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Prospective Randomized Controlled Trial of Traditional Laparoscopic Assisted Vaginal Hysterectomy versus SILS™ Port Laparoscopic Assisted Vaginal Hysterectomy

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Abbreviations.

AE	Adverse Effects
AH	Abdominal hysterectomy
CISH	Classic Intrafascial Supracervical Hysterectomy
cLSK	Conventional laparoscopy
CRF	Case Report Form
DRG	Diagnosis Related Group
EC	Ethics Committee
IRB	Institutional Review Board
IUDS	Intrauterine devices
LAVH	Laparoscopic assisted vaginal Hysterectomy
MPA	Multiple port access
PI-NRS	Pain Intensity- Numerical Rating Scale
SILS	Single Incision Laparoscopic Surgery
SLH	Subtotal laparoscopic hysterectomy
SPA	Single port access
TLH	Total laparoscopic hysterectomy
VH	Vaginal hysterectomy

1 Introduction

Hysterectomy remains the most common major gynecological operation. By the age of 60, every fifth woman in the United Kingdom and every third woman in the United States has had a hysterectomy (1). Analyses of DRG data for the years 2005 and 2006 have shown that, in Germany, overall 3.6 per 1,000 women each year underwent hysterectomy for benign diseases of the genital tract (2).

Despite the introduction of alternative techniques for controlling abnormal uterine bleeding, such as endometrial ablation and the hormone-releasing intrauterine device, the rates of hysterectomy in the United States has not changed significantly over the years (3).

Factors beyond the incidence of genital tract diseases affect the rates of hysterectomy, such as the availability of gynecologists, the availability of hospital beds, the type of health-care insurance available, the social class of the patient and available information about the different treatment modalities among patients and gynecologists (2, 4).

1.1 Hysterectomy

1.1.1 History

Hysterectomy was first performed as a vaginal procedure by Langenbeck in 1813 in Gottingen, Germany. Abdominal hysterectomy (AH) was performed some years later, in 1843, by Clay, in Manchester, England. The technical evolution of AH abdominal hysterectomy underwent a number of stages until it finally reached the simplified extrafascial technique, published by Richardson in 1929, that has become the standard approach. (5, 6). Laparoscopic hysterectomy (LH), defined as the laparoscopic ligation of the major vessels supplying the uterus by electrosurgery desiccation, suture ligature, or staples, was first performed in 1988 (7). In 1991, Prof. Dr. Kurt Semm performed in university of Kiel, Germany, the first classic intrafascial supracervical hysterectomy (CISH), which he believes combines the advantages of supracervical hysterectomy with reducing the risk of cervical cancer (8). In 1993, Donnez developed the traditional laparoscopic hysterectomy in Belgium, which is still performed today (9).

1.1.2 Indication

Benign indications for hysterectomy are dysfunctional uterine bleeding, symptomatic or suspicious myomas, adenomyosis of the uterus, endometriosis and done in combination with prolapse surgery. The main indication for hysterectomy is often not clear, because of the presence of more than one indication in most of the cases. In Germany in 2012, the following frequencies of indications were recorded: myomas in 60.7%, prolapse in 27.9%, abnormal uterine bleeding in 25.2%, endometriosis in 15.1% and hyperplasia and atypia of the endometrium or the cervix in 2.9% (10). On the other hand, in case of malignancy, the indication is almost always a single clear indication.

Abnormal menstrual bleeding affects women of all ages and is the most common gynecological reason for referral to secondary care. Abnormal menstrual bleeding can be caused by fibroids, endometrial polyps or hyperplasia, adenomyosis, or malignancy. In many cases, no definitive diagnosis can be determined. Therapy options include hormone-releasing IUDs, combined contraceptives and endometrial ablation. A recent review showed that the hormone-releasing IUD is the first-line medical therapy for heavy menstrual bleeding, with combined hormonal contraceptives the second choice (11). Despite of the development of several new techniques for endometrial ablation, hysterectomy remains the only treatment that provides permanent symptom relief; thus, a rather large proportion of women with abnormal uterine bleeding prefer hysterectomy. This can explain why rates of hysterectomy have declined less than expected with the introduction of these new treatment modalities (12).

In the United States, 40% of hysterectomies are indicated because of fibroids. Together with abnormal uterine bleeding, they are responsible for 75 % of hysterectomies (13). Other therapy options can be offered; for example, hysteroscopic or laparoscopic removal of the fibroid, uterine artery embolization or medical treatment with a selective progesterone receptor modulator, which reversibly blocks the progesterone receptors in target tissues. Recently published data showed that a 12-week course of once-a-day oral progesterone receptor modulator therapy is effective in stopping uterine bleeding, correcting anemia and shrinking myoma volume. (14, 15)

Hysterectomy is a part of the surgical treatment of endometriosis. In cases of completed family planning and failure of other therapy options, only surgical options remain. Likewise, with adenomyosis, which presents itself with dysmenorrhea and hypermenorrhea, hysterectomy remains the most effective therapy (16, 17).

Atypical endometrial hyperplasia can change to endometrial cancer in four years in 25% of patients even under progesterone therapy (18, 19). Therefore, if family planning has been completed, hysterectomy is indicated. Otherwise, the only option remains progesterone therapy and regular follow-up with endometrial biopsy.

Hysterectomy is also done as a part of prolapse surgery, although this is not evidence based. Other therapy options for prolapse are conservative (such as physiotherapy, pessary, and lifestyle modification) or operative, through correction of the defective compartment (20). Whether vaginal, abdominal or laparoscopic hysterectomy is indicated depends on many factors, including diagnosis, BMI, planned intervention and surgeon’s experience.

1.1.3 Routes of hysterectomy

The surgeon's selection of a particular approach to hysterectomy depends on the indication for surgery, routine practice, patient preference, the level of informed consent, individual skill and experience with each surgical alternative, prior medicolegal conflict, published guidelines and established norms, and patient characteristics such as BMI and prior surgery (3).

A hysterectomy, regardless of the approach, is performed in seven consecutive steps. If these steps are accomplished vaginally, the procedure is called a vaginal hysterectomy. Similarly, the term abdominal hysterectomy indicates removal of the uterus through an abdominal incision.

The steps are as follows:

1. Bilateral desiccation or ligation and transection of the round ligaments and dissection of the broad ligament.

2. Bilateral desiccation or ligation and transection of the ovarian ligament or the infundibulopelvic ligaments with or without removal of the tubes.

3. Bilateral desiccation or suture ligation and transection of the uterine vessels.

4. Preparation of the bladder flap and severing the bladder pillars.

5. Bilateral desiccation or ligation and transection of the cardinal-uterosacral ligament complex.

6. Anterior and/or posterior culdotomy and removal of the uterus.

7. Closure of the vaginal vault (21).

Abdominal hysterectomy: Abdominal hysterectomy has traditionally been the surgical approach for gynecological malignancy, when other pelvic pathology is present (such as endometriosis or adhesions), and in the context of an enlarged uterus. It remains the “fallback option” if the uterus cannot be removed by another approach. Mini-abdominal hysterectomy refers to an approach to hysterectomy where the abdominal incision does not exceed 7 cm (22).

The frequency of abdominal hysterectomy is decreasing due to the increase over the years in laparoscopic, vaginal or combined procedures. Unfortunately, this affects the learning curve of the abdominal technique, in particular for younger colleagues. Abdominal hysterectomy is almost always indicated in complicated cases which are not suitable for training (10).

Vaginal hysterectomy: Vaginal hysterectomy is considered by some authors including the Cochrane review 2015 to be the gold standard in the era of minimal access surgery. (23) Some of the contraindications to vaginal hysterectomy can be overcome by assistance of laparoscope, allowing a potential abdominal hysterectomy to be converted to a vaginal procedure. Evidence-based studies support the use of vaginal hysterectomy, if possible, over laparoscopic and abdominal hysterectomy (24); for example, when the uterus is of fairly normal size. VH is still regarded as less invasive and seems to have the advantages of fewer blood transfusions, less febrile morbidity (fever) and less risk of injury to the ureter. However, the disadvantages include more bleeding complications and greater risk of bladder injury than with abdominal hysterectomy (25).

Laparoscopic hysterectomy: Laparoscopic hysterectomy is where at least part of the operation is undertaken laparoscopically. This approach requires general laparoscopic surgical skills. The main advantages are the possibility of diagnosing and treating other pelvic diseases such as endometriosis, of carrying out adnexal surgery (including the removal of the ovaries), the ability to secure intraperitoneal hemostasis and a more rapid recovery time from surgery compared to abdominal hysterectomy (26).

Three sub-categories of laparoscopic hysterectomy are as follows:

Laparoscopic-assisted vaginal hysterectomy (LAVH) is where part of the hysterectomy is performed laparoscopically and part vaginally, but the laparoscopic component of the operation does not involve division of the uterine vessels. Laparoscopic-assisted vaginal hysterectomy is simple and can be done without the need of learning new techniques. The operation has a low rate of complications and is easy to learn, but the operating time is longer and the procedure more expensive

Laparoscopic hysterectomy (which we have abbreviated to LH) is where the uterine vessels are ligated laparoscopically but part of the operation is performed vaginally. (27, 28).

Total laparoscopic hysterectomy (TLH) is where the entire operation (including suturing of the vaginal vault) is performed laparoscopically and there is no vaginal component except for the removal of the uterus. TLH requires the highest degree of laparoscopic surgical skills (23).

Robotic hysterectomy: In recent years, robotic-assisted laparoscopy has been introduced as an alternative to standard laparoscopy in the management of gynecologic diseases (29). In gynecologic oncology, robotic surgery may present some advantages compared with standard laparoscopy, such as magnified 3-dimensional vision, wristed instruments ameliorating dexterity, and improved surgical precision (30). The role of robotic surgery in the treatment of benign pathology remains controversial. Indeed, robotic hysterectomy is associated with cost augmentation and worse esthetic results when compared with standard laparoscopy, with similar perioperative outcomes (31).

Single-port laparoscopic hysterectomy and **mini-laparoscopic hysterectomy**: In the last decade, single-port laparoscopic hysterectomy SP-LH and mini-laparoscopic hysterectomy (where the incisions do not exceed 3 mm) have been introduced into the endoscopic field (32).

Surgical efforts since then have focused on maximizing the profits of minimally invasive surgery by reducing the number and size of abdominal wall incisions (33). In recent years, laparoendoscopic single-site (LESS) surgery has emerged as a growing trend in minimally invasive surgeries, including total hysterectomy. Single-port access is preferred among women undergoing gynecologic surgery who have cosmetic concerns about skin incisional scarring. Furthermore, these approaches result in clinical outcomes comparable to standard laparoscopic surgery, and perioperative morbidity rates have been reported to be low (34).

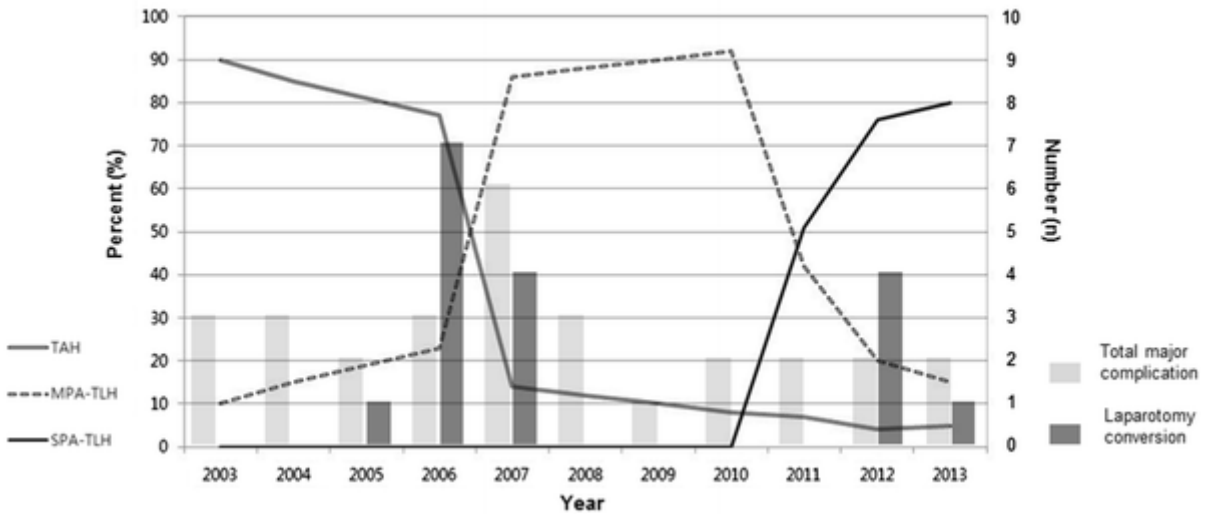

Figure 1-1: The Rate of Operation in Group of TAH, MPA-TLH, SPA-TLH in Daejeon St. Mary's hospital from 2003 to 2013. (34).

1.1.4 Complications

Table 1-1 shows the rate of complications in different routes of hysterectomy on Finland and Germany 2011-2012.

Possible complications of hysterectomy include intraoperative complications like bleeding, injury of the bladder or the ureter, and intestinal injury; or postoperative complications like bleeding, infections, hematoma formation or wound dehiscence.

FINHYST 2011 (Complications)		*n* = 5,279 (%)	AQUA 2012 (complications)	*n* = 103,232 (%)
Blood loss > 1000ml	AH LH VH	5.7 3.0 1.6	Blood loss > 1000ml	
Bladder injury	AH LH VH	0.9 1.0 0.6	Bladder injury	0.59
Ureter injury	AH LH VH	0.3 0.3 0.04	Ureter injury	0.09
Intestinal injury	AH LH VH	0.2 0.4 0.1	Intestinal injury	0.23
Postoperative bleeding or hematoma	AH LH VH	2.6 2.7 2.8	Postoperative bleeding or hematoma	0.94
Ileus	AH LH	1.0 0.3	Ileus	0.09
Wound infection	AH LH VH	2.4 1.5 0.9	Wound infection	

Table 1-1: FINHYST-Study: n = 5,279. Distributed as 1,255 AH, 1,679 LH and 2,345 VH in Finland 2006; AQUA in Germany 2012: n = 103,232 Hysterectomies, (10)

The AQUA-Institutes GmbH stated that in Germany in 2012 the complication rate was 5.4%; 1.4 % intraoperative and 4.0% postoperative complication. (35). The FINHYST study shows the complication of hysterectomies in Finland in 2011 (36).

1.2 Single-port Surgery

Recently, the innovation in technology and techniques allows the surgeon to employ a more minimally invasive surgical approach than traditional laparoscopic surgery. Single-port access (SPA) laparoscopic surgery is one such innovative technique.

Single-port laparoscopic surgery has been described in the literature using a number of terms, including *single-port access surgery (SPA)*, *single-incision laparoscopic surgery (SILS)*, *embryonic natural-orifice trans-umbilical endoscopic surgery (E-NOTES)*, *trans-umbilical endoscopic surgery (TUES)* and *laparo-endoscopic single-site surgery* (LESS surgery) (37).

1.2.1 History

Single-port laparoscopy is not new. It has been around for more than 30 years. Gynecologists have been doing tubal ligation with a single-puncture laparoscope

since the late 1970s (38). Appendectomies were done with a single puncture as early as 1992 (39). The single-incision but multi-port technique was described in 1997 (40). When low-profile and short trocars were used in this technique, they would reduce the clashing of the instruments close to the abdominal wall. The understanding was that going through separate fascial defects at a slight distance from each other increased the maneuverability of the working ports and negated gas leakage. The obvious disadvantage was that the “Swiss cheese” defects left behind could be difficult to close securely (41). Single-incision total hysterectomy was also reported in the early 1990s (42). Single-port surgery then resurfaced in general surgery in 2007 when the experience with single-port cholecystectomy was reported. This and other similar reports sparked interest among other surgeons and within the industry to further develop this field. This, in turn, led to a renewed interest in gynecologic single-port surgery in recent years (43)

1.2.2 Ports

Home-made access ports which use surgical gloves for abdominal access are a cheap solution but have limitations due to the loose grip in the abdomen and loss of gas during the manipulation. On the other hand, the commercially available ports offer various solutions for abdominal access some of which are pictured in Figure 2.

Figure 1-2: Access Ports: (A) AirSeal port (SurgiQuest, Orange, CA) (B) SILS port (Covidien, Mansfield, MA) (C) TriPort multichannel access port (Advanced Surgical Concepts, Ireland) (D) GelPort laparoscopic system (Applied Medical, Rancho Santa Margarita, CA) (37)

AirSeal (SurgiQuest, Orange, CA): The advantage of the AirSeal port is that it allows smoke elimination. It also allows access to multiple instruments. The major disadvantages are the noise of running air and the absence of a fulcrum point since the device is open at the instrument entry site (37).

GelPort. (Applied Medical, Rancho Santa Margarita, CA): The advantages of the GelPort system include the versatility of the GelSeal cap, which allows placement of wide range of instruments, and the 10-cm diameter of the outer ring, which reduces instrument crowding (44).

TriPort and QuadPort (Advanced Surgical Concepts, Co. Wicklow, Ireland). The TriPort and QuadPort systems have several advantages; they are easily introduced, and multiple instruments can be placed and removed without loss of pneumoperitoneum. They can also fit a wide range of depths of abdominal wall, and the angle of the different ports helps reduce instrument crowding.

X-Cone and Endocone (Karl Storz, Tuttlingen, Germany): The X-Cone and Endocone are reusable ports, so they offer reductions in cost. The devices offer well-fixed access in the abdomen and, when used with curved instruments, reduce the loss of triangulation (37).

SILS Port Covidien (Mansfield, MA): The SILS port is a flexible laparoscopic port, which necessitates a fascial incision of 1.8 – 3 cm and can accommodate up to 3 instruments through a single incision. It requires open laparoscopy for introduction but offers a good solution to the crowding of instruments through its low-profile trocars. It also allows 10 mm trocars.

Comparison of Ports

Table 1–2 presents a comparison some of the characteristics of the different ports.

Port	Multiple Standard Trocars	SILS™	TriPort™	AirSeal DFS™
Manufacturer	Multiple	Covidien	Advanced Surgical Concepts (distributed by Olympus)	SurgiQuest
Lumen number (size)	2 or 3 (5 mm)	3 (1×12 mm; 2×5 mm)	3 (1×12 mm; 2×5 mm)	1 (12, 18, or 25 mm)
Fixation mechanism	Friction	Flexible soft-foam port	Inner/outer rings	Pressure barrier
Incision	10–20 mm	15–20 mm	12–25 mm	12–25 mm
Pros	Potentially cheaper if reusable trocars are used	Durable, facilitate port placement	Flexible port allows fascial incision tailored to size needed	Single opening platform allows instrument of diff. sizes
Cons	Bulky trocars may limit maneuverability inside and outside abdomen; may leave fascial defect difficult to close	Slightly larger fascial incision needed to accommodate port	Gel valve ports may need lubrication to allow instrument passage; air leakage through gel valves	Pressure barrier created is noisy

Table 1-2: Comparison of Ports (45)

1.2.3 Advantages

The most apparent benefit of single-port surgery is improved cosmetic outcomes with the surgical incision hidden in the umbilicus. However, the benefits of single-port procedures may extend beyond cosmetics to include reduced pain, reduced operative complications related to trocar insertion (e.g., hernia, hematomas, inferior epigastric artery injury and wound infection), and easier specimen removal through a larger incision (43).

Single-port surgery requires a smaller number of incisions than conventional laparoscopy. Importantly, the single port is often installed in the umbilical area where

there are no muscles, so this technique minimizes abdominal muscle injury and the associated postoperative pain (45).

Studies have demonstrated single-port surgery to have multiple advantages over multi-port or open procedures, including shorter hospital stays, faster recovery times, better cosmetic outcomes, and reduced postoperative pain (46).

1.2.4 Limitations

Single-port access surgery has several limitations, including breakdown of triangulation, in-line view, crowding of surgical instruments, “sword-fighting” between instruments, and others, which are less common in multi-port surgery. The use of multifunctional, articulated and/or curved instruments helps to reduce this problem(47).

1.2.5 Technique

New instruments and camera systems offer a variety of solutions to overcome the limitations of single-incision laparoscopic surgery. For example, the use of the flexible EndoEye™ or deflectable telescope (The Olympus deflectable-tip EndoEYE video laparoscope (Olympus America, Center Valley, PA)) to reduce the bumping of instruments or the use of curved or articulating instruments to regain the triangulation. Also, the use of multifunction high frequency instruments such as LigaSure™ or Thunder beat™ decreases the operative time and the need to change instruments but, on the other hand, increases the cost.

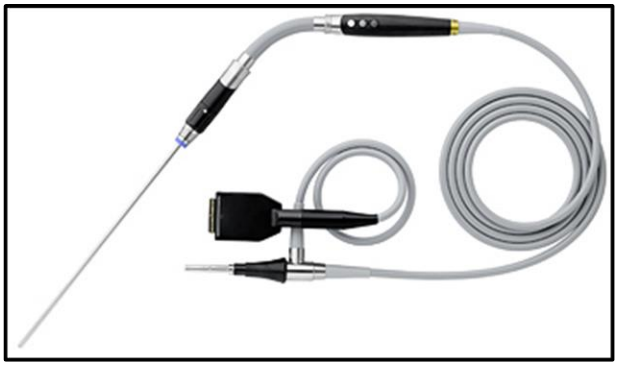

Figure 1-3: EndoEYE LS Laparo-Thoraco Videoscope http://www.olympus-global.com/en/news/2009b/nr091013lesse.jsp.

1.2.6 Problems and Solutions

Table 1-3 shows some of the expected problems and how to avoid them.

Problem	Solution
Damage to light fiber of conventional laparoscope	Use optic with coaxial light fiber (e.g., EndoEye TM)
Clashing of telescope with instruments	Use of deflectable tip telescope
Loss of triangulation	Use of articulating or pre-bent instruments
Clashing of trocars within the abdominal cavity and outside	Use of low profile trocars/short trocars
Multiple incisions unsightly, concern about sheath closure, herniation	Use of access device with single incision (Triport, Quadport, SILS port, XCone)
Clashing of camera head with instruments	Use optic with chip on tip (e.g., EndoEye TM), use long telescope, make assistant sit, hands in a different plane
Difficulty in movement of instruments	Slightly larger incision such as 22-25 mm instead of 17 mm improves play
Access device slips out/leaks gas	Sheath incision too big, suture one end

Table 1-3: Tackling problems in single-port surgery (41)

1.2.7 Learning Curve

Single-incision laparoscopic surgery hysterectomy is associated with a steep learning curve and the need for the gynecologic surgeon to adopt new technologies and develop a new set of surgical skills. A recent study demonstrated that the proficiency for Single-incision laparoscopic surgery was achieved after 40 cases and the operation time and postoperative hemoglobin drop decreased with experience, without increasing complications (48).

2 Patients and Methods

Randomized Controlled Multi-Centric Trial of Traditional Laparoscopic Assisted Vaginal Hysterectomy (LAVH) versus SILS™ Port Laparoscopic Assisted Vaginal Hysterectomy (SILS).

2.1 Patients

2.1.1 Indications

Patients with benign diseases and carcinoma in situ are included in the study.

2.1.2 Inclusion and Exclusion Criteria

All patients who meet eligibility requirements were asked to participate.
Patients were considered enrolled into the study after:

1. The patient has met all the inclusion and none of the exclusion criteria.

2. Signed informed consent has been obtained.

3. The patient is randomized.

2.1.2.1 Inclusion Criteria

1. The patient is between 18 and 70 years old
2. The patient has an indication for LAVH.
3. The patient or patient's legal representative has been informed about the nature of the study and has provided written informed consent as approved by the Institutional Review Board/Ethics Committee (IRB/EC) of the respective clinical site.
4. The patient agreed to return to the same research facility for all study-required post-procedure follow-up visits.

2.1.2.2 Exclusion Criteria

1. Any patient who is pregnant, suspected pregnant or lactating.
2. Any patient who has had a lower midline incision.
3. Any patient with ASA > 3.
4. Any patient who is undergoing peritoneal dialysis.
5. Any patient who has had prior umbilical hernia repair.
6. Any patient who has malignancy of the female genital tract.

2.2 Methods

2.2.1 Randomization

All patients have got pre-surgical randomization.

2.2.2 Sample size

Thirty patients per arm.

2.2.3 Pre-operative

Routine pre-operative care was given to all patients, including detailed demographic, medical and surgical history, general and gynecological examination, blood examination, and quality of life and pain scale surveys.

2.2.4 Methods of Surgical Procedure

2.2.4.1 SILS-LAVH Surgical Technique

The procedure required general anesthesia. A uterus manipulator is optionally placed. The umbilicus is grasped at its base and everted. A vertical skin incision is made within the umbilical fold. The peritoneum is entered at the junction of the base of the umbilicus with the fascia. A SILS™ Port is passed into the peritoneal cavity to assure free space. Pneumoperitoneum is established to 15-16 mm Hg with CO2. Hysterectomy will then be performed in accordance with the standard of care and the judgment of the surgeon. An adnexectomy is optional (if there is indication). Ligasure is used for hysterectomy. The uterus is removed through the vagina. Closure of the vaginal stump is done vaginally. Any fascial defects greater than 5 mm is closed with absorbable sutures. The skin is closed with a 4-0 monofilament running subcuticular

closure. 5 cc of 1% Xylocaine is injected into the skin at the end of the procedure. Following this, the surgeons will place 3 steri-strips (umbilicus, 2-3x inguinal).

Below is a list of advised products that could be used during the procedure. At least one Cambridge articulating instrument should be used during each procedure:

- SILSPT12
- LF5544
- SILSDISSECT36
- 5-mm or 10-mm laparoscope of choice

Other products used will be at surgeon's discretion.

Figure 2-1: SILSPT12 (http://www.covidien.com)

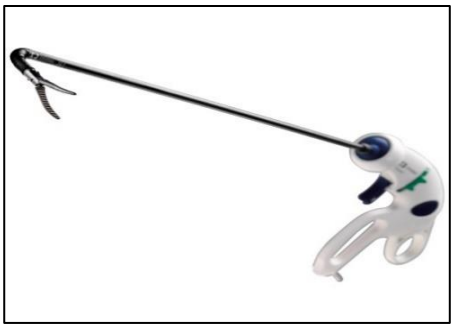

Figure 2-2: SILSDISSECT36 (http://www.covidien.com)

Conversion to standard LAVH or introducing an additional lateral port was at the discretion of the surgeon. The investigator reports if an intraoperative device/instrument malfunction occurred, estimated blood loss, any other intraoperative findings or adverse events, and if there was a conversion to conventional LAVH or laparotomy.

2.2.4.2 Conventional LAVH Surgical Technique

LAVH is performed with use of two or three 5-mm ports and one 10-mm port at the umbilicus. A 5- or 10-mm port is then placed under direct visualization and with upward pulling on the umbilicus. Two or three 5-mm ports are placed in lower abdomen. Hysterectomy is then performed in accordance with the standard of care and the judgment of the surgeon. Ligasure is used. The uterus is removed through the vagina. Closure of the vaginal stump is done vaginally. Any fascial defect greater than 5 mm is closed with a figure of eight absorbable suture. The skin is closed with a 4-0 Monofil running subcuticular closure. At the end of the procedure, 5 cc of 1%

Xylocaine is injected into the skin. Following this, the surgeons places 3 steri-strips (umbilicus, 2-3x inguinal).

The investigator reports if an intraoperative device/instrument malfunction occurred, estimated blood loss, any other intraoperative findings or adverse events, and if there was a conversion to laparotomy.

2.2.5 Postoperative Care

Routine postoperative care is prescribed according to the investigator's standard of therapy. This therapy may include restricted activity, exercises, etc. The prescribed therapy must also be reported on the case report form (CRF).

The investigator lists any postoperative complications that occurred and records any additional comments relative to the study.

A physical examination is conducted post-surgery, and, prior to the patient's discharge, this information will be recorded on the operative CRF. Current medications, post-treatment status of main symptoms and evaluation of pain score will also be recorded.

All patients have steri-strips placed on the traditional hysterectomy sites regardless of which arm of the study they are randomized into as described above. The patient will be instructed not to remove the steri-strips until they come in for their 1-week visit. The steri-strips is removed after the 1-week pain score survey and SF-36 have been administered so as not to bias them.

2.2.6 Follow-up Visits

At each follow-up visit (outlined below), the investigator collects the following information:

- A postoperative history for any signs and/or symptoms which could be interpreted as complications.
- Narcotic use in the recovery room will be reported
- Physical Examination
- Examination for hernia at each incision site

- Current medications
- SF-36 Survey
- Pain intensity numerical rating scale (PI-NRS)
- Hollander cosmesis scale

The outline of the Clinical Study Schedule is shown in table 2-1

Test ↓	Prior to procedure	Surgery	Post-Surgery, Prior to discharge	Day 1 +/- 1 d	Day 3 +/- 1d	Day 5 +/- 1 d	1 week +/- 1 d	2months +/- 1 week
Informed consent	X							
Demographic, medical, surgical history	X							
Medications regimen	X		X				X	X
Physical examination, vital signs, height, weight	X		X				X	X
PT/PTT, HCG	X							
SF-36	X		X				Given before steri-strips removed	X
PI-NRS	X		X	X	X	X	Given before steri-strips removed	X
Hollander Scale							X	X
AE monitoring	X	X	X	X	X	X	X	X

Table 2-1: Outline of the Clinical Study Schedule

2.2.7 Analysis Time

When all subjects have been enrolled and have completed the 8-week follow-up visit, an analysis will be conducted on data up to 2 weeks post procedure.

2.2.8 Evaluation and Reporting Method

2.2.8.1 Reporting Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject. Examples of events that could constitute an AE include signs, symptoms, illnesses, or other medical events that appear *or* worsen during a clinical study.

AE information is collected throughout the study. AEs are recorded on the CRFs by the investigator or a designee. Event description, date of onset, duration, severity, duration, and relationship to procedure or device is recorded on the appropriate CRF.

Throughout this study, all AEs must be recorded on CRFs by the study investigator or a designee and forwarded to the principal investigator, including a 10-day written follow-up for complications resulting in extended hospitalization and/or death.

The investigator must make the following reports regarding AEs: all complications and AEs, device related or not, must be reported and recorded on the complication form.

2.2.8.2 Serious Adverse Event and Death

The investigator decides whether each event meets the definition of a “serious” AE. The regulatory definition of a serious AE is an event that is fatal or life threatening, results in persistent or significant disability, requires intervention to prevent permanent impairment/damage, or an event that results in congenital anomaly, re-admission or prolongation of hospitalization. Any serious AE occurring during the study, regardless of cause, is reported to the primary investigator within 24 hours after the investigator first learns of the event.

2.2.8.3 Documentation and Case Report Forms

Data is collected using CRFs. All CRFs are filled out by the personnel involved in the study procedures and reviewed and signed by the investigator. All entries are completed in a neat, legible manner using black ink to ensure accurate recording of

data. Any changes or corrections made on the CRFs are made by drawing a line through the data to be changed, entering corrected information, and signing (or initialing) and dating the change. Erasing, overwriting, and the use of “white out” are not permitted on the CRFs.

2.2.9 Statistical Analysis

2.2.9.1 Primary Endpoints

Only patients receiving treatments as randomized are included in the primary analysis of feasibility and safety. Those who did not receive any study treatment or were treated according to the wrong study arm will be excluded from the primary analysis. Results experienced by these patients will be described separately.

Safety: The proportions of patients reporting (a) any AEs, (b) any AEs related to the study procedure, and (c) any serious AEs will be calculated for each procedure. For a given AE, the number and proportion of patients reporting it will be tabulated according to the worst severity experienced and the closest relationship assessed to study procedure. These proportions will be compared between the two procedures using Fisher’s exact tests.

Estimated Blood Loss: Depending on the data distributional shape (symmetrical or skewed), the estimated blood loss will be summarized as mean/standard deviation or median/range and compared between the two procedures by either the *t* test or nonparametric tests mentioned above.

Quality of Life: As continuous or near-continuous measures, SF-36 will analyzed. That is, symmetrically distributed measures will be summarized by mean/standard deviation and compared between procedures with *t* tests; measures with skewed distributions will be summarized by median/range and compared by nonparametric tests.

2.2.9.2 Secondary Endpoints

Economic differences: length of hospital stay (the price of day/hospital stay) and use of narcotics and other drugs (the price) will be summarized as median and range for each procedure and compared by nonparametric tests such as the logrank test or the Wilcoxon rank sum test as appropriate.

Operating (OR) Time: Due to the expected skewed data distribution, operating time will be summarized as median and range for each procedure and compared by nonparametric tests such as the logrank test or the Wilcoxon rank sum test as appropriate.

As continuous or near-continuous measures, PI-NRS and SF-36 will analyzed similarly to operative time and estimated blood loss. That is, symmetrically distributed measures will be summarized by mean/standard deviation and compared between procedures by *t* tests; measures with skewed distributions will be summarized by median/range and compared by nonparametric tests. The 7-point modified Hollander cosmesis scale will be analyzed via the Wilcoxon rank sum test.

3 Results

All continuous data are expressed as mean ± *SD*, and categorical data are reported as an absolute number or percentage. Frequency distributions were compared using a chi-square test and mean or median values were compared using Student's *t* and Mann–Whitney U tests. All calculated *p* values were two-sided, and $p < 0.05$ was considered statistically significant. Data were analyzed using SPSS software.

Sixty-four patients were recruited in the study in the time between May 1, 2012 and August 18, 2016 in three centers. All 64 patients were randomized (1:1) to conventional laparoscopic hysterectomy (*n*=32) or SILS hysterectomy (*n*=30). Five patients were excluded because of screening failures.

Center	**Number of patients**
University Medicine Greifswald	19
Damme Hospital	40
Medical University Aachen	5

Table 3-1: Overview of patients and centers

3.1 Patient Characteristics

The baseline characteristics of the patients are summarized in Table 3-2. Patients in both groups were similar in terms of age. Median age was 45 years, ranging from 24 to 62 years, and median BMI was 24.5 kg/m², ranging from 17.2 to 49 kg/m². There was no statistically significant difference between the two groups. Of all patients (*n*=34), 56.7% experienced at least one previous abdominal (laparoscopy or laparotomy) surgery.

	Total	SILS	cLSK	*P*-Value
Number of patients	60	29	31	
Age median (yrs.), range	45 (24-62)	45 (24-62)	46.5 (30-55)	0.728
BMI median (kg/m²), range	24.5 (17.2-49)	24.4 (21-31.1)	24.65 (17.2-49)	0.554
Prior laparoscopy median (*n*), percent	23 (38.3)	10 (34.5)	13 (41.9)	0.553
Prior Laparotomy median (*n*), percent	19 (31.7)	9 (31)	10 (32.3)	0.919

Table 3-2: Clinical characteristics of the patients

3.2 Indications for Hysterectomy

Table 3-3 and Figure 3-1 present summaries of the distribution of the indications for hysterectomy among the patients. Indications for hysterectomy were hypermenorrhea (*n* = 37, 61.7%), atypical hyperplasia (*n* = 7, 11.7%), dysmenorrhea (*n* =9, 15%) and postmenopausal bleeding (*n* = 2, 3.3%). Diagnosis was not available in 5 cases.

Indication for Hysterectomy	Total	SILS	cLSK	*P*-Value
atypical hyperplasia, *n* (%)	7 (11.7)	2 (6.9)	5 (16.1)	0.142
hypermenorrhea, *n* (%)	37 (61.7)	21 (72.4)	16 (51.6)	
dysmenorrhea, *n* (%)	9 (15)	2 (6.9)	7 (22.6)	
postmenopausal bleeding, *n* (%)	2 (3.3)	2 (6.9)	0	
not available, *n* (%)	5 (8.3)	2 (6.9)	3 (9.7)	

Table 3-3: Indications for Hysterectomy

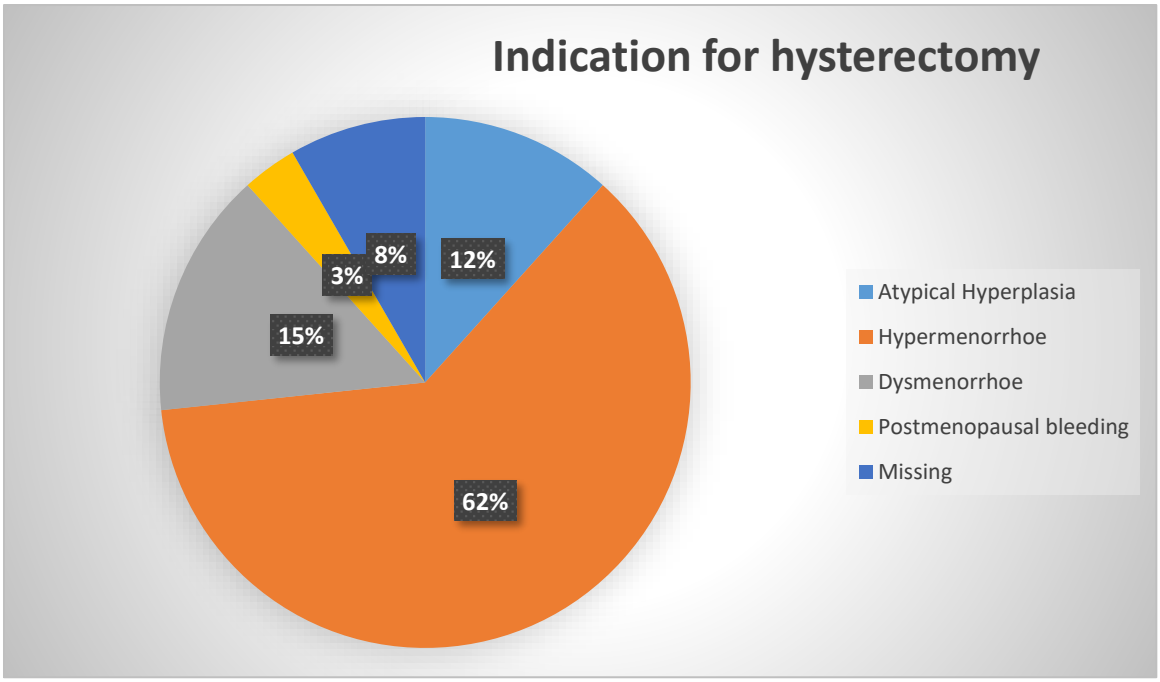

Figure 3-1: Indications for hysterectomy

3.3 Surgical Outcome

The surgical outcome metrics are summarized in Tables 3-4, 3-5 and 3-6. The mean operative time was comparable in both groups (68.2 vs 73.6 min., p = 0.409; 95% CI: -18.69 -7.12), this difference was not statistically significant. Insertion of an additional trocars or conversion to laparotomy were not needed in all cases.

	Total	**SILS**	**cLSK**	***P*-Value**
Operative Time Mean (min.)	70.72	73.64	68.16	0.409
Blood Loss Mean (ml.)		106.7	105	0.915
Intraoperative Complications	0	0	0	
Conversion rate	0	0	0	

Table 3-4 Surgical Outcomes

Within the two groups, no differences were seen regarding estimated blood loss (p = 0.915; 95% CI: -21.02 -18.88). No intraoperative complications were observed in either group.

Blood loss (ml)	Frequency	%	Valid %	Cumulative %
10	1	1.6	1.7	1.7
50	4	6.3	6.9	8.6
70	3	4.7	5.2	13.8
80	6	9.4	10.3	24.1
100	30	46.9	51.7	75.9
120	3	4.7	5.2	81.0
150	6	9.4	10.3	91.4
180	2	3.1	3.4	94.8
200	3	4.7	5.2	100
Missing	6	9.4		
Total	64	100		

Table 3-5: Intraoperative Blood Loss

	N	**Mean (min)**	***SD***	***SE* (mean)**
cLSK	32	68.16	21.312	3.767
SILS	28	73.64	29.566	5.587

Table 3-6: Operative Time

Table 3-7 presents a summary of postoperative outcomes. There was no statistically significant difference between both groups in terms of postoperative complications ($p = 0.944$) and wound infection rates ($p = 0.944$).

Only one patient within the control group received blood transfusions after surgery ($p = 0.337$). Furthermore, the median durations of hospital stay were comparable in both groups ($p = 0.551$): for the control group the median was 3 days (ranging from 2 to 10 days) and, for the SILS group, the median was 4 days (ranging from 2 to 13).

Postoperative outcome.	**Total**	**SILS**	**cLSK**	***P*-Value**
postoperative complications, *n* (%)	2 (3.3)	1 (3.4)	1 (3.1)	0.944
wound infection, *n* (%)	2 (3.3)	1 (3.4)	1 (3.1)	0.944
blood transfusion, *n* (%)	1 (1.6)	0	1 (3.1)	0.337
Hospital stay, in days, median, (range)	3 (2-13)	4 (2-13)	4 (2-13)	0.551

Table 3-7: Postoperative Outcomes

More than half the patients in the entire study population had a pain score of 5–6 on the first postoperative day, whereas on day three more than 65 % of patients had a pain score of 2–4 as shown in Table 3-8 and figure 3-2.

Day 3 PI-NRS Score	Frequency	%	Valid %	Cumulative %
0	2	3.1	3.4	3.4
1	3	4.7	5.1	8.5
2	11	17.2	18.6	27.1
3	16	25.0	27.1	54.1
4	16	25.0	27.1	81.4
5	5	7.8	8.5	89.8
6	2	3.1	3.4	93.2
7	2	3.1	3.4	96.6
8	2	3.1	3.4	100
Missing	5	7.8		
Total	64	100		

Table 3-8: PI-NRS, Day 3

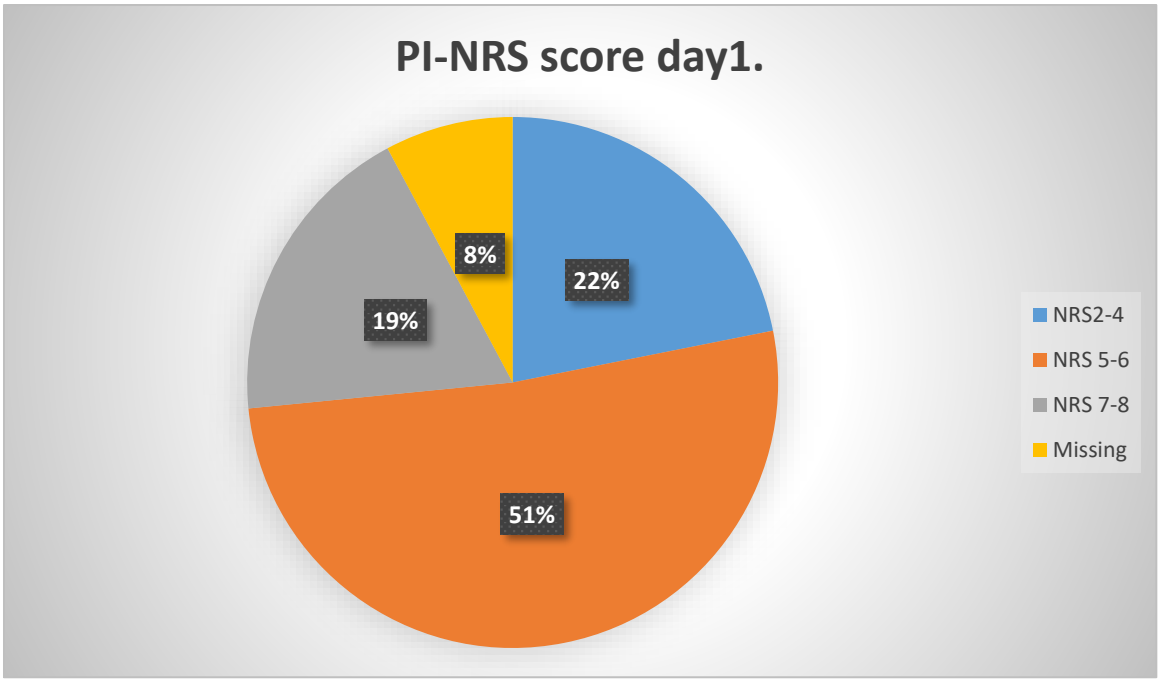

Figure 3-2: Postoperative pain, day1

Patients in the SILS group experienced significantly less pain than those in the control group in the first 24 hours postoperatively (p = 0.006), while pain scores in both groups at days 3, 5, 7 and 2 months postoperatively were comparable. Table 3-9 shows a comparison between both groups regarding the postoperative pain score in different postoperative days and the pain medication requirement on day of discharge.

PI-NRS pain score, mean	**Total**	**SILS**	**cLSK**	**P-Value**
24 h post-op.		4.89	5.84	0.006
At day 3		3.36	3.55	0.667
At day 5		1.96	2.33	0.356
At day 7		1.85	1.38	0.411
2 months post-op.		0.43	0.11	0.154
required pain medication at time of discharge, *n* (%)	11 (18.6)	6 (21.4)	5 (16.1)	0.602

Table 3-9: Postoperative Pain Compared

Table 3-10 and 3-11 show a comparison between both groups regarding intraoperative blood loss and postoperative pain.

Study arm		***N***	**Mean**	***SD***	***SE* (mean)**
Intraoperative Blood loss in ml	cLSK	30	105.00	33.810	6.173
	SILS	28	106.07	41.841	7.907
PI-NRS Score, 1st day post-op	cLSK	31	5.84	1.293	0.232
	SILS	28	4.89	1.227	0.232
PI-NRS Score, 3rd day post-op	cLSK	31	3.55	1.823	0.327
	SILS	28	3.36	1.545	0.292
PI-NRS Score, 5th day post-op	cLSK	30	2.33	1.749	0.319
	SILS	28	1.96	1.201	0.227
PI-NRS-Score, 7th day post-op	cLSK	8	1.38	1.302	0.460
	SILS	13	1.85	1.214	0.337
PI-NRS Score, 2 months post-op	cLSK	19	0.11	0.459	0.105
	SILS	23	0.43	0.896	0.187

Table 3-10: t-test

		Levene's Test for Equality of Variances		t-test for Equality of Means			
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference
Blood loss in ml	Equal variances assumed	0.892	0.349	-0.108	56	0.915	-1.071
	Equal variances not assumed			-0.107	51.967	0.915	-1.071
NRS-Score 1. postop day	Equal variances assumed	0.078	0.781	2.873	57	0.006	0.946
	Equal variances not assumed			2.881	56.851	0.006	0.946
NRS-Score 3. postop day	Equal variances assumed	0.595	0.444	0.432	57	0.667	0.191
	Equal variances not assumed			0.436	56.785	0.664	0.191
NRS-Score 5. postop day	Equal variances assumed	2.876	0.095	0.930	56	0.356	0.369
	Equal variances not assumed			0.942	51.580	0.351	0.369
NRS-Score 3 months postoperative	Equal variances assumed	9.600	0.004	-1.452	40	0.154	-.330
	Equal variances not assumed			-1.537	34.002	0.134	-.330
Operative time	Equal variances assumed	0.190	0.664	-0.832	58	0.409	-5.487
	Equal variances not assumed			-0.814	48.415	0.420	-5.487

Table 3-11: Independent Sample Test

Table 3-12 shows the confidence interval of difference in both groups when comparing intraoperative blood loss, postoperative pain on different postoperative days and operative time.

		T-test for Equality of Means		
		***SE* Difference**	**95% Confidence Interval of the Difference**	
			Lower	**Upper**
Intraoperative blood loss	Equal variances assumed	9.958	-21.019	18.876
	Equal variances not assumed	10.031	-21.201	19.058
PI-NRS-Score 1. postop day	Equal variances assumed	0.329	0.287	1.605
	Equal variances not assumed	0.328	0.288	1.603
PI- NRS-Score 3. postop day	Equal variances assumed	0.442	-0.695	1.077
	Equal variances not assumed	0.439	-0.687	1.070
PI- NRS-Score 5. postop day	Equal variances assumed	0.397	-0.426	1.164
	Equal variances not assumed	0.392	-0.417	1.155
PI-NRS-Score 2 Months postop	Equal variances assumed	0.227	-0.788	0.129
	Equal variances not assumed	0.214	-0.765	0.106
Operative time	Equal variances assumed	6.596	-18.690	7.717
	Equal variances not assumed	6.739	-19.033	8.060

Table 3-12: Confidence interval

The required painkillers at time of discharge were also comparable within the two groups (p = 0.602). as shown in table 2-13

		Study arm		Total
		1 cLSK	2 SILS	
Pain killer at time of discharge	1 yes Count	5	6	11
	%within study arm	16.1%	21.4%	18.6%
	2 no Count	26	22	48
	% within study arm	83.9%	78.6%	81.4%
Total Count		31	28	59
% within study arm		100.0%	100.0%	100.0%

Table 3-13: Required pain medication at discharge

4 Discussion

This randomized trial evaluated the safety and effectiveness of SILS hysterectomy compared to the conventional laparoscopic hysterectomy.

Our findings confirm the findings from 3 meta-analyses, defining SILS hysterectomy as a safe surgical procedure. (49, 50)

The primary aim of the trial was to evaluate the blood loss during surgery. Blood loss was comparable in both arms of the study. This study's findings demonstrate that the SILS hysterectomy has no higher rate of intraoperative complications. This agrees with a randomized control trail by Chung et al., which found no significant difference between Single port and conventional three port total laparoscopic hysterectomy regarding blood loss during surgery, perioperative hemoglobin changes, uterine weight and postoperative pain score, but showed also more consumption of analgesics in the single port group (46). The results also support the meta-analysis by Sandberg et al., which found no differences between complication rates when comparing SILS hysterectomy to conventional hysterectomy and clustering into major complications and minor complications (51). Furthermore, no differences regarding conversion rate to laparotomy were observed. In the SILS approach, no additional port was needed. In other trials, a frequency of 3.5% conversion to additional port was reported (52).

These results demonstrate that SILS hysterectomy is comparable to conventional laparoscopic hysterectomy, mainly depending on the experience of the surgeon. All participating surgeons were certified as MIC-II-III by the German Study Group for Gynecologic Endoscopy (*Arbeitsgemeinschaft Gynäkologische Endoskopie*). Additionally, the results demonstrate that the operative time is comparable for both types of hysterectomy, which confirms the findings of other recent trials. (49, 50, 52). The results contradict the finding of a systemic review by Sandberg et al., which found that the operative time was significantly longer in the SILS group than the LAVH group. On the other hand, his results also indicated comparable intraoperative blood loss for both procedures, which confirms the results of this study (51).

Furthermore, in this study, the median durations of hospital stay were comparable for the LAVH (3 days) and SILS (4 days) groups ($p = 0.551$). Lee et al. reported no

difference in hospital stay or operation time between conventional and SILS hysterectomy. (53) In contrast, studies by Y.S. Choi et al. and Kim et al. agreed that SILS had both a longer time of operation and hospital stay. (34, 54)

In this study, patients within the SILS group experienced significantly less pain 24 hours postoperatively ($p = 0.006$), while pain scores were comparable at days 3, 5, 7 and 2 months postoperatively. The required pain medication at time of discharge was also comparable between the two groups ($p = 0.602$).

Postoperative pain is an important issue regarding hysterectomy. Oral pain medication such as paracetamol or NovaMin is commonly sufficient for postoperative pain treatment in these patients. This study's finding that patients treated in the SILS group reported less pain 24 hours postoperatively confirm the results from other trials although not clinically significant (51). The results of the trial by Sandberg et al., show that the SILS hysterectomy is a feasible and safe surgical procedure in gynecologic surgery. However, there was no significant differences in postoperative pain found. Directly and 24 hours after SILS hysterectomy, a lower pain score was observed. However, this difference was not observed when analyzing only the randomized controlled trials (RCTs). Furthermore, the mean difference did not exceed 1.09, and studies have shown that only a mean difference of at least 2 points on a 10-point scale should be considered as clinically relevant (52).In addition, it cannot be excluded that enrolled patients in the study were 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 RCT applied accurate blinding. (46) Patients and anesthesiology staff who measured the postoperative pain scores did not know which type of approach had been performed, while similar pain scores were found, One RCT showed no difference in postoperative pain (55); however, two other RCTs found statistically significant lower postoperative pain with SILS compared to conventional laparoscopy. Furthermore, the work of Faggotti et al. was on adnexal surgeries (45, 56).

These results also align with the study of Tormena et al. that showed that, in 20 Patients operated on with SILS, reported postoperative pain was minimum, and no anti-inflammatory or morphine-like drugs were necessary. Ordinary routine analgesics were used until the 6th postoperative day. It must be taken into

consideration that this study was not randomized and there was no control group (47).

The strength of the present study includes the randomized study design and the homogeneity of the included patients. A high BMI limit was not an exclusion criterion (range, 17.2-49 kg/m^2). The participating surgeons were well experienced and qualified for the trial.

Cosmetic outcomes are also suggested as an important improvement with the single-site approach but, surprisingly, only a few studies on SILS hysterectomy have reported on this topic (57–59).

5 Conclusion

Taken together, the results of this study demonstrate that SILS hysterectomy is a reliable and safe setup in gynecologic surgery. Compared to conventional laparoscopic hysterectomy, SILS surgery demonstrated comparable surgical properties regarding blood loss, duration of surgery, and intra- and postoperative complications. Notably, patients undergoing SILS hysterectomy experienced less pain postoperatively.

6 Summary

Background/Aim: Laparoscopic single-port surgery has emerged as a growing trend in minimally invasive surgery. Single-port access is preferred among women undergoing gynecologic surgery who have cosmetic concerns about scarring. Furthermore, this approach results in comparable clinical outcomes to standard laparoscopic surgery and perioperative morbidity rates have been reported to be low. The hypothesis is that a single-port technique might offer such advantages over the standard multi-port laparoscopy as less postoperative pain and better cosmetic results by decreasing abdominal wall tissue trauma. The potential disadvantages of single-port approaches are the larger umbilical incision and the technical difficulties. There are only a few randomized studies in the literature that investigate the value and safety of single-incision laparoscopic surgery in gynecological surgery. The aim of this study was to compare the safety and quality of life in patients who undergo single-incision laparoscopic assisted vaginal hysterectomy and those who undergo conventional laparoscopic assisted vaginal hysterectomy.

Methods: In a prospective randomized trial, 64 patients from three different centers in Germany were randomized (1:1) to conventional laparoscopic assisted vaginal hysterectomy (*n*=32) or single-incision laparoscopic assisted vaginal hysterectomy (*n*=30). Data was collected on 60 patients who fulfilled the criteria.

Results: The baseline characteristics of patients were similar in both groups. The mean operative time was comparable in both groups (68.2 vs 73.6 min., $p = 0.409$). Within the two groups, no differences were seen regarding estimated blood loss ($p = 0.915$), intra- and postoperative complications ($p = 0.944$), and wound infection rates ($p = 0.944$). Patients within the single-incision laparoscopic surgery group experienced significantly less pain in the first 24 hours postoperatively ($p = 0.006$), while pain scores at days 3, 5, 7 and 2 months postoperatively were comparable

Conclusion: This study demonstrates that single-incision laparoscopic assisted vaginal hysterectomy is a reliable and safe setup in gynecologic surgery. Compared to conventional laparoscopic assisted vaginal hysterectomy, Notably, patients undergoing single-incision laparoscopic assisted vaginal hysterectomy experienced less pain postoperatively.

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8 Eidesstattliche Erklärung

Hiermit erkläre ich, dass ich die vorliegende Dissertation selbständig verfasst und keine anderen als die angegebenen Hilfsmittel benutzt habe.

Die Dissertation ist bisher keiner anderen Fakultät, keiner anderen wissenschaftlichen Einrichtung vorgelegt worden.

Ich erkläre, dass ich bisher kein Promotionsverfahren erfolglos beendet habe und dass eine Aberkennung eines bereits erworbenen Doktorgrades nicht vorliegt.

Datum

Unterschrift

9 Curriculum Vitae

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To

Asser and Laila Elmeligy