Enhanced Recovery After Hysterectomy
to Josef, Aron, and Adina,
with all my love
Örebro Studies in Medicine 164

LENA WIJK

Enhanced Recovery After Hysterectomy
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Title: Enhanced Recovery After Hysterectomy.

Publisher: Örebro University 2017
www.oru.se/publikationer-avhandlingar

Print: Örebro University, Repro 08/2017

ISSN 1652-4063
Abstract


Objectives: To study recovery after hysterectomy under Enhanced Recovery After Surgery (ERAS) care, and in relation to different operation techniques.

Materials and Methods: An observational study was conducted comparing 85 patients undergoing hysterectomy with ERAS care to 120 patients immediately before establishing ERAS. In a prospective cohort study of 121 consecutive patients undergoing hysterectomy, the outcome was compared for patients with malignant versus benign indications. The main outcome measure was length of stay (LOS). A randomised controlled trial (RCT) of 20 women scheduled for hysterectomy compared robot-assisted laparoscopic with abdominal hysterectomy in terms of the development of insulin resistance, inflammatory reactions, and clinical recovery, and examined the relation to hormonal status. All studies were conducted in 2011–2015, at the Department of Obstetrics and Gynaecology, Örebro University Hospital, Sweden.

Results: Implementation of a structured ERAS protocol significantly reduced LOS compared to non-ERAS care. The effect was similar between patients with malignant and benign indications for surgery. No difference in complications was found. There was no difference in development of insulin resistance between robotic and abdominal technique, but clinical outcomes and inflammatory responses significantly favoured robot-assisted hysterectomy. Female sex hormone status was associated with the development of insulin resistance.

Conclusions: Recovery after hysterectomy can be influenced. ERAS care seems to be effective and safe. Clinical outcome can also be influenced by operational technique. Hysterectomy triggers a stress reaction in both the metabolic and the inflammatory system. It remains unclear why the reduced inflammatory reaction and favourable clinical outcome in robotic surgery were not mirrored by less insulin resistance. This could not be explained by female sex hormone status.

Keywords: Hysterectomy, ERAS, Insulin Resistance, Female Sex hormones.

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IV  Wijk L, Ljungqvist O, Nilsson K. Female sex hormones in relation to insulin resistance after hysterectomy. (In manuscript)

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**Abbreviations**

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<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AH</td>
<td>Abdominal hysterectomy</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<td>E2</td>
<td>Oestradiol</td>
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<td>EIAS</td>
<td>ERAS® interactive audit system</td>
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<td>ERAS</td>
<td>Enhanced recovery after surgery</td>
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<tr>
<td>FSH</td>
<td>Follicle-stimulating hormone</td>
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<tr>
<td>IL-6</td>
<td>Interleukin 6</td>
</tr>
<tr>
<td>LH</td>
<td>Luteinizing hormone</td>
</tr>
<tr>
<td>LOS</td>
<td>Length of stay</td>
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<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>RTLH</td>
<td>Robotic total laparoscopic hysterectomy</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>tLOS</td>
<td>Target length of stay</td>
</tr>
<tr>
<td>6MWT</td>
<td>Six minutes walking test</td>
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</table>
## Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity of daily living</td>
<td>Getting in and out of bed, handling personal hygiene, going to the toilet, walking, and eating and drinking.</td>
</tr>
<tr>
<td>Day 0</td>
<td>The period of time from the operation until 08:00 the next morning.</td>
</tr>
<tr>
<td>LOS</td>
<td>Number of days spent in hospital until the day of discharge, counting the day of surgery as day 0.</td>
</tr>
<tr>
<td>tLOS</td>
<td>The day set as the target for discharge from hospital.</td>
</tr>
<tr>
<td>M-value</td>
<td>Measure of insulin sensitivity: mg glucose infused intravenously per (kg body weight x minute) to maintain steady state glucose levels during a physiological rise of insulin using insulin infusions.</td>
</tr>
</tbody>
</table>
Introduction

Hysterectomy is one of the most common major gynaecological operations. Perioperative care of these patients is an everyday clinical situation, including large volumes. In Sweden alone, with a population of 10 million, about 7,800 operations are conducted per year. The indications vary from benign symptoms to malignant disease in age groups from around 40 years of age and older. Benign symptoms mainly consist of bleeding disorders or fibroids, while malignant disease consists primarily of low-grade uterine cancer, as well as some cases of low-grade ovarian cancer and cervical cancer. Improving postoperative outcome and recovery in such a large patient group could have considerable impact, with the most important effects being those for the individual woman such as shorter hospital stay, less postoperative pain, and earlier return to daily activities. The shorter time in hospital could also free up hospital beds and thereby have an impact on hospital wards and economy.

Perioperative care differs greatly around the world, both in a historical view and up to the present, and hence there are also differences in recovery time and time in hospital. Enhanced Recovery After Surgery (ERAS) is a well-documented perioperative care programme. It started in an attempt to use the best evidence for each perioperative element, forming this into a coherent care program aimed at improving recovery. In colorectal surgery, it has led to shorter length of stay (LOS) after surgery, improved recovery, and reduced number of complications. The program has now begun to spread among many other specialities in many countries. The first international ERAS guidelines for gynaecology were presented as recently as 2016.

It is not only perioperative care that is changing; surgical technique for hysterectomy has undergone major changes during recent decades, also affecting recovery. Less invasive techniques such as vaginal or laparoscopic operations are now recommended as first-choice approaches when feasible. However, about 45–50% of hysterectomies in many countries, including Sweden and the USA, are still performed by open technique. In some cases, the uterus is too large for laparoscopy, but other reasons for the large number of open cases include tradition, medical co-factors, and surgical skills. The latest laparoscopic technique is robot-assisted hysterectomy, which has been in use in gynaecology since 2005 and is becoming more common for both benign and malignant surgery. Despite its fast spread in use, it is not sufficiently studied. Very few randomised trials on the use of
robotic surgery have been published, and there is still debate regarding its benefits over other techniques, mainly traditional laparoscopy. Further research is still needed in order to confirm for which patient groups and for what type of surgery robot-assisted laparoscopy is of benefit.

These changes in practice and my clinical interest in recovery after gynaecological surgery formed the starting point for this thesis, which includes research about different aspects of recovery after hysterectomy.
Background

Recovery and stress response

Recovery after surgery is a complex phenomenon involving many different modalities; biological as well as social and psychological factors. The biological reactions have been studied in part, but much is still unknown about what controls and what improves recovery. Many cascades of reactions occur in response to the trauma of operation. When injured, the body reacts by releasing inflammatory mediators and neuroendocrine hormones mobilising substrates including fat, protein, and carbohydrates for use in the reconstruction and healing processes. This places the body in a metabolic stress situation, in which the normal actions of insulin are blocked and insulin resistance develops. Glucose is released from its hepatic stores, and at the same time glucose uptake in insulin-sensitive cells, mainly muscle, is reduced. This occurs with the loss of the normal activation of the glucose transporting protein GLUT 4 in skeletal muscle cells. Glucose production in the liver is also increased after surgery. The main effect is in the glucose uptake, while the glucose production in the liver contributes to a lesser extent (about 10–15%). The net effect is that the body enters a diabetes-like situation, not unlike type 2 diabetes mellitus, with hyperglycaemia despite insulin elevation. Insulin resistance also causes protein loss from the muscle cells, causing structural decline, and together these factors cause impaired mobilisation.

This insulin resistance is believed to be one of the main reactions to any form of trauma, including elective surgery, and has been related to prolonged recovery. Studies have demonstrated that the degree of insulin resistance is linked to the magnitude of the operation. In major colorectal surgery, 75–80% of the insulin sensitivity is lost and remains low up to 2–3 weeks after surgery. Insulin resistance is also believed to be one of the key mechanisms causing complications, especially infections, a common complication after surgery. Another study have linked insulin resistance to poor wound healing. It is important to better understand the physiological reactions to surgery, in order to reduce the risk of complications and to further improve recovery.

The other important part of the stress response triggered by surgery is the inflammatory response, which is often clinically measured by C-reactive protein (CRP) or white blood cell count, and in studies also by a number of cytokines such as interleukin 6 (IL-6). As with insulin resistance, the
magnitude of this reaction is linked to the severity of the tissue trauma. The link between insulin resistance and inflammation is not clear, and is currently a focus for research.

In terms of age the population of interest range from late premenopausal, through perimenopausal, to postmenopausal. The range of their sex hormone status is therefore broad. Physiological levels of oestradiol in premenopausal women are linked to favourable status of insulin sensitivity, while oestrogen deficiency is linked to the development of insulin resistance. However, the underlying mechanisms are not fully understood. Previous studies have tried to explore the relation between the phase in the menstrual cycle and insulin sensitivity, but the results are not consistent. The impact of the hormonal status, such as sex hormone levels or the menopausal status, on recovery after surgery or on the development of insulin resistance, has not to our knowledge been previously studied.

**Perioperative care – Enhanced Recovery After Surgery**

The perioperative care process involves several events and procedures during the patient’s journey, from the time of making the decision to operate until full recovery after surgery. Many care processes have an impact on outcomes, and can either facilitate or counteract recovery. Some have a psychological impact and others have physiological effects. Surgeons have always studied surgical techniques, while anaesthesiologists have focused on the procedures of anaesthesia and pain relief as ways to improve outcome. Many of the procedures around surgery today are aimed at reducing the operative stress triggered by the operation. The effects of the different procedures have often been studied in isolation, but it has now become evident that the entire process around the operation may also be important for the enhancement of recovery.

**The history of ERAS**

The ERAS Study Group was formed in 2001 with participants from Sweden, the UK, Norway, Denmark, and the Netherlands. Inspired by work in the 1990s by Professor Henrik Kehlet of Copenhagen, Denmark, on multimodal surgical care, the group found that there was a great discrepancy between actual practice in the different units, and moreover that none of these units followed what the group found to be best practice based on the literature. After a review of the literature, in 2005 the group published the first consensus protocol for patients undergoing colonic surgery, and a similar protocol soon followed for rectal surgery; both of these protocols were
Later updated. In 2010, the non-profit ERAS® Society was officially founded. The mission of the Society is “to develop perioperative care and to improve recovery through research, education, audit and implementation of evidence-based practice.” Along with its continuous work in producing and updating guidelines, the ERAS Study Group developed the ERAS® Implementation Program in order to help clinical departments to implement the guidelines in clinical practice. So far this program has been introduced in more than 25 countries covering all continents around the world.

ERAS began as a protocol for patients undergoing colonic surgery, but its principles have now spread to include a variety of specialties. Since 2012/2013, guidelines for pancreatic and urological surgery have been published and implemented. These were followed by guidelines on gastric resections, anaesthesia, liver resection, bariatric surgery, and most recently head and neck cancer surgery and breast reconstruction. Protocols differ slightly between the different specialties and different surgical procedures, although the main principles remain the same. The guidelines are continuously updated as new evidence emerges.

Most research so far has been on colorectal surgery. ERAS has been widely studied in this field, with consistent findings of faster functional recovery, shorter LOS after surgery, and reduction in complications. A recent five-year follow-up of more than 900 colorectal cancer patients found a clear association between better compliance with the ERAS protocol and survival.

ERAS in gynaecology

In the 1990s, isolated studies were published on pathways for gynaecological surgery, including some of the perioperative care elements seen in ERAS, with the aim of shortening LOS for both patients with malignant and benign disease. In the 2000s, the Danish group led by Professor Kehlet launched the concept of fast-track, which included many of the ERAS elements, and published a number of prospective cohort studies all showing short LOS. They reported one day LOS for laparoscopic and two days for abdominal hysterectomy (AH), and for ovarian cancer patients a reduction of two days and as well as a reduction of complications. A few studies using similar protocols, named fast track or ERAS, in observational cohorts followed from different parts of the world, with the common findings of shorter LOS, and in Sweden and Denmark, a few randomised controlled trials (RCTs) were published comparing different anaesthetic techniques or laxatives in patients otherwise treated according to fast-track principles.
This is the context in which we started the implementation of the ERAS program, and initiated our studies. Interest in using ERAS in gynaecology increased in parallel and the literature now includes original studies and systematic reviews covering vaginal, laparoscopic, and abdominal staging surgery as well as ovarian cancer surgery. The first international evidence based guidelines from the ERAS Society were published in 2016.

**ERAS care elements**

Enhanced recovery programs combine several unimodal evidence-based interventions aimed at supporting recovery of bodily functions and reducing the stress reaction of the operation, in order to avoid unnecessary organ dysfunction by targeting factors that delay postoperative recovery, such as gut dysfunction, immobility, and pain, and thereby support the return to normal functions. The interventions are aligned through the entire chain of perioperative care. The elements recommended by the ERAS Society are presented in brief in Figure 1.

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**Figure 1. Elements of the ERAS program in different phases.**

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Work inside hospitals is often carried out in isolated “silos” (wards, units, departments) which do not communicate with each other; one silo does not really know what another silo is doing (Figure 2).²

![Diagram: Patient's journey through surgery until recovery after the operation. OR=operating room, PACU=post anaesthesia care unit. (Adapted from reference 2. Used by permission of the ERAS® Society.)](image)

The ERAS program focuses on the patient’s journey, which includes all the different wards and departments involved in the care. The protocol also focuses on the importance of all members of the team participating in order to optimise the patient pathways: all the different nurses, surgeons, anaesthesiologists, dieticians, and physiotherapists. The patients themselves are involved, too. It is crucial that everyone understands how actions taken by any member of the team along the chain affects the treatments given later, the patient, and ultimately the outcome. ERAS emphasises the importance of working together towards the same goal and applying the best evidence available.²
In order to support the implementation and care, ERAS® Society supplies the ERAS® Interactive Audit System (EIAS), which allows continuous registration of the ERAS elements and the perioperative care in one common international database. The EIAS has several purposes. The database is used to test the guidelines and serve as a basis for further research, and the system allows the clinics themselves to gain feedback about their care and how well they have implemented the ERAS protocol.

**Changes in surgical technique**

In parallel with the change in perioperative care, there has been a shift in surgical technique from AH in favour of less-invasive techniques such as vaginal and laparoscopic hysterectomy, in the form of either laparoscopically assisted vaginal hysterectomy or total laparoscopic hysterectomy. These minimally invasive techniques are now recommended as first choice whenever feasible, due to their clinical advantages including faster recovery and fewer infections.

The most recently adopted technique is robot-assisted total laparoscopic hysterectomy (RTLH), which has been in use since 2005 and is now widely available in many countries. In gynaecology, it is used for both hysterectomy and more advanced surgery such as lymph node sampling and radical hysterectomy. Until 2010, only a few descriptive studies had been published, but in the past five years the publication rate has risen increasingly fast, and today more than 90 published original articles are available. Still, the majority of publications are retrospective registry or prospective cohort studies. To date, there have only been four published RCTs on benign hysterectomy and two on endometrial cancer staging surgery. The comprehensive result is that clinical and surgical outcomes for robot-assisted laparoscopy in hysterectomy are quite similar to traditional laparoscopy and comparable to the vaginal approach, and like the other minimally-invasive techniques RTLH results in clearly faster recovery compared to AH.

In endometrial staging surgery, the method seems to be safe, with similar oncological results regarding number of lymph nodes sampled and relapse, although further studies are needed. There are some indications that robot-assisted surgery can manage more complex cases such as large uteri, obesity, and adhesions, and also has fewer conversions than other minimal invasive surgery. Apart from the clinical results, the debate is now largely around the economic aspects, focusing on the cost effectiveness of different procedures.
Several studies have shown that, in general, the minimally-invasive approach reduces the inflammatory response in vaginal or traditional laparoscopic operations compared to the abdominal approach.\textsuperscript{19-22, 70} Regarding metabolic reactions, only two early articles have been published comparing change in glucose levels after different techniques used for hysterectomy, and none have examined insulin resistance.\textsuperscript{71, 72} To our knowledge, the stress response in terms of development of insulin resistance or the inflammatory response in simple hysterectomy has not been studied in robotic surgery.
**Ethical Considerations**

One fundamental idea of the ERAS concept is to evaluate the best available evidence about the entire perioperative process and combine all single elements into a care pathway in order to give the best possible care. Studying the implementation process of a new clinical practice is important in many aspects. Even though ERAS is well-studied for patients undergoing colorectal surgery, it is not certain that the same benefits will be seen in another group of patients. On the other hand, if effective, the knowledge needs to be spread in order for many patients to benefit.

ERAS proposes continuous auditing based on data collection, and the EIAS functions as a quality register. However, registration of patient data takes time and resources. As with all clinical quality registries, it would be unethical not to also make use of the registered data in a more systematic scientific way in studies. Patients generally assume that the data collected are used by the health care system for development and improvement.

Introducing new, expensive techniques needs to be done carefully. It has to be shown that the technique is safe and as effective as the old one. When a technique is very expensive, thorough studies are even more important in order to make sure that the common health care resources are used in the most cost-effective way; otherwise, there is a risk that other groups of patients will be affected by lack of resources.

As researchers, we should strive not only to observe the effect of a clinical procedure or invention, but also to bring knowledge forward for better understanding of the biological explanations and mechanisms behind clinical improvements. Only with a deeper understanding of the mechanisms behind our outcomes will we be able to continue to link the biological processes back to the clinical situation to further enhance clinical recommendations.

All studies were approved by the Regional Board of Research Ethics in Uppsala, Sweden. (Studies I-II: reg. no. 2012/258: 7 November 2012; Studies III-IV: reg. no. 2014/235: 10 September 2014).
**Aims**

Perioperative care and operation techniques in gynaecological surgery have undergone major changes in recent decades. The overall aim of this thesis was to study recovery after gynaecological surgery in a normal clinical setting for a common type of surgery, hysterectomy; firstly, by studying the clinical impact of the implementation of an Enhanced Recovery After Surgery protocol, and secondly, by comparing different operative techniques. We also broadened our perspective to include the biological reactions to surgery, by examining endocrine reactions, metabolic stress, and inflammation. The objectives of the included studies were as follows.

**Study I**
To investigate whether the introduction of a structured ERAS protocol modified for gynaecological surgery could shorten LOS without increasing complications after AH.

**Study II**
To investigate whether the nature of the underlying disease (malignant or benign) altered LOS and complications in a setting with ERAS care.

**Study III**
To investigate whether the minimally-invasive technique of RTLH would induce less insulin resistance or inflammatory response than AH. In addition, clinical outcome was compared.

**Study IV**
To explore the relationship between postoperative insulin resistance after surgery and female sex hormone levels in women undergoing hysterectomy.
Methodology

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Method</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Observational study, with before-and-after design.</td>
<td>Registration one year before and one year after implementation of ERAS.</td>
<td>Length of stay.</td>
</tr>
<tr>
<td>II</td>
<td>Prospective cohort study.</td>
<td>Prospective registration of clinical parameters of two groups under ERAS care.</td>
<td>Length of stay.</td>
</tr>
<tr>
<td>IV</td>
<td>Secondary analysis of RCT.</td>
<td>Analysis of blood samples collected in Study III.</td>
<td>Female sex hormones in relation to insulin resistance.</td>
</tr>
</tbody>
</table>

**Studies I-II**

The ERAS program was implemented in clinical practice for all AH at the Department of Obstetrics and Gynaecology at Örebro University Hospital during December 2011 and January 2012. Study I was a single-center observational study comparing outcomes after AH (± salpingo-oophorectomy ± omentectomy) in a prospective cohort the first year after implementation of an ERAS protocol (n = 85), with the immediately preceding year used as control period (n = 120). Patients were included consecutively, and both benign and malignant indications for surgery were included. All hysterectomies were total and performed by experienced surgeons as well as surgeons in training.

The ERAS protocol is described in Figure 3. The care in 2011 was more traditional with no written perioperative care pathway, without standardised information, fasting from midnight, and carbohydrate loading. Moreover, there were no protocols or actions to avoid excessive use of intravenous fluids, prolonged fasting after the operation, or postoperative immobilisation. There were no formal criteria for discharge, although the implicit discharge criteria were approximately the same as after ERAS. No follow-up was planned. Premedication, pain and nausea treatment, and thromboprophylaxis were the same before and after introduction of ERAS.
**Before Surgery**

- **Guidelines**: Written guidelines for perioperative care.
- **Information**: Standardised oral and written information.
- **Admission**: On the morning of the day of surgery.
- **Premedication**: Paracetamol 1 g. Oral midazolam only for pronounced anxiety.
- **Antibiotic prophylaxis**: Oral metronidazole 1.2 g and trimethoprim/sulfamethoxazole 160/800 mg, 2 h before surgery.

**During Operation**

- **Fluid treatment**: Warm fluids and a hot air blanket (Warm Touch™ Blanket) to maintain the body temperature. Goal for peroperative fluids: 2-4 ml/kg/h of crystalloids (Ringer’s Acetate). When needed, 500-1000 ml hydroxyethyl starch 130/0.4 (Voluven® www.fresenius-kabi.com) or noradrenaline injections.
- **Urinary catheter**: Inserted in the operating room. Terminated morning of day 1.
- **PONV prophylaxis**: Droperidol 0.625 mg i.v. and betamethasone 4 mg i.v.
- **Pain treatment**: Parecoxib 40 mg i.v. Bupivacaine 0.25% 20 ml injected in the wound edges at closure.

**After Surgery**

- **Pain treatment**: Paracetamol 1330 mg and diclofenac 50 mg three times daily. Patient-controlled analgesia pump with morphine, no basal infusion, removed at 08.00 on day after surgery.
- **Nausea**: Ondasetron as first choice and metoclopramide as second.
- **Nutrition and fluid**: Maximum of 1000 ml i.v. fluids, terminated as soon as drinking. Oral fluid offered immediately when lucid, and food offered from 2 h after surgery. Nutritional drinks (200 ml, 200 kcal, 20 g protein, Fortimel® www.nutricia.com) in between meals.
- **Mobilisation**: Daily goals for mobilisation: out of bed for 2 h on day of surgery and for 8 h on the following days.
- **Thrombo-prophylaxis**: Tinzaparin 3500 IE sc (7 days for benign disease) or 4500 IE sc (20 days for malignant disease).
- **Discharge**: Standardised discharge criteria: when mobilised, eating and drinking normally, managing pain by oral analgesics, voiding normally, and showing no sign of bowel obstruction. Passage of flatus need not have occurred. tLOS 2 days after surgery.
- **Follow up**: Telephone call from nurse.

*Figure 3. ERAS protocol used in Studies I-IV (betamethasone was excluded in Studies III and IV). NRS = Nutritional Risk Screening, PONV = post operative nausea and vomiting.*
All medical records were reviewed for baseline patient demographics, surgical data, and clinical outcomes. In 2012, the patients also reported data in a logbook placed beside all hospital beds. ERAS parameters were then registered in the EIAS.

The study period for Study II was 2012–2014. In this study, a prospective cohort of all eligible patients with malignant disease (International Federation of Gynaecology and Obstetrics [FIGO] stage I or II) were compared to all eligible patients with benign diagnosis who underwent the same operation: AH and salpingo-oophorectomy (± omental resection). A total of 121 patients were included consecutively (81 with benign indications and 40 with malignant disease). The same ERAS protocol as in Study I was used for all patients, and the same data collection were collected and registered.

The main outcomes in both studies were LOS, the proportion of patients achieving the target LOS (tLOS) of 2 days, and complications.

In Study I, mean total compliance with protocol was calculated as the proportion of pre- and perioperative ERAS interventions fulfilled in relation to the total number of interventions (Figure 4). In addition, the effect of compliance with these parameters, regardless of period, was compared with the proportion of patients reaching tLOS.

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- Pre-admission counselling
- Carbohydrate loading
- No bowel preparation
- No long-acting sedatives
- No intra-abdominal drain
- Active warming
- PONV prophylaxis
- Limited amount of i.v. fluid
- Mobilisation out of bed on day 0

Figure 4. Pre- and perioperative elements used to calculate total mean compliance.
The complications registered are presented in detail in the original articles and here according to the Clavien-Dindo grading system (Figure 5).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>Complication without need for pharmacological treatment* or other intervention. Wound infections included.</td>
</tr>
<tr>
<td>II</td>
<td>Complication requiring pharmacological treatment with drugs other than those allowed in grade I.</td>
</tr>
<tr>
<td>III</td>
<td>Complication requiring surgical, endoscopic, or radiological intervention.</td>
</tr>
<tr>
<td>IV</td>
<td>Life-threatening complication requiring intensive care management.</td>
</tr>
<tr>
<td>V</td>
<td>Death of patient.</td>
</tr>
</tbody>
</table>

* Drugs such as anti-emetics, antipyretics, analgesics, diuretics, and electrolytes allowed.

Figure 5. Clavien-Dindo grading system for complications.

**Discussion of methodology in Studies I-II**
Methodologically, RCTs are considered the best choice for studying an intervention, but these are quite often hard to conduct. Separate items in a multimodal program are suitable for randomisation, and should be studied in this way. On the other hand, it would not be practical to randomise between the entire ERAS program and more traditional care in the same department, and the risk of overlapping of care impending. In addition, given the already existing evidence on ERAS care from other specialties, and prior research about many of the individual elements, we felt it unethical to further withhold the implementation from some patients by performing a randomised trial. Although studies with a before-and-after design have obvious limitations, in particular the risk of disregarding other elements of change during the study period, we consider these limitations to be less likely in the present case since the study periods followed immediately after one another and no other changes took place. Under these circumstances, we considered the study design for Study I to be the only possible choice. At the time of Study II, few fast-track studies had been performed on patients with gynaecological malignancies. In our experience attitudes toward patients with malignant disease have been that they are not expected to recover as fast as...
patients with benign disease, regardless of undergoing the same surgery. Given the results from Study I, a prospective cohort study where the patients with malignant disease could be seen as “exposed” and patients with benign conditions as “unexposed” was considered the most appropriate study design for the effect and safety of the ERAS protocol in malignant gynaecological conditions.

An important aspect of intervention studies is knowing whether the intended intervention ever occurred. Clinicians may overestimate their compliance with an implemented routine. Therefore, when studying a complex implementation such as a multimodal recovery program, it is particularly important to present the compliance with the protocol. Insights into compliance not only help the interpretation of the data but also facilitate comparison of results with other studies in the future. Further, the number of items in the ERAS protocol has been shown to be a crucial factor related to LOS. Presenting the compliance is also important since the term “traditional care” is not a uniform concept. As in our studies, some parts of the protocol may be in place before the implementation of the entire protocol. Choosing the pre-ERAS data from a time earlier than the year prior to implementation could have possibly shown a greater difference in outcomes, due to fewer ERAS elements being practiced. On the other hand, going back further in time could have resulted in greater uncertainty over any other bias that might have occurred. The conduct of the study in a general setting, we believe, is good for the external validity so the results can be generalised to similar situations.

LOS is a surrogate endpoint for recovery. This will be addressed further in the discussion section.

Studies III-IV
Study III was an open randomised controlled single-center trial. Patients from all planned hysterectomies at the department of Gynaecology and Obstetrics at Örebro University Hospital during the study period (October 2014–May 2015) were assessed for eligibility. Twenty women met the inclusion criteria, and were randomised to either RTLH or AH. Pre- and perioperative care were performed according to the same ERAS protocols as in Studies I-II, and the anaesthesia was standardised and equal for both groups. Patients with both malignant and benign disease were included. Inclusion criteria were: over 18 years of age, adequate knowledge of Swedish language, and assessed as being suitable for both techniques. The uterus had
to be able to be removed vaginally without morcellation. Patients were excluded if any of the following criteria were met: metabolic disease like diabetes mellitus or medication affecting insulin resistance, severe inflammatory disease, chronic pain and/or pain medication, known severe adhesions in the abdomen, allergy or contraindications to non-steroidal anti-inflammatory drugs, mental disability or severe psychiatric disease.

**Intervention**

All hysterectomies were total and performed by experienced gynaecological surgeons. The robotic technique is a laparoscopic surgical technique. Like traditional laparoscopic surgery, it uses small ports to enter the abdomen, but the camera and the instruments are docked to robotic arms and not directly manoeuvred by the surgeon. This means a lack of haptic feedback, but on the other hand hinders any effects of eventual tremor. The surgeon sits in a separate console not in direct contact with the operating table. This console gives a three-dimensional view of the operating field and allows the surgeon to control the instruments and the camera. The instruments are quite flexible, and can move like a human hand. All open operations used Pfannenstiel incision and either LigaSure™ vessel sealer or traditional technique.

*Figure 6. Operating with the da Vinci® Surgical System. Photograph: Lena and Jan Wijk.*
Outcome
The main outcome was insulin resistance measured by the hyperinsulinemic normoglycaemic clamp method. This test was performed before surgery and on the day after surgery, allowing a comparison of sensitivity to insulin before and after surgery. Insulin resistance was calculated as the relative change, in percentage, of M-value before and after surgery for each patient. During the clamps and three hours after surgery, blood samples were drawn to determine levels of circulating inflammatory parameters. Clinical outcome was registered during the time at the hospital ward and by a telephone call 30 days after the operation. Clinical mobility was tested by the 6-minute walk test (6MWT) before surgery and on the first day after surgery.

The clamp method is described in detail in Paper III (appendix) and summarised in Figure 7.

---

**Clamp method**

Fasting overnight. Start at 08:00. Blood glucose level measured at start.

Insulin infused i.v. at a fixed rate adjusted for weight aiming at levels seen after a standard meal.

Glucose infused to balance the glucose-lowering effect of insulin, maintaining normal blood glucose level (5.0 mmol/l).

Blood glucose measured every 10 minutes and infusion rate adjusted continuously to maintain glucose levels.

Steady state between infusions reached at approximately 60 minutes, and sustained for 40-60 minutes.

M-value: Amount of glucose infused to sustain steady-state glucose balance (mg/kg x min)

---

**Figure 7. Summary of the clamp method.**
Blood samples drawn before the onset of each clamp session were collected, and plasma isolated and stored at -80°C, for later analysis of female sex steroid hormones and gonadotropins in Study IV. Oestrogens were analysed with tandem mass spectrometry (LCMS/MS), progesterone by two-site immunoenzymatic assay, and gonadotropins by enzyme-linked immunosorbent assays (ELISA).

**Discussion of methodology in Studies III-IV**

Several methods for measuring insulin sensitivity/resistance are described in the literature. There are two major types of tests: dynamic and simple indices. The hyperinsulinemic normoglycemic clamp is considered the gold standard. It is a dynamic test, where blood samples are drawn repeatedly. Most clamp protocols capture the effect of insulin at levels when the hormone is in the active phase; that is, the levels seen after a standard meal, usually 5–6 times above basal fasting levels. At these levels in the non-stressed control situation, endogenous glucose is completely suppressed and the uptake of glucose is dominant. In the postoperative situation, there is a small increase in glucose production, and at the same time a very strong reduction in insulin-stimulated glucose uptake which is only evident when the insulin is raised to the levels seen after a meal.

The downside of the clamp method is that it is costly in terms of both time and personnel, and therefore not suitable for use either in large studies such as epidemiological studies or in clinical practice. For this reason, simpler tests have been developed using single samples of fasting levels of glucose and insulin for mathematically calculating insulin resistance. The most common simple test in studies is the homeostatic model assessment (HOMA), which has been used for various study situations including surgery. Knowledge of the test’s abilities and limitations is crucial, but unfortunately these aspects are often misunderstood, giving confusing results in the literature. The problem with the HOMA method is that it does not capture the main mechanism causing insulin resistance after surgery. Research into insulin resistance originated with the interest in diabetes mellitus and the metabolic syndrome. However, in healthy populations, fasting glucose and insulin is kept within a very narrow range even when the insulin sensitivity varies widely. At most 10–15% of the total insulin resistance seen after surgery can be attributed to glucose production; the remainder is mainly due to decreased uptake of glucose in the muscle cells. This mechanism is only activated at the levels of insulin seen after a normal meal. The clamp method measures this, but a method like HOMA, which uses the
basal level of insulin and glucose, cannot detect the major part of postoperative insulin resistance and so the results are different from the clamp method. For this reason, the clamp method was chosen for measuring insulin resistance.

To avoid any bias, blinding on top of randomisation is always better. We did not achieve this for all our parameters. The clinical test of recovery was blinded, but other parameters were not. It is almost impossible to tamper with the infusion rate during the clamp method, since this would potentially harm the patients by inducing hypo- or hyperglycaemia, and so this aspect was not blinded. However, the interpretation of the clamp data was blinded; this interpretation was performed by a member of our team who was not otherwise involved in the clamp, and if there was any uncertainty, the data were reinterpreted by another expert outside the team.

Apart from our main outcome, insulin resistance, we chose to measure inflammatory parameters for several reasons. The inflammatory reaction after hysterectomy is quite well studied, with generally consistent results. The specific parameters selected here were based on known outcomes from earlier studies. This enabled us to compare the reaction to previous studies, and strengthen the validity of our main outcome. We also wanted to compare the inflammatory reaction to the metabolic reaction.

Since the women in our study were in the late menopausal and postmenopausal ages, oestrogens were potentially very low and therefore was measured by the LC-MS/MS assay, which now can detect levels down to 1–5 pmol/L.

**Statistical methods**

Data are presented as numbers and percentages, means and standard deviations for parametric data, and medians and ranges for non-parametric variables. Proportions were analysed using a two-sided chi-squared test, chi-test for trend, or Fisher’s exact test when appropriate, and continuous variables were analysed using the Mann–Whitney U-test or t-test for two independent groups. A paired samples t-test was used for matched data. A p-value < 0.05 was considered statistically significant. In Study II, odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated for the primary outcome. Logistic regression was used to adjust for confounders and Pearson’s correlation was used to test for correlation. In Study III, all data analyses were carried out according to the pre-established analysis plan, according to intention to treat. Multivariate linear regression analyses
were used in Study IV. Statistical data were analysed using versions 21–24 of IBM SPSS for Macintosh (IBM Corp, Armonk, NY, USA).

**Sample size**

To investigate the implementation of ERAS (study I) we chose to include the population within the time-frame of one year before and after implementation. This time period was chosen to reduce the risk that, over time, outside factors could have an impact on the care and thereby influence the outcome, while still yielding a sample of sufficient size. This was estimated to generate about 100 patients in each group, which is a comparable size to other similar studies.

In Study II, we chose to include all eligible patients during the time-frame, and found three years to be an acceptable time period. We ended up including fewer patients than expected, since routines changed during this time period to incorporate more frequent use of laparoscopic hysterectomy.

The calculation of sample size in Study III was performed on the outcome of insulin resistance. There are no previous studies in gynaecological surgery regarding development of insulin resistance after surgery to compare with. One previous study compared laparoscopic and open cholecystectomy (sample size n = 6 in each group), finding a 40% difference in favour of the laparoscopic group.\(^{15}\) Based on this and the assumption that the difference could be smaller, with a mean reduction of 40% in the open group and 20% in the robotic group, with SD 13, alpha 5%, and 80% power, the sample size was calculated as seven. To allow for possible loss of patients and the uncertainty of the level of insulin resistance in this group, we included ten patients in each arm.
Results

Study I

In Study I, we compared outcomes in a cohort after implementation of an ERAS protocol with outcomes before the implementation. No significant differences were found in patient demographics before and after implementation in terms of age, body mass index (BMI), and previous treatments or diseases. Apart from a higher proportion of lower transverse incisions in the pre-ERAS group, there were no significant differences between the groups regarding type of surgery performed, the length of the operation, or perioperative bleeding. The type of incision did not affect LOS. Malignant disease, mainly endometrial cancer, was present in 28% of the patients pre-ERAS versus 38% after implementation (p = 0.124). The rest of the study population had a benign indication for surgery, mainly fibroids. The main outcomes were tLOS, LOS, and complications. Significantly more patients in the ERAS population (73% versus 56%, p = 0.012) were discharged within 2 days of surgery, and the mean LOS was slightly but significantly reduced after ERAS implementation (Table 1).

Table 1. Main results: LOS in days for the whole population and by operation type.

<table>
<thead>
<tr>
<th></th>
<th>Pre-ERAS</th>
<th>ERAS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All operations n=120</td>
<td>n=85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged 0-2 days (tLOS)</td>
<td>67 (56)</td>
<td>62 (73)</td>
<td>0.012</td>
</tr>
<tr>
<td>LOS</td>
<td>Mean (±SD)</td>
<td>2.60 ± 1.09</td>
<td>2.35 ± 1.17</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>2 (1-10)</td>
<td>2 (1-10)</td>
</tr>
<tr>
<td>HSOE n=74</td>
<td>n=64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged 0-2 days (tLOS)</td>
<td>35 (47)</td>
<td>43 (67)</td>
<td>0.019</td>
</tr>
<tr>
<td>LOS</td>
<td>Mean (±SD)</td>
<td>2.81 ± 1.26</td>
<td>2.45 ± 1.30</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>3 (1-10)</td>
<td>2 (1-10)</td>
</tr>
<tr>
<td>Hysterectomy n=46</td>
<td>n=21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged 0-2 days (tLOS)</td>
<td>32 (70)</td>
<td>19 (90)</td>
<td>0.063</td>
</tr>
<tr>
<td>LOS</td>
<td>Mean (±SD)</td>
<td>2.26 ± 0.61</td>
<td>2.05 ± 0.59</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>2 (1-4)</td>
<td>2 (1-4)</td>
</tr>
</tbody>
</table>

HSOE = hysterectomy and salpingo-oophorectomy.
There were no significant differences in complications, reoperations, or re-admissions between the two groups. The majority of complications were minor (grade I-II) according to Clavien-Dindo grading (Table 2).

Table 2. Complications according to Clavien-Dindo grading.

<table>
<thead>
<tr>
<th></th>
<th>Pre-ERAS</th>
<th>ERAS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>During primary stay</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Grade II</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Grade III</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>After primary stay &lt;30 days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Grade II</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Grade III</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Compliance with protocol is presented in Table 3. The major pre- and perioperative improvements in compliance with protocol after the implementation of ERAS were in organised preoperative counselling, carbohydrate loading, and reduction of the amount of i.v. fluids. Patients were mobilised earlier, eating earlier, and managing with oral pain relief earlier. The total amount of morphine used after surgery on day 0 was significantly lower in the ERAS group: 24 mg (0–111) pre-ERAS versus 19 mg (0–76) with ERAS (p = 0.008).
Table 3. Compliance with protocol and secondary outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Pre-ERAS (n=120)</th>
<th>ERAS (n=85)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative compliance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preadmission counselling</td>
<td>0</td>
<td>65 (77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carbohydrate drink</td>
<td>0</td>
<td>52 (72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No bowel preparation</td>
<td>120 (100)</td>
<td>85 (100)</td>
<td></td>
</tr>
<tr>
<td>No long-acting sedatives</td>
<td>120 (100)</td>
<td>85 (100)</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>120 (100)</td>
<td>85 (100)</td>
<td></td>
</tr>
<tr>
<td><strong>Peroperative compliance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No intra-abdominal drain</td>
<td>119 (99)</td>
<td>85 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>Thrombosis prophylaxis</td>
<td>120 (100)</td>
<td>85 (100)</td>
<td></td>
</tr>
<tr>
<td>Active warming</td>
<td>104 (89)</td>
<td>80 (94)</td>
<td>0.198</td>
</tr>
<tr>
<td>PONV prophylaxis</td>
<td>102 (89)</td>
<td>73 (86)</td>
<td>0.552</td>
</tr>
<tr>
<td><strong>Postoperative compliance/outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous fluids, total day 0, ml</td>
<td>3000(1300-6500)</td>
<td>2000(1000-4500)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mobilisation out of bed, day 0</td>
<td>39 (32)</td>
<td>61 (73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Eating full meal, day 0</td>
<td>13 (11)</td>
<td>18 (21)</td>
<td>0.038</td>
</tr>
<tr>
<td>Eating full meal, day 1</td>
<td>90 (75)</td>
<td>77 (91)</td>
<td>0.005</td>
</tr>
<tr>
<td>Oral nutritional supplements</td>
<td>0</td>
<td>53 (62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary catheter removal, day</td>
<td>1 (0-10)</td>
<td>1 (1-2)</td>
<td>0.223</td>
</tr>
<tr>
<td>First flatus, day</td>
<td>1 (1-3)</td>
<td>1 (0-3)</td>
<td>0.291</td>
</tr>
<tr>
<td>Only oral pain medication, day 1</td>
<td>87 (72)</td>
<td>72 (85)</td>
<td>0.039</td>
</tr>
<tr>
<td>Nursed back to ADL, day</td>
<td>2 (1-4)</td>
<td>1 (1-4)</td>
<td>0.303</td>
</tr>
<tr>
<td>Telephone call from nurse</td>
<td>0</td>
<td>72 (85)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ADL = activities of daily living, PONV = postoperative nausea and vomiting.
In both periods, the proportion reaching tLOS increased with higher compliance with the ERAS protocol items (Figure 8). The total mean compliance after implementation was 84% versus 59% before ERAS.

Figure 8. Percentage reaching the tLOS of 2 days (in green) in relation to number of pre- and perioperative ERAS parameters fulfilled during both time periods in total.

Conclusions of Study I
The proportion of patients reaching the tLOS of two days increased by nearly 20% after implementation of ERAS, without increasing the rate of complications. This improvement in LOS was seen even though many of the ERAS parameters were already in use before the actual implementation. The more compliance with ERAS elements, the more patients reached the tLOS.

Study II
In Study II, we compared patients operated for malignant disease with those undergoing the same operations for benign disease. Several differences between the groups were found; patients with malignant disease were older, had a higher frequency of diabetes, were twice as likely to be on cardiac
medication, and had a higher BMI. More patients with benign disease reported smoking. The diagnosis in the group of patients with a malignant disease consisted mainly of endometrial cancer stage I, while the group of patients with benign indications was dominated by uterine fibroids. The groups differed significantly in peroperative bleeding (50 versus 100 ml), but this difference is unlikely to be of any clinical relevance. Otherwise, peroperative data did not differ between the groups. There were no significant differences between patients operated for malignant versus benign disease in terms of average or median LOS or the proportion of patients discharged at tLOS (Table 4).

Table 4. Main outcomes: LOS in days and complications.

<table>
<thead>
<tr>
<th></th>
<th>Malignant (n=40)</th>
<th>Benign (n=81)</th>
<th>p-value</th>
<th>OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tLOS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2 days</td>
<td>25 (62)</td>
<td>56 (69)</td>
<td>0.465</td>
<td>0.74 (0.3-1.6)</td>
<td>1.3 (0.5-3.2)</td>
</tr>
<tr>
<td>LOS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>2.40 ± 0.74</td>
<td>2.49 ± 1.42</td>
<td>0.505</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>2 (1-5)</td>
<td>2 (1-11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary stay</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>1 (2.5)</td>
<td>6 (7.4)</td>
<td>0.423</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade III</td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>3 (7.5)</td>
<td>9 (11.1)</td>
<td>0.749</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade II</td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Of the demographics, only age was found to be a true confounder. A higher percentage of younger patients reached tLOS; the median age was 58 (30-88) among those who reached tLOS compared to 70 (42-93) among those who did not (p = 0.003). There was a negative correlation between tLOS and age (R = -0.28; p = 0.002). However, the age-adjusted OR comparing tLOS for patients with malignant versus benign disease was 1.3 (95% CI: 0.5-3.2), and so there was no difference between the two groups of patients in terms of LOS or the frequency of patients reaching the planned discharge day, when adjusted for age. There were few and mainly minor complications, mostly wound infections, and no difference between groups overall (Table 4).
Compliance with the same preoperative and peroperative ERAS protocol items described in Study I was generally high (82–100%). There were no significant postoperative differences between the two groups in any of the outcomes (use of i.v. fluids, mobilisation, eating a full meal, amount of morphine used, day of first flatus). In 2012, the ERAS protocol was implemented actively, and in 2013–2014 the protocol became a part of the standard clinical practice. No significant change in LOS was seen over the three years.

Conclusions of Study II
We found no difference between the groups with regard to LOS or complications. This study suggests that in gynaecological surgery the ERAS protocol seems to work well regardless of whether the disease is malignant or not.

Study III
Study III was a RCT comparing RTLH with AH for the development of insulin resistance, inflammatory reactions, and clinical recovery. Of the 79 women assessed for eligibility, 59 were excluded (mainly for not meeting the inclusion or meeting the exclusion criteria, seven declined and two were not informed). The remaining 20 were randomised and they were all allocated, given the intervention and analysed as planned.

Intraoperative bleeding, showed a clinically irrelevant difference of 20 versus 50 ml between the groups, but otherwise there were no differences in baseline characteristics. No intraoperative complications occurred. Postoperatively, one patient developed nausea (RTLH group) delaying discharge by one day, and one patient (AH group) was readmitted for fever of unclear origin and was given antibiotics.

Blood glucose and plasma insulin concentrations taken immediately before clamp studies and levels during steady state are presented in Table 5. None of the values differed significantly between the groups at any time. During the clamp at steady state, insulin levels were slightly but not significantly lower postoperatively compared to preoperatively. Preoperative insulin sensitivity showed a wide range among the patients studied (2.18–11.50 mg/kg min), but did not differ between groups (p = 0.686).
Table 5. Basal and steady-state clamp values.

<table>
<thead>
<tr>
<th></th>
<th>RTLH Before</th>
<th>After</th>
<th>AH Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>4.68 ± 0.4</td>
<td>4.97 ± 0.5</td>
<td>4.51 ± 0.4</td>
<td>4.81 ± 0.3</td>
</tr>
<tr>
<td>Steady</td>
<td>5.09 ± 0.2</td>
<td>5.19 ± 0.3</td>
<td>4.98 ± 0.3</td>
<td>5.07 ± 0.3</td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>5.30 ± 2.2</td>
<td>5.66 ± 2.4</td>
<td>6.93 ± 3.9</td>
<td>8.60 ± 6.0</td>
</tr>
<tr>
<td>Steady</td>
<td>50.69 ± 19.6</td>
<td>43.21 ± 11.8</td>
<td>54.22 ± 16.2</td>
<td>48.79 ± 18.9</td>
</tr>
<tr>
<td>M-value</td>
<td>6.6 ± 3.0</td>
<td>3.5 ± 1.1</td>
<td>6.1 ± 2.3</td>
<td>3.4 ± 1.2</td>
</tr>
</tbody>
</table>

Both groups had developed a significant reduction in insulin sensitivity at the postoperative clamp, but there was no difference between the robotic and the open group in the average development of insulin resistance (Figure 9). The mean reduction of sensitivity was 39% ± 21 and 40% ± 19 respectively (p = 0.948; 95% CI: -18-20).

Figure 9. Relative insulin sensitivity before and after operation expressed as the percentage insulin sensitivity, developed after operation compared to preoperative value. Group operated with RTLH compared to AH. No significant difference between groups. Boxplot presenting median, interquartile ranges, and range.
None of the inflammatory parameters differed between groups at baseline. In both groups, IL-6, white blood cell count, and CRP were raised from basal values after surgery. The levels peaked at 3 h postoperative for IL-6 and early day 1 for white blood cell count. For CRP, the increase began on day 1. Cortisol showed a significant increase from basal levels at 3 h after surgery in the AH group, while the RTLH group showed no increase from basal levels after operation. The increase in all inflammatory parameters, except CRP, from basal value to peak value was found to be significantly higher in the AH group than in the RTLH group (Figure 10).

Figure 10. Inflammatory parameters. T1 & T2 preop clamp (basal vs steady state), T3 3 h after surgery, T4 & T5 postop clamp (basal vs steady state). Mean and SD. WBC = white blood cell. RTLH in blue and ----, AH in green and ———.
Many clinical outcomes were improved by robotic surgery. Several parameters of recovery while in the hospital were improved, including LOS (1 [1–2] versus 2 [1–3] days, \( p = 0.005 \)), opioid consumption (15 [5–39] mg versus 40 [10–67] mg, \( p = 0.019 \)), time to tolerance of food, and time to mobilisation. Also, after discharge the patients operated with RTLH needed less time on pain medication (2.5 [1–16] versus 7.5 [2–27] days, \( p = 0.035 \)) and had a faster return to activities of daily living (2.0 [2–5] versus 4.0 [2–21] days, \( p = 0.009 \)). Six patients in the open group prolonged their sick leave, while in the robotic group, four reduced their sick leave and two prolonged it. In the 6MWT, walking distance did not differ between groups preoperatively. In both groups, walking distance was reduced significantly postoperatively, by 127 ± 70 m (\( p = 0.001 \)) in the robotic group and 255 ± 164 m (\( p = 0.002 \)) in the open group. The reduction was significantly larger in the open group than in the robotic group (\( p = 0.047 \)).

**Conclusions of Study III**

Robotic surgery improved recovery compared to open technique in hysterectomy, with less inflammatory and endocrine responses, but failed to show any difference in postoperative insulin resistance. In the current setting, the clinical gains seem to be more associated with the early reactions in the inflammatory system rather than with the development of insulin resistance.

**Study IV**

Study IV comprised a secondary analysis of the population in Study III, focusing on the relation between insulin resistance and female sex hormones. Baseline data were the same as in Study III.

Levels of pre- and postoperative oestrone (E1), oestradiol (E2) showed a large variation but did not differ between the surgery groups, nor did progesterone. Statistically significant differences were seen in follicle stimulating hormone (FSH) pre- and postoperatively and luteinizing hormone (LH) preoperatively indicating the uneven distribution in menopausal status between the groups (data not shown). In terms of hormonal levels, a total of nine patients were in the postmenopausal hormonal state, defined as FSH >25 IU/L (six operated with RTLH and three with AH).
Pre- and postoperative hormone levels (oestrogens and gonadotropins), and insulin sensitivity are presented in Table 6.

Table 6. Sex hormone levels and Insulin sensitivity.

<table>
<thead>
<tr>
<th></th>
<th>Premenopausal</th>
<th>Postmenopausal</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 11*</td>
<td>n = 9**</td>
<td></td>
</tr>
<tr>
<td>E1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>222 (118-589)</td>
<td>115 (48-204)</td>
<td>0.010</td>
</tr>
<tr>
<td>Postop</td>
<td>218 (63-682)</td>
<td>81 (52-270)</td>
<td>0.131</td>
</tr>
<tr>
<td>E2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>279 (48-1456)</td>
<td>18 (7-118)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postop</td>
<td>40 (19-577)</td>
<td>22 (6-51)</td>
<td>0.031</td>
</tr>
<tr>
<td>FSH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>6 (3-12)</td>
<td>81 (17-125)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postop</td>
<td>6 (2-13)</td>
<td>70 (26-122)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>10 (5-24)</td>
<td>65 (30-102)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postop</td>
<td>13 (5-29)</td>
<td>60 (33-101)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progesterone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>0.8 (&lt;0.6-35.0)</td>
<td>&lt;0.6 (&lt;0.6-0.6)</td>
<td>0.038</td>
</tr>
<tr>
<td>Postop</td>
<td>&lt;0.6 (&lt;0.6-8.9)</td>
<td>&lt;0.6 (&lt;0.6-1.5)</td>
<td>0.503</td>
</tr>
<tr>
<td>E2%</td>
<td>74 (44-92)</td>
<td>4 (-43-69)</td>
<td>0.001</td>
</tr>
<tr>
<td>M1</td>
<td>7 (2-12)</td>
<td>5 (2-10)</td>
<td>0.230</td>
</tr>
<tr>
<td>M2</td>
<td>3 (2-5)</td>
<td>4 (2-5)</td>
<td>0.456</td>
</tr>
<tr>
<td>IR%</td>
<td>51 (17-69)</td>
<td>21 (10-56)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

E1 = oestrone (pmol/L), E2 = oestradiol (pmol/L), FSH= follicle stimulating hormone (IU/L), LH = luteinizing hormone (IU/L), Progesterone (nmol/L), M1 = preoperative insulin sensitivity, M2 = postoperative insulin sensitivity (mg/kg x min) IR = insulin resistance, E2% = relative decrease in E2 from preoperative to postoperative value. *One patient operated with bilateral salpingo-oophorectomy (BSO) and one patient with hormonal intrauterine device and oestriadiol patch. ** Four patients operated with BSO.
In the premenopausal group, there was a significant decrease in absolute levels of E2 after operation (p = 0.016), which could not be seen in the postmenopausal group (p = 0.730). Also, the relative decrease in oestradiol from preoperative to postoperative values (E2%) was significantly different between the pre- and postmenopausal groups, as seen in Table 6 and Figure 11. None of the other hormones analysed (E1, progesterone, FSH and LH), differed between pre- and postoperative values.

![Boxplot showing correlation between pre- and postmenopausal status (blue and green, respectively) and E2%.](image)

There was no correlation between any of the oestrogens, progesterone or gonadotropins and preoperative insulin sensitivity (M1). In the entire population, age (p = 0.006), BMI (p = 0.020) and M1 (p < 0.001) were all correlated with IR%. There was a weak but significant positive correlation in the entire study population between preoperative E2 and IR% (r = 0.55, p = 0.013, r² = 0.3) which remained when adjusted for operation type (p = 0.010) or BMI (p = 0.016) respectively, but was not significant when adjusted for age or M1.
However, development of insulin resistance differed when analysed according to menopausal status, where the premenopausal group developed significantly more insulin resistance than the postmenopausal group (Figure 12).

![Boxplot showing correlation between pre- and postmenopausal status (blue and green respectively) and IR%.

There was also a significant positive correlation between E2% and IR% in the whole study population ($r = 0.72$, $p < 0.001$, $r^2 = 0.51$). This association remained significant when adjusted for age ($p = 0.028$), BMI ($p = 0.001$) and M1 ($p = 0.011$) separately, but not when adjusted for all three possible covariates together, where the association was just above the significance level ($p = 0.07$).

In Study III, the development of IR% did not differ significantly between type of surgery, and this remained the case when adjusted for menopausal status ($p = 0.404$; CI -23-10).
Conclusions of Study IV
In this exploratory study, the female sex hormonal status was not correlated to insulin sensitivity in the non-stressed situation before operation. Postoperatively, the premenopausal group developed a higher degree of insulin resistance, which was associated with a parallel relative change in oestradiol levels compared with the postmenopausal women. It remains unclear whether these are independent phenomena in the overall stress response or whether a causal relationship exists.
Discussion

Summary of main findings

Recovery can be enhanced in several different ways. We have shown that a structured implementation of a multimodal perioperative program is important and can enhance recovery. Higher compliance with the included elements of the program was linked to earlier discharge to home, and the shorter LOS did not increase complication rates or readmissions. An additional way to enhance recovery was by changing the operative technique. The biological mechanisms following the trauma of the operations included both metabolic and inflammatory changes. The reaction after surgery is complex and needs to be explored further, but the inflammatory reaction seems to play an important role.

Length of stay as a measure of recovery

From a holistic perspective, recovery is a very complex phenomenon including different aspects; not only physiological or biological aspects but also strong psychological, emotional, and social aspects. The patient’s expectations and previous experiences play a role, and the surrounding society and family also have expectations of what recovery is supposed to look like. These factors vary between societies and between countries. This means that recovery can be studied in many different ways and from many different angles, depending on the chosen perspective. This thesis is grounded in a positivistic tradition, and therefore uses quantitative and biological methods. Measuring recovery in a quantitative way has the advantage that this well-defined group can serve as a sample of the total population of women under similar circumstances, allowing the possibility to draw conclusions and generalise our results to the larger population. Since this is such a common clinical situation, the findings may affect many. It also gives the benefit of the possibility to compare our data to data from other studies on perioperative care.

LOS was chosen as the main quantitative surrogate measurement for recovery. The operational definition of counting the day of operation as day 0 is well-defined, and has been used in most similar studies. LOS is not the same as the physiological recovery, and can be influenced by other factors. Social circumstances and home environment have an effect, and can often prolong stay for patients who are ready for discharge from a strictly medical point of view. Health care systems vary between countries, and can...
also have an impact on time spent in hospital. In some countries, a short LOS has economic benefits for the caregivers, while other systems may depend on a number of nights in hospital to receive full payment. In many high-income countries, a shorter LOS could have medical benefits for the patient, as it eventually can minimise the risk of hospital-related complications such as infections, while for a population lacking basic resources, the hospital environment may be a safer place than the home. It is important to keep these non-biological aspects in mind when comparing results from around the world.

In an attempt to minimise the effects of factors other than medical, strict criteria for when the patient was ready to go home were used within the ERAS care programme: return of bladder function, mobilisation out of bed, pain control by oral analgesics, eating normally, and showing no sign of bowel obstruction. A new parameter in the ERAS register was introduced recently: ready for discharge, which means that the patient is assessed as medically ready to go home, based on the above criteria and the absence of any complications in need of hospital care. Using this as an outcome instead of LOS would narrow down the comparison even further to really focus on the biological recovery, leaving social aspects, health care traditions, and psychological circumstances aside, even when patients are not discharged when medically ready.

An early return to home should never be considered a purpose in itself. It must be founded on better recovery and not driven by an economic agenda. The patient’s feelings of security are important. Studies has confirmed that the patients feel more content within the ERAS program compared to before, in spite of earlier discharge, and in general are pleased with their overall care.54, 83, 84

**Clinical relevance of results**

Our findings of shorter LOS with ERAS are in accordance with the pre-existing literature both in colorectal surgery and in gynaecology.3 A meta-analysis of several observational studies from different parts of the world, although all at risk of bias due to the non-randomised design, showed congruent results of shorter LOS in populations with both benign and malignant indications for surgery and with different types of operation.51 Some studies also showed cost savings.52, 54, 84, 85 The first randomised trial was published only recently, which as opposed to previous studies could not find any benefit in the ERAS group.86 However, there are methodological issues that needs to be considered in that RCT. Only some of the ERAS elements
were implemented. The care in the control group was not standardised, and since the compliance with the included ERAS elements were not fully described, either in the intervention group or in the control group, there is no clear evidence of a difference in the actual treatment between the study groups. It is debatable whether the same caregivers can distinguish between patients without transmitting their expectations and incorporating some of the ERAS elements, which in the study is supported by the fact that both groups reduced their LOS compared to historical controls.

Judging the effect of implementation is dependent on the LOS prior to implementation. The difference found in our study was not as pronounced as that reported after implementation of ERAS in colorectal surgery (2-3 days), but the reduction in colorectal patients was from a longer average primary LOS (6-12 days). Our baseline data were already low compared to available LOS in the published gynaecological literature, and at a level comparable to the results after introducing similar ERAS programs. Still, our active implementation was able to significantly improve the number of patients reaching tLOS by 20%. This shows that it is possible to further improve outcomes even in a clinical situation where the baseline care is close to the protocol.

Records from the Swedish National Register for Gynaecological surgery (GynOp) show that in 2015, the median LOS for benign hysterectomy was 1–3 days when including all types of hysterectomy and just over 2.5 days for the subgroup of AH. These are findings regardless of fully implemented ERAS care or not. Gynaecological care in Sweden has long been partly influenced by fast-track ideas. Already in 2006, Oscarsson et al. compared different techniques for hysterectomy and showed that perioperative care is important for LOS. The process of change is ongoing, with results from studies gradually changing care, and many of the elements of an ERAS program are part of the regular care in Sweden today.

The proportion of patients operated using lesser invasive surgical techniques also influences LOS and recovery. The literature now includes published data reporting the feasibility of day care surgery for laparoscopic and vaginal hysterectomy, and sometimes describing differences in LOS between these different techniques in hours, within the same day. The clinical relevance of differences of a few hours is disputable; it may eventually be interesting in large cohorts from the economic perspective for care givers, but can hardly stand for a difference in patient recovery. At the same time, it is important that the pursuit of shorter LOS does not cloud the patient perspective and does not compromise patient satisfaction. Comparisons of
the outcome for hysterectomy in the future should therefore instead focus more on measuring recovery in terms of time to returning to daily activities, satisfaction, and quality of life rather than time in hospital.

Time on sick leave is also contextual, due to differences in health care systems between countries. In Sweden, median sick leave after hysterectomy ranges from about 22 to 40 days between different hospitals, including all techniques.\textsuperscript{8} The large difference may be partly due to different proportions of abdominal technique. In Study III, the median sick leave was 28 days in the robotic group and 39 days in the open group, with a range of 14–46 days.

In a multimodal intervention, the question arises of which element is of most importance for the outcome. A meta-analysis by de Grooth et al. showed that the published reports on ERAS in gynaecology are diverse, and that the pathways used in the different studies include different numbers of ERAS elements.\textsuperscript{51} The international ERAS® Society guidelines are relatively new and not yet tested in full.\textsuperscript{4, 5} In our setting, some of the ERAS elements were already in place before implementation. A colorectal study showed that changing from the overnight fasting state to preoperative carbohydrate loading and controlling i.v. fluids was of importance for improved outcomes,\textsuperscript{32} and these care elements were also significantly enhanced after implementation in our setting. However, it is precarious to single out isolated elements, because many elements interact both clinically and biologically in giving the total effect. This does not counteract the need for RCTs of single elements in a setting with otherwise standardised ERAS care; on the contrary, more studies are needed to verify the best way forward, especially for situations specific to gynaecology.

Although a multimodal approach to pain management is the key aspect in ERAS programs, epidurals are traditionally part of the ERAS concept, at least for open surgery. Besides the effect on pain and the reduction of need for oral opioids, this has a known effect in reducing the stress reaction.\textsuperscript{11, 91} We chose not to include epidurals in our protocol which might seem strange. Despite the positive effect on biological response, there is a risk that an epidural could hinder mobilisation and therefore counteract the positive biological effects. Spinal anaesthesia could have been the alternative, and has been shown to have positive effects after hysterectomy, although not crucial for LOS.\textsuperscript{48} In any case, in our study the opioid use was reduced after ERAS even without a change to regional anaesthesia, and this has also been seen in other studies.\textsuperscript{32, 34}
In this thesis, we present the only published RCT comparing RTLH with AH. The study shows shorter LOS and faster recovery in robotic compared to open abdominal surgery. Lack of blinding could potentially have influenced the clinical outcome. The results of the 6MWT, which was performed by a blinded examiner, suggest that there was a real clinical improvement with the less invasive technique. Our findings of shorter LOS and faster recovery are in line with the overall reports from other minimally-invasive techniques.\textsuperscript{5,7} This is not surprising, since robotic surgery is another form of laparoscopy, and at first glance it could be argued that given this pre-knowledge it would not be ethical to perform a randomisation including an abdominal approach. Even so, although laparoscopy and the vaginal approach have been used for about 40 years, a large proportion of hysterectomies are still performed with open technique.\textsuperscript{8,92} However, there are now studies showing that the introduction of the robot-assisted technique has finally increased the frequency of minimally-invasive operations.\textsuperscript{61} In our institution, by the time of the study, very few vaginal or traditional laparoscopic hysterectomies were performed. Moreover, the main focus of the study was on biological processes and responses to both techniques that had not yet been studied.

Four RCTs have been published on RTLH for benign indication, all comparing the technique with total laparoscopic hysterectomy. Sarlos\textsuperscript{58} and Paraiso\textsuperscript{56} focused on operative time, and found that robotic surgery took longer. The operative time reported in their studies was 1.5–2.4 times longer compared to our data, and also in contrast to the results of Lönnerfors\textsuperscript{55} and Diemling,\textsuperscript{57} both of whom showed shorter operating times using robotic surgery and had operating times similar to ours. These differences are probably due to lack of robot experience in the early studies. In any case, operative time must be interpreted as more of a surrogate for economic aspects and not related to recovery within the current time frames. Clinical outcomes were very similar between the groups; if anything, there were some indications of fewer complications and less bleeding in the robot group. Lönnerfors et al. focused on economic aspects, finding that robotic surgery had a similar cost to traditional laparoscopy when the purchase cost was excluded, but was more expensive than the vaginal approach.\textsuperscript{55} Studies on robotic surgery for endometrial cancer show good oncological outcome, and for staging surgery, shorter LOS and in some studies even lower costs than open surgery.\textsuperscript{59,68} Overall, the literature suggests that robotic surgery is as effective and safe as other minimally-invasive techniques, regarding the in-
individual patient perspective of recovery. Some studies even show fewer complications, less bleeding, and fewer conversions for robotic surgery, and the technique seems feasible for obese patients, older patients, and for more complex surgery. Given the small differences, the best choice of minimally-invasive technique is probably mostly related to the individual surgeon’s competence with the different techniques. The issue remaining is more of a health care issue regarding in which situations the potentially higher cost is acceptable.

**Biological results**

All patients in our study developed insulin resistance after hysterectomy, irrespective of mode of operation. The mean degree of resistance was quite high, and at the same level as open colorectal surgery. We also found a large variation in insulin resistance in both study groups, without any obvious explanation. While in cholecystectomies an almost 3-fold difference has been found between the two techniques, in this setting and in contrast to our hypothesis no such difference in insulin resistance between the two different surgical techniques could be confirmed.

The pathways triggering insulin resistance after surgery are not fully understood. The tissue trauma is well known, but there might be other mechanisms too. Difference in anaesthesia has previously been shown to have an effect, which is why we chose the same protocol for both groups. In robotic gynaecological laparoscopy, the patient lies in a tilted position with the head down in strict Trendelenburg position, meaning that the head is placed low (in this case around 20 cm above the floor), and the body and legs are on an inclined plane. This position is maintained during the whole time of console surgery (the time of operation minus the time to insert and pull out trocars, docking, and wound closure), which in our study lasted for 30-60 minutes. Lying in this position when awake triggers heavy pressure over the chest and head; it is quite uncomfortable and painful, and is not voluntarily tolerated for more than a few seconds. Which effect this has on the metabolic reaction is unknown, and has never to our knowledge been studied. If it triggers insulin resistance, this could be one factor that could have masked a difference between the two surgical types with regard to the surgical trauma, and then such a difference could eventually exist despite the results from our study. Since many elements of the ERAS pathway are believed to reduce the stress responses, nursing the patients under ERAS care could have been a pathway to even out the difference between the groups. Against this is the overall high level of development of resistance.
In two early articles, Schricker et al.\textsuperscript{71,72} showed that vaginal hysterectomy induced higher levels of postoperative glucose than both laparoscopic assisted vaginal hysterectomy and AH. They speculated that traction, which is mostly used in vaginal hysterectomy could influence the metabolic reaction suggesting that other mechanisms than the size of the abdominal incision may influence the reaction when surgery is performed in this area of the body.

Our population consisted of women of late premenopausal, perimenopausal and postmenopausal ages, meaning that many of them had quite variable and unpredictable hormonal status. The literature have linked the physiological levels of oestradiol in women to insulin sensitivity, where in premenopausal women normal oestradiol levels are linked to a favourable insulin sensitivity status, and the oestrogen receptors have been seen to play a role in the glucose metabolism and regulation.\textsuperscript{24,25} This was in contrast with our results, where we could not find any correlation between sex hormone levels and insulin sensitivity in the non-stressed preoperative situation. The knowledge of the association between oestrogens and glucose metabolism is to a far extent derived from animal models and experimental research. Also, there are indirect indications where oophorectomised mice or postmenopausal women with exogen treatment with oestrogens improve their insulin sensitivity.\textsuperscript{24,25}

In earlier clinical studies, there have not been a clear link between menopausal status and insulin sensitivity.\textsuperscript{95,96} In our study, we found a strong association between the menopausal status and the development of insulin resistance after surgery. In addition, we found a prominent fall in oestradiol levels after surgery, which also was associated with the amount of insulin resistance. This association has to our knowledge not previously been reported. The present study cannot reveal whether this is a parallel phenomenon or whether a causal relationship exists, but given the knowledge from the basic research, it is an intriguing question whether these acute changes in oestradiol levels in conjunction with surgery have an effect on insulin resistance in the short-term perspective. If so, one can speculate if this is a factor contributing to the rather large development of insulin resistance after hysterectomy regardless of surgical technique.

Our results showing less inflammatory reactions after robotic surgery are in line with previous studies. The lower rise in both IL-6 and CRP was found after the less invasive hysterectomies.\textsuperscript{19,20,22} Different kinds of laparoscopy have previously been shown not to differ from each other in terms of the inflammatory reaction.\textsuperscript{80} In our study, inflammatory responses showed the
same profile as reported by others, with IL-6 peaking a couple of hours after surgery and CRP beginning to rise on day one.\textsuperscript{19, 21} We may not have captured the peak of CRP reaction, which often occurs on day two,\textsuperscript{20, 70} and this may be why our study found no significant difference between the two groups. The decision not to sample on day two was made since we presumed that a number of our patients already would be discharged on day one.

The two systems, inflammation and metabolism, are both triggered by surgery, but it remains unclear whether they are parallel phenomena or linked in a certain way. Further studies on insulin resistance and inflammation are needed to confirm or reject our results. It is also still not totally certain what factors matter the most for recovery. In our study, clinical recovery was found to be more connected to the magnitude of inflammation than to changes in the metabolic system. Maybe, in this fairly healthy population the load of insulin resistance can be managed in a way which would not be possible for a more fragile population.

**Strengths and limitations**

The strength of the studies included in this thesis lies in the completeness of data. The groups were well-defined, and patients were included consecutively. Data were collected either prospectively in a standardised way, or in a randomised way. For the pre- and post-implementation data, the time periods were chosen near in time, in order to reduce the risk that factors other than the intervention could have influenced the results. We chose to be transparent in presenting the compliance with protocol, as discussed earlier. Demographics were comparable between groups, and the surgery and populations were well-defined. The populations were well-representative of the current procedure, and we believe our results can be generalised to others in similar situations. Laboratory measurements were made in standardised ways using appropriate methods.

There are also limitations. LOS as a surrogate measurement for recovery, the lack of blinding, and the non-randomisation of Study I are discussed before. In Studies II-IV, the number of patients was relatively small. The change in our department towards more minimally-invasive surgery during the study period limited the number of patients in Study II, but the confidence intervals were still relatively narrow, suggesting that this had less impact. Study III was of comparable size with other studies measuring inflammation and insulin resistance.

None of our studies were designed for longer follow-up than 30 days after surgery. However, long term effects represent a different scope and
area of research, and was beyond the aims of the current studies focusing on short-term outcomes. Long-term recovery after hysterectomy beyond the first postoperative period is less studied, but the reported prevalence of chronic pain ranges from 5% to 32% and in two Danish studies only 15–27% of the patients developing chronic pain, experienced pain as a new symptom after surgery. Pain is a common indication for hysterectomy, and although the majority of patients will be better after surgery these results suggest that it is important to inform women with preoperative pain of the possibility of persisting pain. None of the studies showed a difference in relation to operational technique.

**Recommendations for future research**

Recovery needs to be studied further. Perioperative care will continue to change. The ERAS philosophy includes the continuing and regular audit and updating of guidelines, and the knowledge that the best evidence known today will change alongside new surgical techniques, anaesthesiological progress, and future research.

Due to the increasing numbers of ERAS elements used in daily practice, there is no longer a common traditional care. Given the evidence for many of the separate ERAS elements, randomisation between a non-ERAS and ERAS care can hardly be done, for both practical and ethical reasons. Instead, the main focus should now be to study distinct elements within an otherwise established ERAS care, particularly elements which may have a different impact in gynaecological situations or have not yet been studied thoroughly. The population in this thesis are similar to other abdominal surgery groups in many ways, but the knowledge of the effects of ERAS in patients undergoing really extensive ovarian cancer surgery is sparse. This group have many specific challenges which differ from other forms of surgery. Patients are generally in a very advanced stage of cancer, have poor nutritional status, and massive ascites. The operation often includes multiple organs, anastomosis, and extensive perinecctomy. The major fluid shifts during the operation and the postoperative phase create special difficulties in managing fluids, and have implications for the questions of both drains and epidurals. In addition, further studies on the relationship between compliance with elements and outcome are needed in gynaecology, as are studies using merged data from multicentre studies.

Further exploration of the biological mechanisms contributing to recovery would allow transmission of this knowledge back to the clinical situation, helping to enhance recovery even further. The new and interesting area
of linking the inflammatory system to the metabolism and immune regulation may eventually give us new keys to a better understanding of recovery.

There is also room for studies on recovery after surgery in a broader sense of the concept. The impact of psychological mechanisms as well as social and economic aspects is of interest. More use of patient-related outcomes such as patients’ experience of operation type and care is needed. Further studies are needed on the outcome in the longer perspective, including the risks of chronic pain and quality of life aspects, and any potential role of perioperative care or surgical techniques in long term survival among cancer patients. The results from colorectal surgery, suggesting that perioperative care could impact survival rate, need to be confirmed in the gynaecological field.
General conclusion

The overall conclusion in this thesis is:

Recovery after hysterectomy can be influenced in different ways in a normal clinical setting. An ERAS program seems to be effective and safe regardless of patient category. Recovery also seems to be affected by operational technique. Hysterectomy triggers stress reactions in both the inflammatory system and the metabolic system, including the development of relatively pronounced insulin resistance. The inflammatory reaction can be reduced by the use of a less invasive laparoscopic robotic technique. It remains unclear why the same benefit was not seen in the metabolic reaction and although sex hormonal status was associated with insulin resistance, the lack of difference in insulin resistance between the two methods of surgery could not be explained by the female sex hormonal status of the patient.
Sammanfattning på svenska


Syftet med studierna som ingår i denna avhandling var att se om återhämtningen efter hysterektomier kan förbättras. Dels genom införandet av ett strukturerat ERAS-program för olika patientgrupper. Vidare genom att jämföra olika operationstekniker där återhämtning studerades i form av de biologiska reaktionerna som följer på kirurgi, i form av insulinresistens och inflammation.

ERAS, infördes på kvinnokliniken, Universitetssjukhuset i Örebro 2012. Åtiofem konsekutiva patienter som genomgick hysterektomier och vårdades enligt ERAS-programmet under 2012 jämfördes med 120 konsekutiva patienter året innan införandet. ERAS-programmet innehöll bland annat riktlinjer för preoperativ information, nutrition och fasta, vätskebehandling under och efter operation, katetrar och drän, smärtlindring, behandling av illamående, mobilerande och matintag efter operationen samt regler för utskrivning. Målet var att patienterna skulle vara redo för hemgång inom två dagar efter operationen. Vårdsedaren var redan vid införandet av programmet förhållandevis korta men kunde sänkas ytterligare något (2.35 ± 1.17 jämfört med 2.60 ± 1.09, p = 0.012) och efter införandet av programmet ökade andelen som gick hem inom två dagar från 56% till 73%, (p = 0.012), utan att andelen komplikationer eller återinläggningar ökade. Fölsamheten
till programmets delar var i medeltal 84%. Andelen som kunde skrivas hem
inom två dagar ökade med följsamheten till programmet. Vid minst fyra
parametrar uppfyllda gick 33% hem dag två, vid sex parametrar 57%, vid
sju parametrar 76% och vid 8 parametrar 80% (p < 0.001).

Därefter genomfördes 2012–2014 en prospektiv kohort-studie. Patienter
som opererades på grund av cancer (n=40) jämfördes med patienter som
opererades på benigna indikationer (n=81). Alla vårdades enligt samma
ERAS-program. Följsamheten till programmet var generellt högt i
båda grupperna (82–100%). Ingen signifikant skillnad i utfall av
vårdtiden kunde ses mellan grupperna (2.40 ± 0.74 resp. 2.49 ± 1.42, p =
0.505, OR 0.74 (0.3–1.6). Korrigerat för åldersskillnader i grupperna var
OR 1.3 (0.5–3.2). Inga skillnader i komplikationer sågs. Vårdtiden förhöll
sig stabil de tre studerade åren.

En randomiserad kontrollerad interventionsstudie genomfördes på 20
kvinnor som planerades för hysterektomi vid kvinnokliniken på Universi-
tetssjukhuset i Örebro, oktober 2014 till maj 2015. Patienterna randomise-
rades till robotassisterad laparoskopisk eller öppen abdominell hyste-
rektomi. Huvudsyftet med studien var att mäta den metaboliska reaktionen
efter kirurgin i form av insulinresistensutveckling. Vidare mättes det inflam-
matoriska svaret och kvinnans hormonstatus genom blodprover och den
kliniska återhämtningen registrerades. Båda grupperna utvecklade i medel-
tal en relativt kraftig insulinresistens, men ingen skillnad mellan grupperna
kunde påvisas (39% ± 21 respektive 40% ± 19 (p = 0.948; 95% Cl. -18-
20). Kvinnans hormonella status förändrade inte denna slutsats även om
den hormonella reaktionen i samband med kirurgin föreföll vara korrelerad
till utvecklingen av insulinresistens. Däremot utvecklade robotgruppen sig-
nifikant lägre nivåer av inflammation. Den robotassisterade kirurgin gav
flera kliniska fördelar med bland annat kortare vårdtider 1(1–2) vs. 2(1–3)
p = 0.005.

Denna avhandling har visat att återhämtning efter hysterektomi kan på-
verkas på olika sätt. Den kliniska återhämtningen kan påverkas dels genom
att systematiskt förändra den peroperativa vården. ERAS-programmet för-
reföll säkert och effektivt för alla de patientgrupper som genomgår hyste-
rektomier. Återhämtningen kunde också påverkas genom valet av opera-
tionsteknik där robotassisterad laparoskopisk hysterektomi gav snabbare
återhämtning än öppen abdominell teknik.

Hysterektomier utlöser biologiska stressreaktioner i både det inflamma-
toriska och det metaboliska systemet. Den inflammatoriska reaktionen
minskades vid robotassisterad laparoskopisk teknik medan det metabola
svaret i form av insulinresistens inte skiljde sig åt mellan operationsteknikerna. Orsakerna till detta är oklar. Skillnader i kvinnornas hormonella status kunde inte förklara det oförväntade resultatet av det metabola svaret. Vidare studier behövs för att finna större förståelse för de biologiska reaktionerna i samband med operation och hur inflammationen och metabolismen samspeiar. Även återhämtningen efter operation på längre sikt behöver studeras vidare.
Acknowledgements

This thesis has only been possible thanks to the help and collaboration of many people, for which I am so very grateful. First of all, I want to express my gratitude to all the women who participated in the studies.

I would also especially like to thank:

My main supervisor, Kerstin Nilsson, for taking this journey with me from my very first steps in becoming a gynaecologist, into research, and all the way through my PhD education. I admire you for your clarity of mind, integrity, and the courage to always stand up for what’s right. Thank you for believing in me all these years, and after a meeting with you, no matter how troubled, always making me feel better than before.

My assistant supervisor, Olle Ljungqvist, for taking me on, sharing your deep knowledge in this field, and introducing me to the world of ERAS. And although very often far away, regardless of time zone, never further away than an e-mail or a phone call.

My co-author, Karin Franzen, for working alongside me in the demanding implementation phase, and Bayar Baban, for your friendship and for teaching me “to clamp”.

The present and former Heads of the Department of Gynaecology and Obstetrics at Örebro University Hospital, Ingrid Strandman, and Rene Bangshøj, for facilitating the hard combination of clinical work and research. Also, Gill Kullberg, for taking care of me when most fragile.

The nurses and midwives who worked alongside me in the ERAS team. Without you, no implementation. Linda Gustafsson, for your truly hard work, devotion to our patients, positive mind, and computer skills.

The Department of Clinical Trials (AKP), Åsa Kälvesten, and Eva Norgren-Holst, for support, and all the nurses who made “the clamps” happen. All my colleagues in our research group “mikro-miljön”, for sharing the same interest.
All the staff at the Clinical Research Laboratory (KFC), especially Elisabeth Tina, Robert Kruse, Lena Jansson, and Seta Kurt, for your always happy and professional helping hands, especially in times of need. Elisabeth, thanks for caring, for laughter, for Bitmojis, for M&Ms, and for just being you.

Anders Magnusson, for valuable statistical support.

Ravinder J Singh, and Sarah A Andersson, at the Immunochemical Laboratory, Mayo Clinic, USA, for your instant, positive, and kind response to help out in a very difficult situation. You saved me! I will always be thankful to you.

Jonas Bergquist, and Kumari Ubhayasekera, at the Uppsala Department of Chemistry, for laboratory analyses.

Anette Trygg, for your work with the walking tests.

All the staff at the Medical Library, Campus USÖ, and the IT department, Örebro University, for many times of fast and efficient service when needed.

My colleagues in the gynaecological cancer surgical team. Fatma Bäckman, for being an inspiration and a true role model. You have a heart of gold. Thank you for seeing me in both happy times and sad times. Rene Bangshøj, for letting me grow and sharing so many happy moments during surgery. Clelia Flodström, Luz Ladi, and Inga Steinberga, for your never-ending hard work.

All my other colleagues, at the Department of Obstetrics and Gynaecology. I really enjoy working with you. To Hanna Östling, for being my friend and tricking me into becoming a gynaecologist, to Lovisa Bergengren, for being my friend since day one in medical school, and to Ann-Kristin Rönnberg, for sharing your PhD student experience with me.

All OR nurses. No matter how distressed or sad before, after a day working with you, I have always a smile on my face. You make me feel good. The OR is really the place to be!
The nurses and midwives at the Department of Women’s Health in Örebro, Ward 23. Keep up the good work!

All the nurses and doctors at the Anaesthesiological Department, especially Anil Gupta, and former Head of Nurses Maria Engström.

My nearest friends. Thank you all for sharing my life outside the hospital.

To my family: My parents, Lennart and Eva Thörn, for the secure and loving upbringing that gave me the self-confidence to walk this way. My brother, Kristian Thörn, for truly a lifelong friendship, and my sister, Matilda Limani, for love and laughter. And Ulrika Thörn, to have a sister-in-law like you to share my daily life, children, and work environment, is a gift.

My three beautiful children, Josef, Aron, and Adina, for truly filling my life with music and for the joy of watching you grow in beauty and talent. I love you more than anything. You are my biggest achievement and greatest gift. And Jan, for staying with me all these years. ...hold my hand and have no fear, I will be here... (SC Chapman).

And to God, who made the human body such a miracle. To God be all the glory!
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