously aware that the evidence-based approach is primarily based on statistics. As such, it may focus on irrelevant measurable outcomes rather than on outcome measures that are directly relevant for the individual patient. The introduction of VBHC is a revolutionary step in determining valuable care and should be further explored. With the introduction of national databases and the collection of patient specific outcomes, we see great opportunities for providing care that is tailored to a specific patient population.

Finally, the expertise of the doctor and the preferences of the patient should be much more valued that they have been over the last decades. High quality of care can only be provided by shared decision making, i.e. based on a permanent dialogue between the individual patient and his/her doctor supported by evidence from relevant outcome measures. Interestingly, this is exactly in accordance with the first definition of evidence-based medicine formulated thirty years ago.

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Chapter 14

Summary
Samenvatting

Summary

Over the past decades, minimally invasive surgery (MIS) has been widely implemented in the field of gynecology.[1] Compared with open surgery, MIS is associated with relevant advantages such as decreased postoperative pain, shorter hospital stay and reduced number of (wound) infections.[2] Because of these advantages, the MIS approach is nowadays often considered as the self-evident technique of many surgical procedures.

However, as this surgical technique was introduced so rapidly, it is probable that surgeons have developed policies based on their own expert opinion, resulting most probably in medical practice variation between hospitals and/or surgeons. In a time period of increasing transparency and strive for standardization, these *expert-based* medical practices should be addressed and sufficient scientific support for medical management should be provided. In this thesis, we concentrated on clinically relevant topics within the field of minimally invasive gynecology and formulated best practices for these issues.

Firstly, we focused on laparoscopic hysterectomy (LH), a complex MIS procedure in gynecology. The ultimate goal was to cover all (technical) aspects of LH and to standardize the steps of this procedure. As such, we developed, in collaboration with the Dutch Society of Endoscopic Surgery (WGE), an evidence-based guideline providing insight into best practices for LH. To assess the quality of the available evidence, the GRADE method was used. In **chapter 2** a summary of the guideline is provided. A considerable finding during the development of the guideline was the fact that the quality of the available evidence was frequently graded as *low* or *very low*.[3] This was partly attributed to the limited available evidence but, interestingly, we also discovered that the GRADE method itself has several important limitations. It even seems that the GRADE method is not an appropriate tool to assess the quality of surgical outcomes. This insight was essential to consider in **chapter 2** when formulating recommendations for LH. With the development of the guideline of LH, we got insight into clinical relevant topics with insufficient evidence. In this thesis, we performed further research on some of these issues (**chapter 3** to **chapter 7**).

In **chapter 3**, we focused on the best surgical approach for hysterectomy, which has been a matter of debate ever since LH was introduced. According to the Cochrane review, vaginal hysterectomy (VH) should be, when feasible, the first choice of approach.[2] Though, looking at current trends in practice, the rate of performed LH often surpasses the rate of VH.[1;4;5] As a result, we compared in **chapter 3** these two procedures, based on up to date literature and with the inclusion of cohort studies in addition to randomized controlled trials. Our findings demonstrated that the differences between LH and VH have become minimal over time but that VH still offers more relevant benefits and should remain the

surgery of first choice for benign hysterectomy. In **chapter 4**, a similar systematic review was performed where we analyzed the benefits of laparoendoscopic single site surgery (LESS) over LH. Although our findings showed that the LESS technique is feasible, safe and equally effective compared to the conventional approach, no clinically relevant advantages were identified. As a result, there are at the moment insufficient valid arguments to broadly implement LESS approach.

In **chapter 5**, we focused on the utility of cystoscopy after LH. We retrospectively analyzed a cohort of 1982 patients who had undergone a hysterectomy with or without cystoscopy at the end of the surgery. Of the observed urinary tract injuries, none had been detected by direct cystoscopy. However, most injuries were thermal and consequently could never have been discovered during surgery. As a result, we recommend selective instead of standard use of cystoscopy after LH.

In **chapter 6 and 7**, we evaluated post-operative indwelling catheter management. In **chapter 6**, we demonstrated that most Dutch hospitals (78%) removed the urinary catheter one day after surgery, despite the lack of scientific support for this regimen. In addition, the results of a nurse survey revealed that 78% of the nurses would recommend direct removal to a family member or friend. In **chapter 7**, the results of a non-inferior randomized controlled trial are presented that compares direct catheter removal after LH to delayed removal. A higher rate of bladder retention was observed after direct catheter removal (13% versus 0%). Though, direct removal had other advantages, such as a lower risk of urinary tract infection and a faster postoperative mobilization. As a result, direct catheter removal after LH is recommended as the advantages outweigh the risk of bladder retention.

In the second part of the thesis, we concentrated on laparoscopic myomectomy (LM) (**chapter 8** to **chapter 10**). In **chapter 8**, we performed perintoneal washings after abdominal myomectomy and demonstrated that even after these open procedures, micro-spillage of tissue in the abdomen occurrs. This finding shed new light in the current debate regarding the use of contained tissue extraction during MIS. Although the clinical relevance of tissue dissemination at microscopic level is not yet clear, it is questionable if contained tissue extraction is for myomectomy safe at all from oncological point of view.

In **chapter 9**, we studied the risk factors associated with conversion to open procedure in LM, based on a cohort of 966 patients. We observed that myomectomy with fibroids weighing more than 500 grams are associated with an increased risk of conversion (0.5% to 4.2%). These cases should be preferably referred to skilled surgeons in expert-centers.

Besides myomectomy, a wide range of uterine-sparing treatment options have become nowadays available for women desiring uterine preservation. In **chapter 10**, the relative

efficacy of these different techniques was evaluated in a meta-analysis by comparing long term re-intervention risks and quality of life after treatment. Although it often seems that the newest technique must be associated with the best results, we demonstrated that re-intervention risk after High Intensity Focused Ultrasound (HIFU) is not necessarily encouraging. All surgeons using these newest techniques should urgently collect long term data as these are currently lacking, even though all these techniques have been FDA approved.

In the final part of the thesis, aspects of MIS were evaluated from patient's perspectives. With the reduced length of stay associated with MIS procedures, it can be challenging to maintaining vigilance in the post-operative period where no direct medical surveillance is available. In **chapter 11**, recommendations are provided to optimize postoperative recovery. Additionally, to determine care that is being judged as substandard by patients, we performed in **chapter 12** an analysis of the medical claims for the field of MIS in gynecology. Delay in recognizing a postoperative adverse event was the most encountered reason for granting financial compensation in litigation cases.

With this thesis, clinical relevant issues within the field of minimally invasive gynecology were identified and best practices were formulated. As the MIS techniques further evolve, new challenges will inherently be faced. It is therefore essential to keep evaluating the clinical outcomes of (new) surgical techniques. Over the last 30 years, the principles of evidence-based medicine have served as guidance for that purpose. However, these principles, including for example the GRADE approach, need to be critically assessed as well. In **chapter 13**, the drawbacks of evidence-based medicine are discussed and suggestions are made. Firstly, we recommend to only study outcome measures that are directly relevant for the patients and not to concentrate on clinically irrelevant statistics. Secondly, data should be collected at a national level to allow for proper evaluation of the provided care. In that light, randomized controlled trials should not be the only focus. Finally, the expertise of the doctor and the preferences of the patient should be much more taken into consideration than they have been over the past decennia. In conclusion, to formulate best practices, i.e. to provide the highest quality of care, a permanent dialogue between the individual patient and his/her doctor is essential, in combination with the support of relevant evidence-based data. Interestingly, this is exactly in accordance with the first definition of evidence-based medicine formulated thirty years ago.

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Samenvatting

De afgelopen decennia is de minimaal invasieve chirurgie (MIC) breed geïmplementeerd binnen de operatieve gynaecologie.[1] In tegenstelling tot 'open chirurgie', wordt bij de MIC techniek geopereerd via een aantal kleine incisies en met gebruik van een camera die beelden op een scherm projecteert. Deze minimaal invasieve benadering, ook wel laparoscopie genoemd, kent veel voordelen, zoals verminderde pijn postoperatief, een kortere opnameduur en een lager risico op (wond)infectie.[2] Hierdoor wordt MIC tegenwoordig bij veel ingrepen gezien als de benadering van eerste keus.

Deze laparoscopische techniek is echter zeer snel en massaal geïmplementeerd, waardoor mogelijk een gebrek aan uniformiteit van uitvoering is ontstaan. Doordat chirurgen hun eigen individuele *best practices* hebben ontwikkeld, ligt praktijkvariatie op de loer. Hoewel praktijkvariatie niet per definitie slecht hoeft te zijn, is het zaak, om in een tijdperk waarin gestreefd wordt naar transparante (en vaak gestandaardiseerde) zorg, deze *expert-based* verschillen in geleverde zorg te onderkennen en te evalueren. Dit is in het bijzonder relevant om de kwaliteit van zorg van geavanceerde en nieuwe technieken, zoals in MIC, te verbeteren. Het doel van dit proefschrift was dan ook om klinisch relevante onderwerpen binnen de laparoscopische gynaecologie te bestuderen en de MIC waar zinnig te standaardiseren. Er werd getracht wetenschappelijke onderbouwing te leveren voor klinisch relevante onderwerpen waar gebrek aan consensus bestond.

In het eerste deel van dit proefschrift lag de nadruk op de laparoscopische uterusextirpatie (baarmoederverwijdering middels kijkoperatie, hier verder laparoscopische hysterectomie (LH) genoemd). Deze meest uitgevoerde geavanceerde MIC ingreep werd in Nederland voor het eerst in 1991 uitgevoerd. Omdat er tot op heden geen Nederlandse richtlijn beschikbaar was over deze ingreep, werd samen met de Werkgroep Gynaecologische Endoscopie (WGE) besloten een evidence-based richtlijn voor de LH te ontwikkelen. Het doel was om de LH op zinvolle punten te standaardiseren en inzicht te geven in haar *best practices*. In **hoofdstuk 2** wordt een samenvatting van deze richtlijn weergegeven.

Een belangrijke bevinding tijdens het ontwikkelen van deze richtlijn was dat de kwaliteit van het wetenschappelijke bewijs waar vervolgens de aanbevelingen op werden geformuleerd, over het algemeen *laag* tot *zeer laag* was. De kwaliteit van het bewijs werd beoordeeld aan de hand van de GRADE-methode, een internationaal erkend instrument om systematisch de methodologische kwaliteit van een uitkomst te bepalen.[3] Tijdens de ontwikkeling van de richtlijn ontdekten wij, dat de GRADE-methode zelf ook beperkingen had, die in acht moesten worden genomen bij het formuleren van gepaste aanbevelingen voor een chirurgische techniek. Daarnaast heeft deze richtlijn ons inzicht gegeven in de

klinisch relevante deelonderwerpen van de LH waar nog onvoldoende wetenschappelijk bewijs voor beschikbaar was. In **hoofdstuk 3** tot en met **hoofdstuk 7** werden deze onderwerpen nader bestudeerd.

Een terugkerend discussiepunt binnen de MIC gynaecologie is welke chirurgische benadering de eerste keuze is bij een baarmoederverwijdering. De Cochrane review over dit onderwerp concludeerde dat de vaginale benadering de voorkeur heeft boven de LH.[2] In Nederland echter, laten de meest recente cijfers zien dat er tegenwoordig meer LH's uitgevoerd worden dan vaginale hysterectomieën.[1] Deze trend wordt ook gezien in andere landen.[4;5] Om die reden werden in **hoofdstuk 3** de chirurgische uitkomsten van deze twee ingrepen vergeleken aan de hand van recente literatuur. Er werd niet alleen naar gerandomiseerde studies gekeken, maar er werden ook observationele studies meegenomen in de analyses. Uit onze review blijkt dat de verschillen tussen de twee ingrepen minimaal zijn geworden, maar dat de vaginale benadering nog steeds de meest relevante voordelen biedt. Hierdoor wordt de vaginale hysterectomie (vooralsnog) gezien als benadering van eerste keus.

Op dezelfde manier werd in **hoofdstuk 4** gekeken naar de voordelen van laparoendoscopic single site surgery (LESS) (toegang tot de buikholte voor camera en hulpinstrumenten via één incisie in de navelplooi) ten opzichte van de conventionele LH (naast incisie in de navelplooi ook meerdere kleine incisies in de onderbuik voor de hulpinstrumenten). Het blijkt dat de LESS techniek haalbaar is en even veilig en effectief als de conventionele LH, maar dat relevante voordelen ontbreken. Momenteel zijn er onvoldoende argumenten om voor de hysterectomie de LESS techniek breed te implementeren.

In **hoofdstuk 5** werd de toegevoegde waarde van een cystoscopie aan het einde van een LH bestudeerd. Hiervoor werd een retrospectief cohort geanalyseerd van 1982 patiënten die een LH hadden ondergaan met of zonder cystoscopie. Geen van de urinewegletsels uit het cohort werd ontdekt met behulp van de cystoscopie, en alle letsels die pas postoperatief ontdekt werden, waren van thermische aard. Thermische letsels ontstaan in het algemeen pas na een aantal dagen postoperatief en zullen dus ten tijde van de operatie bijna nooit gedetecteerd kunnen worden. Om die reden werd standaardgebruik van een cystoscopie aan het einde van een TLH niet aanbevolen.

In **hoofdstuk 6** en **hoofdstuk 7** werd het postoperatieve blaaskatheterbeleid geëvalueerd. Eerst werd gekeken naar het nationaal katheterbeleid na LH (**hoofdstuk 6**). Onze bevindingen lieten zien dat 78% van de Nederlandse ziekenhuizen de katheter een dag na de operatie verwijderen, ondanks het gebrek aan wetenschappelijk bewijs voor dit beleid. Ook werden in **hoofdstuk 6** de verpleegkundigen werkzaam op een gynaecologieafdeling

gevraagd om hun mening te geven over het postoperatieve katheterbeleid na LH. Uit de enquête kwam naar voren dat 78% van de verpleegkundigen een directe verwijdering van de katheter zouden aanbevelen aan een familielid of vriendin die geopereerd zou moeten worden. In **hoofdstuk 7** werd een gerandomiseerde studie uitgevoerd waarin het direct verwijderen van de katheter na LH werd vergeleken met vertraagde verwijdering. De groep waarbij de katheter direct werd verwijderd had een hoger risico op blaasretentie (14%). Desondanks wordt dit beleid aanbevolen vanwege de andere voordelen geassocieerd met directe katheterverwijdering (een significant snellere mobilisatie, een lager risico op urineweginfecties en geen klachten van de katheter waarvoor (vervroegde) verwijdering noodzakelijk was).

In het tweede deel van dit proefschrift werd gekeken naar de laparoscopische myomectomie (LM). Met deze ingreep worden via een kijkoperatie myomen (vleesbomen) verwijderd. Een LM kan technisch uitdagend zijn en vereist expertise van de operateur. In **hoofdstuk 9** werd gekeken naar de risicofactoren die geassocieerd zijn met conversie naar een laparotomie (open chirurgie). In een cohort met 966 patiënten zagen wij bij myomen van meer dan 500 gram een significant verhoogd risico op conversie (4.2% versus 0.5%). Wij adviseren dan ook om deze patiënten alleen te opereren in gespecialiseerde centra. In **hoofdstuk 8** werd geobserveerd dat zelfs bij open myomectomie (buiksnede) er sprake was van *spill* van myoomweefsel. Dit is een belangrijke bevinding gezien het huidige debat over de veiligheid van de power morcellator, in het bijzonder bij benigne ogende myomen die achteraf kwaadaardig blijken te zijn (sarcomen). Het is op dit moment nog onduidelijk wat de klinische relevantie is van de micro-spillage die gevonden werd in **hoofdstuk 8**. Echter, men kan zich afvragen of tijdens myomectomie het morcelleren in een zak überhaupt wel veilig is vanuit een oncologisch perspectief.

Naast het chirurgisch verwijderen van myomen, zijn er steeds meer verschillende minimaal invasieve behandelmogelijkheden beschikbaar geworden voor vrouwen met myomen met wens tot behoud van hun baarmoeder. In **hoofdstuk 10** werd gekeken naar de relatieve effectiviteit van deze verschillende technieken door specifiek het risico op re-interventie op lange termijn te evalueren evenals de kwaliteit van leven na behandeling. De nieuwste techniek wordt vaak geassocieerd met de beste resultaten. In onze meta-analyse werd echter gezien dat het risico op re-interventie na High Intensity Focused Ultrasound (HIFU) veel hoger was dan na meer conventionele behandelopties zoals myomectomie of embolisatie. Daarbij werd gezien dat, ondanks dat al de behandelopties goedgekeurd zijn door de Food and Drug Administration (FDA), langetermijndata ontbreken om een goed beeld van de gevolgen van deze (nieuwste) technieken te krijgen.

In het laatste deel van dit proefschrift werden MIC onderwerpen geëvalueerd vanuit patiëntperspectief. Wij zien dat door de verkorte ligduur door toepassen van MIC, patiënten tegenwoordig grotendeels thuis herstellen. Om de hoogste kwaliteit van zorg te kunnen waarborgen, vergt deze verandering de nodige aanpassingen. In **hoofdstuk 11** werden aanbevelingen gedaan om de postoperatieve periode in de thuissituatie zo optimaal mogelijk te laten verlopen. In **hoofdstuk 12** werden de medische claims na MIC ingrepen van de afgelopen twintig jaar in Nederland bestudeerd. Deze claims geven een uniek inzicht in wat door patiënten als suboptimale zorg wordt beschouwd. Dit hoofdstuk liet zien dat een vertraging in het herkennen van een complicatie de belangrijkste reden was om een patiënt financieel te compenseren.

Concluderend, met dit proefschrift is getracht om wetenschappelijk bewijs te leveren voor verschillende klinisch relevante aspecten van de laparoscopische hysterectomie en laparoscopische myomectomie. Deze nieuwe inzichten zullen moeten bijdragen aan het verder zinvol standaardiseren van de MIC zorg en het optimaliseren van de kwaliteit hiervan. Het is echter wel belangrijk zich te realiseren, dat het proces van verbetering altijd zal voortduren. Wanneer de chirurgische technieken in de MIC zich verder ontwikkelen, zullen zowel de clinicus als de wetenschapper geconfronteerd worden met nieuwe uitdagingen. Om die reden is het belangrijk om de uitkomsten van chirurgische ingrepen te blijven monitoren. De afgelopen dertig jaar hebben wij de geleverde zorg geëvalueerd volgens de principes van evidence-based medicine. In dit proefschrift (**hoofdstuk 13**) hebben wij ons echter gerealiseerd dat deze basisprincipes (inclusief de GRADE-methode) zelf ook kritisch bekeken moeten worden en een keerzijde kennen. Hierdoor zijn wij van mening dat evidence-based medicine zich in eerst instantie alleen moeten richten op uitkomsten die relevant zijn voor de patiënten en niet op irrelevante statistische uitkomsten. Daarnaast is het belangrijk, dat data op nationaal niveau worden verzameld. Tot slot, de expertise van de dokter en de voorkeur van de patiënt zouden weer een veel belangrijkere rol moeten gaan spelen in de gezondheidszorg. Alleen wanneer deze aspecten centraal staan, ondersteund door evidence-based medicine, kunnen wij adequate *best practices* formuleren en de hoogste kwaliteit van zorg leveren.

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Chapter 15

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Evelien Sandberg was born on April 26th 1987 in Guildford, UK. At the age of five, she moved to Belgium with her family. She attended a French-speaking primary and secondary school and graduated cum laude in 2005. After high school, she took an English course in Cambridge (UK) and visited Guatemala where she learned Spanish and volunteered for the Red Cross.

In 2006, she started medical school at Leiden University in the Netherlands. She studied for one semester at Karolinksa Institute in Stockholm, Sweden (2007) and did her ophthalmology internship in Pokahara, Nepal (2012). In 2009–2010, she interrupted her study to become the president of the student society Minerva. In 2011, she did a nine-month research internship at the Brigham and Women's Hospital, Boston, USA under supervision of Prof. Dr. J.I. Einarsson and Dr. S.L. Cohen. Her research project became the start of this thesis.

After graduating cum laude from medical school in 2014, she worked at the Bronovo Hospital as a resident not in training and worked for six weeks at the gynecology department of Mulago Hospital in Kampala, Uganda. In February 2015, she enrolled in a PhD program under supervision of Prof. Dr. F.W. Jansen, Dr. A.R.H. Twijnstra and, oversees, Prof. Dr. J.I. Einarsson. She combined her PhD with a part-time teaching position for medical students and obtained her Basiskwalificatie Onderwijs (BKO) certificate.

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It is always the small pieces that make the big picture

– Anonymous –

Thank you!