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ENHANCED RECOVERY AFTER SURGERY (ERAS – ENHANCED RECOVERY AFTER SURGERY PROTOCOL) IN GYNECOLOGIC SURGERY

THESIS SUMMARY

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The thesis is presented on 152 pages and is illustrated with 7 tables and 16 figures. The bibliography includes 432 literature sources. The thesis research was carried out at the Gynecology Clinic at St. Anna Hospital – Varna.

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The defense materials are available in the library of the Medical University – Varna.

CONTENTS

ABBREVIATIONS

ACCP – American College of Chest Physicians

AWIB – Abdominal wall infiltration with bupivacaine

CC– Cervical cancer

CDC – Centre for Disease Control and Prevention

DVT – Deep Vein Thrombosis

EIN – Endometrial Intraepithelial Neoplasia

ERAS – Enhanced Recovery After Surgery

FDA – US Food and Drugs Administration

GIT – Gastrointestinal Tract

IB – Anesthetic infiltration of bupivacaine

LAVH – Laparoscopically Assisted Vaginal Hysterectomy

LOS – Length of Hospital Stay

MIS – Minimally invasive surgery

NSAIDs – Non-steroidal anti-inflammatory drugs

SSI – Surgical site infection

VAS – Visual Analogue Pain Assessment Scale

VTE – Venous Thromboembolism

INTRODUCTION

ERAS (Enhanced Recovery After Surgery) program is a complex system of procedures requiring a multidisciplinary team of trained specialists – nursing staff, anesthesiologists, gynecologists, and psychologists who participate in pre-, intra-, and postoperative care of the patient. Currently, this system is seen as an initiative aiming to improve the global quality of surgery, which ultimately affects clinical benefits and lowers hospital costs. The ERAS protocol includes sequential implementation of various procedures: patient education and preoperative consultation, preoperative carbohydrate loading of the patient with fluids and carbohydrates in order to reduce preoperative fasting, multimodal approach to pain management, reduction of opioid analgesics, prevention of infections associated with the surgical incision, prevention of venous thromboembolism, and early mobilization. The procedures aim to reduce the consequences of surgical stress and facilitate early patient recovery after surgery.

Birth of the idea of enhanced recovery in surgery

Discussions about fast recovery after surgical treatment started in the 90s of the last century. A new "rapid recovery" approach was undertaken on 280 patients undergoing cardiopulmonary bypass surgery. Along with cardiac surgery-specific procedures, the expedited protocol includes patient education, early discharge, and one follow-up appointment within a week of discharge. The authors reported a reduction of about 1.5 days in hospital stay and a 30-day period with no increase in mortality and readmissions. ERAS, known initially as fast-track surgery, was introduced by Henrik Kehlet in 1997. He developed a protocol of procedures in colorectal surgery intending to suppress the pathophysiological processes associated with surgical stress and the neurohormonal response, thereby reducing organ dysfunction and enhancing quick recovery. The idea of rapid recovery in surgery gained supporters over the years. In 2001 the ERAS Study Group was founded, which grew into the ERAS Society.

The ERAS program in gynecologic surgery

In gynecology, initial publications were related to benign pathology. Ottesen et al. (2003) described a multimodal rehabilitation model leading to a shortened convalescent period in vaginal surgery for genital prolapse. The authors reported a 1 to 3-week shorter recovery period. Møller et al. (2001) emphasized early mobility and early feeding in laparoscopic-assisted vaginal and abdominal hysterectomies. Marx et al. (2006) first demonstrated the role of accelerated rehabilitation in patients with ovarian cancer, focusing on shortened hospital stays, early nutrition, and early patient mobilization. The researchers describe the role of continuous epidural analgesia and hypothesize a possible positive effect of euvolemia on rapid recovery after surgery. Kalogera et al. (2013) demonstrated improved recovery in gynecologic malignancies undergoing major abdominal surgery associated with cytoreductive surgery. Reduced hospital stay and good postoperative pain control were reported. The researchers concluded that adherence to components of the ERAS protocol improved quality without favoring specific elements of the ERAS protocol. The question of whether these benefits result in patient satisfaction is further explored by Philp et al. (2015). The authors found a high level of satisfaction on behalf of the patients and, in terms of the shortened hospital stay, they also found satisfaction on the part of the medical staff - physicians and nurses. The Royal College of Obstetricians and Gynecologists (RCOG) reviewed the essential components of ERAS in 2013 and suggested that the ERAS program offers safe, high-quality perioperative care and should become a standard practice for all women undergoing elective gynecologic surgery. Miralpeix's team (2016) proposed a system of procedures as part of the ERAS program for gynecologic oncology patients, including pre-, intra-, and postoperative strategies. The authors emphasize some elements of ERAS: counseling the patient before hospital admission, avoiding preoperative bowel preparation, using minimally invasive techniques, and encouraging postoperative early nutrition and early mobilization. The researchers recommend functionally oriented multimodal analgesia techniques, team efforts, and active patient participation.

Establishing guidelines for ERAS application in gynecologic surgery

In 2016, the ERAS Society published two-part recommendations on pre-, intra-, and postoperative care in gynecologic/oncology surgery. It presents guidelines related to the best evidence in gynecologic surgery and ERAS. Where data for gynecologic oncology patients were not of the best quality, recommendations were made based on findings from other surgical disciplines, primarily colorectal surgery, because of the similarity in surgical access. The guidelines were updated in 2019 with the accumulation of scientific evidence and experience in ERAS and gynecologic oncology surgery. In 2020, the ERAS Society published guidelines regarding specific procedures for applying the ERAS system in cytoreductive gynecologic surgery with or without hyperthermic intraperitoneal chemotherapy.

Since 2014, there have been an increasing number of publications on the application of ERAS procedures in minimally invasive gynecologic surgery, reporting additional benefits over those inherent to minimally invasive techniques. The researchers evidenced an additional reduction in hospital stay without an increase in morbidity and rehospitalization rates in the postoperative period, adequate pain control, postoperative nausea and vomiting, and reduced opioid intake. The accumulation of scientific evidence led to the creation, in 2021, of guidelines for minimally invasive surgery in gynecology and the features of the ERAS protocol. A guideline designed explicitly for vulvar and vaginal surgery conditions has also been developed.

Currently, the ERAS program is represented in many gynecologic centers worldwide – in 38% of the centers in Europe, 33% of the centers in the Americas, 19% of the centers in Asia, and 10% of the centers in Africa.

I. AIM

To assess the applicability and positive effects of the ERAS protocol in surgical gynecology by auditing and reporting perioperative outcomes.

II. TASKS

1. To investigate the applicability of early mobilization as an ERAS component for the recovery of patients in the early postoperative period.

2. To investigate the feasibility and effect of early oral feeding on the recovery of patients without prior mechanical bowel preparation.

3. To investigate the effect of carbohydrate fluid intake before surgery on glycemic control in the early postoperative period.

4. To evaluate the influence of antimicrobial prophylaxis on the occurrence of postoperative infections and/or fever.

5. To evaluate the effect of opioid-sparing analgesia and antiemetic therapy in the postoperative analgesia of patients undergoing open, laparoscopic and vaginal gynecologic surgeries.

6. To investigate the incidence and nature of early postoperative complications following adherence to components of the ERAS protocol in gynecology.

7. To assess the impact of adherence to ERAS protocol and the applicability of its components for accelerated recovery of bowel function after gynecologic surgeries.

8. To assess the applicability of normothermia and avoidance of hypothermia during surgery, as well as the correlation between normothermia and intraoperative blood loss.

9. To study the applicability and effect of ERAS protocol in minimally invasive gynecologic surgery.

10. To study the applicability and effect of ERAS protocol in gynecologic oncology surgeries.

11. To calculate the recovery time and the possible minimum postoperative stay after various gynecologic surgeries (gynecologic oncology, open, and laparoscopic) performed according to the ERAS protocol guidelines.

III. MATERIALS AND METHODS

1. Clinical cohort

For a period of 14 months, from July 1st 2020 to June 30th 2022 (for 10 months, the Gynecology Clinic at St. Anna Hospital – Varna functioned as a Covid department), the patients undergoing planned surgeries at the Gynecology Clinic at St. Anna Hospital – Varna were included in a prospective cohort study regardless of the type and complexity of the operative intervention. The ERAS methodology was applied following a previously developed protocol. An exclusion criterion was the patient's refusal to participate in the study and sign an informed consent. Patients operated on in an emergency were also not included in the study due to the impossibility of being prepared preoperatively according to the ERAS protocol. All patients signed informed consent. Patient care was provided by a pre-trained staff of nurses and doctors who ensured adherence to the individual steps of the ERAS and reporting of the results.

2. Methodology

2.1. Specific procedures regarding the implementation of the ERAS set of protocols

The study methodology is based on the measures of the ERAS protocol, which are specific to the individual stages of patient care:

1. The day before surgery;

2. The day of surgery (before, during, and after surgery);

3. Day 1 after surgery;

4. Day 2 after surgery.

2.1.1. The day before surgery includes:

1. Eating without restrictions until midnight;

2. Low molecular weight heparin at 21 hrs.;

3. Avoiding mechanical bowel preparation (Mannitol) and laxative medications;

4. In case of expected intestinal resections, an enema is performed twice, and Gentamycin and Metronidazole are administered orally;

5. A carbohydrate drink is given to the patient – Fresubin 2 kcal.

2.2.2. The day of surgery

On the day of surgery, measures for enhanced recovery after surgery are divided into three stages: before the patient enters the operating room, during the operative intervention, and after surgery. Each event and its results are documented and audited.

Before the patient enters the operating room:

- Bowel preparation – rectal enema only, no mechanical preparation such as Mannitol or X-Prep;
- Oral fluid intake up to 2 hours before surgery – carbohydrate-rich drinks 200 mL – Fresubin 2 kcal, 200 mL;
- Mechanical prevention of thromboembolic complications – use of elastic bandages or elastic stockings;
- Antibiotic prophylaxis includes intravenous administration of a cephalosporin of the 1st generation to cover the skin flora 30 – 60 min before skin incision. The dosage is planned according to the patient's weight. Anti-anaerobic treatment with Metronidazole – only in oncologic surgeries;

- Antiemetic preparation – 8 mg Dexamethasone (2-amp x 4 mg).

During surgery:

- Ensuring normothermia for the patient – maintaining an optimal temperature in the operating room, infusing pre-warmed in hot water bags with infusion solutions;
- Targeted infusion therapy depending on the duration of the surgery and intraoperative blood loss – 1000 mL of infusion solutions for the duration of the surgery up to 2 hours and blood loss up to 200 mL;
- Regional anesthesia techniques – application of infiltration anesthesia with Bupivacaine – 4 amp/80 mg in the abdominal wall;
- Avoidance of drains and nasogastric tubes.

After surgery:

- Targeted infusion therapy – infusions of water-salt solutions 50 mg/hour (total about 1L) until the following day at the expense of rapid initiation of oral fluid intake;
- Opioid-sparing analgesia;
- Control of postoperative hyperglycemia;
- Early verticalization and mobilization around the bed and to the bathroom – 6 hours after the surgery. Fraxiparin 0.4 – 0.6 s.c and 1-hour later mobilization;
- Removal of the urethral catheter immediately after the patient is mobile;
- Removing the signal drain – in case one is left;
- Oral liquid intake, which is a prerequisite for early feeding – the total amount of liquids is 500 – 800 mL and includes: Fresubin rich in proteins 200 mL, 500 mL of mineral water, yogurt, and yogurt drink. Early oral intake begins 1 hour after mobilization.

Opioid-sparing analgesia is achieved through the synergistic action of local anesthesia and postoperative analgesia

Local anesthesia is achieved by infiltrating a local anesthetic at the end of the surgery before closing the abdominal wall: Bupivacaine – amp. 5%, 4 mL (20 mg). Two ampoules of Bupivacaine (8 mL) are aspirated into two 20 cc syringes, which are diluted to 16 mL with physiological serum (0.25%

Bupivacaine). The total dose that is infiltrated is 4 ampoules (80 mg Bupivacaine), the maximum dose being 120 – 150 mg, and the total amount of infiltrated solution is 32 mL.

The infiltration site, regardless of the type of incision (Pfannenstiel, lower median laparotomy), is fascia and subcutaneous (subdermal).

Postoperative analgesia is provided by the following protocol:

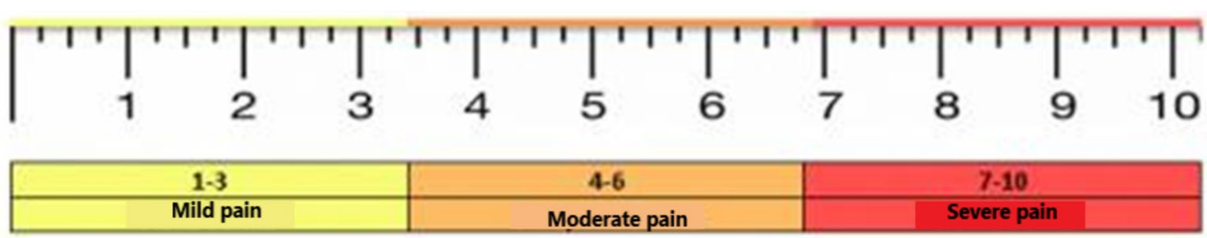
1. Morphine is stopped at the end of the surgery. Adverse effects of morphine are nausea, vomiting (gastrostasis), and intestinal paresis (slows recovery of bowel function);

2. One hour after the surgery – intravenous infusion of 1 vial of Paracetamol 100 mL (1000 mg). This is repeated every 6 hours, with a maximum daily dose of 2 grams.

3. Two hours after the surgery, 1 ampoule of Dicloflex/Diclofenac – 25 mg, 1 ampoule of Degan and 1/2 ampoule of Chlorpromazin (Chlorazin) are added. They are repeated after 12 hours. This protocol provides analgesia and dual antiemetic action.

The audit recorded postoperative pain and reported nausea and vomiting of operated patients between 18:00 and 19:00 hrs. on the day of surgery. Then the readiness for early mobility and early feeding of the patients is assessed. A visual-analogue system was used to report pain.

Visual Analogue Scale (VAS) for pain assessment:



The reporting of indicators and results on the day of the surgery, day 1, day 2, and the remaining postoperative days is carried out by employing the **"ERAS system survey template "** (Table 1).

Table 1. Survey template for the ERAS (Enhanced recovery after surgery) system (presented in a tabular form for clarity)

Names	Age (years)	Initials	Diagnosis	
Surgery date	Type of surgery	Type of laparotomy		
Baseline hemoglobin	Baseline blood sugar			
Day 0	**Day 1**	**Day 2**	**Day 3**	**Day 4**
Pain assessment (VAS)	Pain assessment (VAS)	Febrility (>37,8°C)	Febrility (>37,8°C)	Complications
Blood sugar	Temperature	Surgical site complications (hematoma, abscess, dehiscence)	Surgical site complications (hematoma, abscess, dehiscence)	**Day 5** Complications
Nausea	Intestinal passage	Bowel obstruction (subileus, ileus)	Bowel obstruction (subileus, ileus)	
Vomiting - once, repeatedly	Motor activity	Motor activity	Motor activity	**Day 6**
Early agitation	Liquid intake (1.5 – 2 L)	Intestinal passage	Intestinal passage	Complications
Liquid intake (protein shakes) – 500-800 mL	Early feeding Diet 1	Pain assessment (VAS)	Pain assessment (VAS)	
Hemoglobin (g/L)	Hemoperitoneum (re-operation)			
Hemoperitoneum (re-operation)				

2.2. Statistical methods

Descriptive statistics were used to analyze data. Continuous variables are described as mean with standard deviations for normal distribution and ACT median with interquartile range for non-uniform distribution of values. Categorical parameters are described as frequencies in percentages.

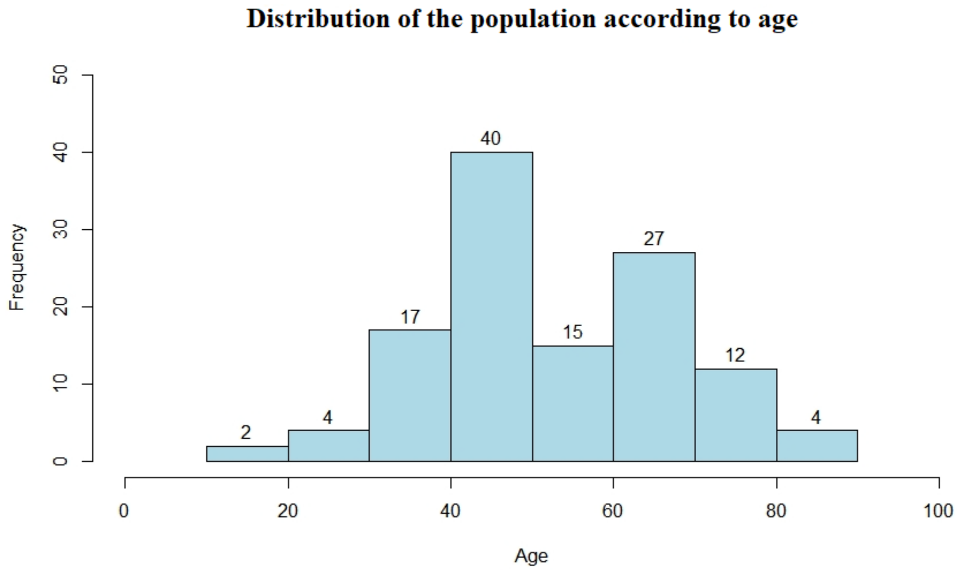
IV. RESULTS AND DISCUSSION

For solving the set 11 tasks, we will consider the obtained results and their discussion in a continuum of 14 points, which is the essence and practical benefit of the complex application of perioperative measures and set of procedures for enhanced recovery after surgery. The ultimate goal of all these measures is to shorten hospital stays, respectively, to reduce costs, without this being at the expense of increased complications and the frequency of rehospitalizations. Last but not least, in addition to cost savings, one of the goals of this revolutionary approach to perioperative care is improving outcomes and patients' overall experience and quality of life.

1. Study population

1.1. Age of patients participating in the study

For the period of 14 months, 121 patients were included in the study. The mean age of the patients was 52.6 years (± 14.6), and the median age was 50 years (IQR 42, 64 years). The youngest patient was 17 years old; the oldest was 84 years old. The age distribution of the study population is presented in Figure 1.



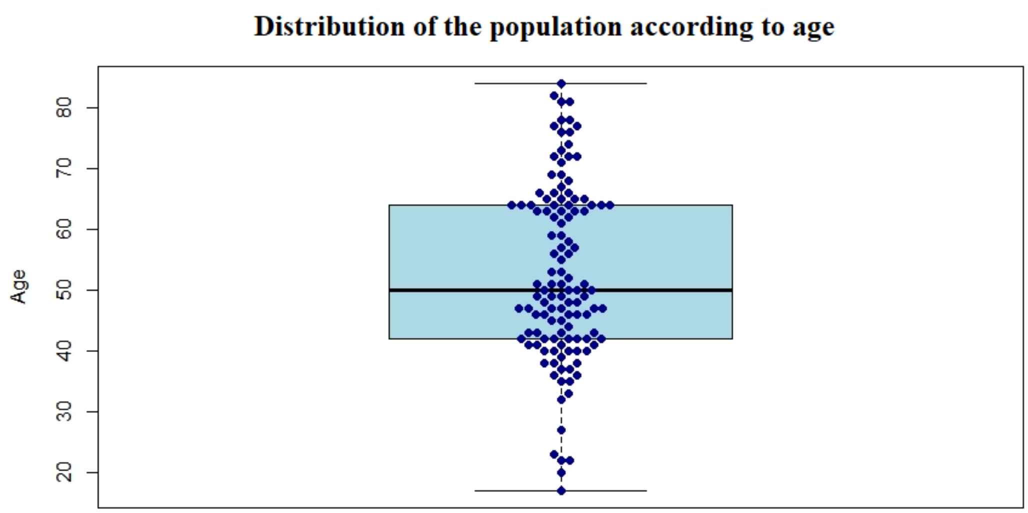


Figure 1. Distribution of patients by age. Upper diagram – age distribution histogram; bottom diagram – box-plot of the age distribution

1.2. Distribution of patients according to the type of surgery and diagnosis

Of the 121 patients included, 83 underwent open gynecologic surgery, 28 – laparoscopic gynecologic surgery, and 10 – vaginal gynecologic surgery (Figure 2).

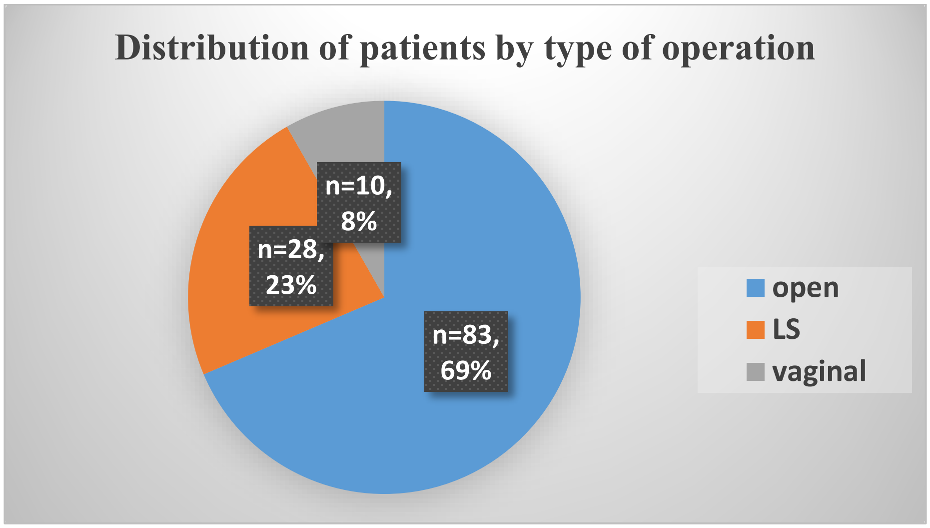


Figure 2. Distribution of the total population (n=121) by type of surgery. LS – laparoscopic

Of the 121 patients included, 78 were operated on due to benign pathology, and 43 patients were with an oncological diagnosis (Figure 3).

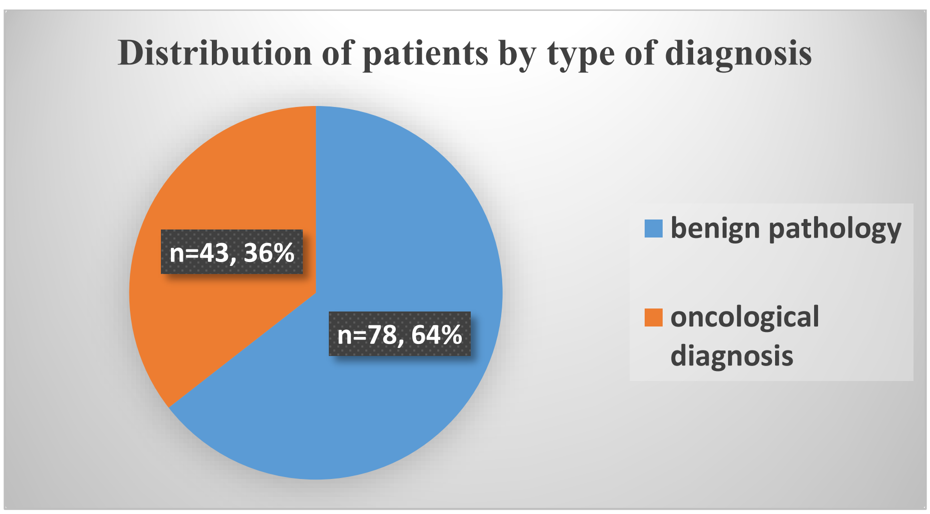


Figure 3. Distribution of the general population (n=121) by

type of diagnosis – oncological and benign

The patients (n=83) who underwent open gynecologic surgery had the following distribution according to the diagnosis that necessitated surgery: 47 patients had benign pathology, and 36 had an oncological diagnosis. A detailed description of the diagnoses and the type of surgical interventions are shown in Tables 2 and 3.

Table 2. Distribution of patients (n=83) undergoing open gynecologic surgery by diagnosis

Diagnosis	Number
Myoma	33
Endometrial carcinoma	10
Ovarian fibroma	3
Uterine carcinosarcoma	2
Ovarian carcinoma	11
Ovarian cyst	10
Carcinoma of the cervix	11
Pseudomyxoma peritonei (Carcinoma of the appendix)	1
Vaginal carcinoma	1
Tubo-ovarian abscess	1
Total number	83

Table 3. The distribution of patients (n=83) operated on by laparotomy, by types of surgeries

Type of operation	Number of patients
CRT with bilateral adnexectomy	25
CRT without adnexectomy	7
Laparomyomectomy	13
Unilateral adnexectomy	8
CRT with bilateral adnexectomy + appendectomy and omentectomy	1
CRT with unilateral adnexectomy	2
CRT with bilateral adnexectomy + pelvic lymphatic dissection and vaginectomy	1
CRT with bilateral adnexectomy, left uretero-ureterostomy and stenting	1

Type of operation	Number of patients
CRT with unilateral adnexectomy, infracolic omentectomy and pelvic lymph node dissection	1
CRT with bilateral adnexectomy, infracolic omentectomy and anterior pelvic peritoneectomy	1
Radical hysterectomy without adnexectomy	1
Class III radical hysterectomy, pelvic and para-aortic lymph node dissection	4
Class II radical hysterectomy, para-aortic lymph node dissection and supracolic omentectomy	1
Class II radical hysterectomy and pelvic lymph node dissection	2
Class III radical hysterectomy, pelvic and para-aortic lymph node dissection and infracolic omentectomy	1
Class III radical hysterectomy and pelvic lymph node dissection	5
Partial vaginectomy + class III radical hysterectomy, pelvic and para-aortic lymph node dissection	1
CRT with bilateral adnexectomy + pelvic lymph node dissection	2
CRT with bilateral adnexectomy + pelvic lymph node dissection and infracolic omentectomy	2
CRT and supracolic omentectomy	1
Unilateral adnexectomy and contralateral cystectomy	1
Unilateral cystectomy	1
Bilateral adnexectomy and pelvic and para-aortic lymph node dissection	1
Total	83

The distribution of patients undergoing laparoscopic surgeries by type of diagnosis is presented in Figure 4 and Table 4.

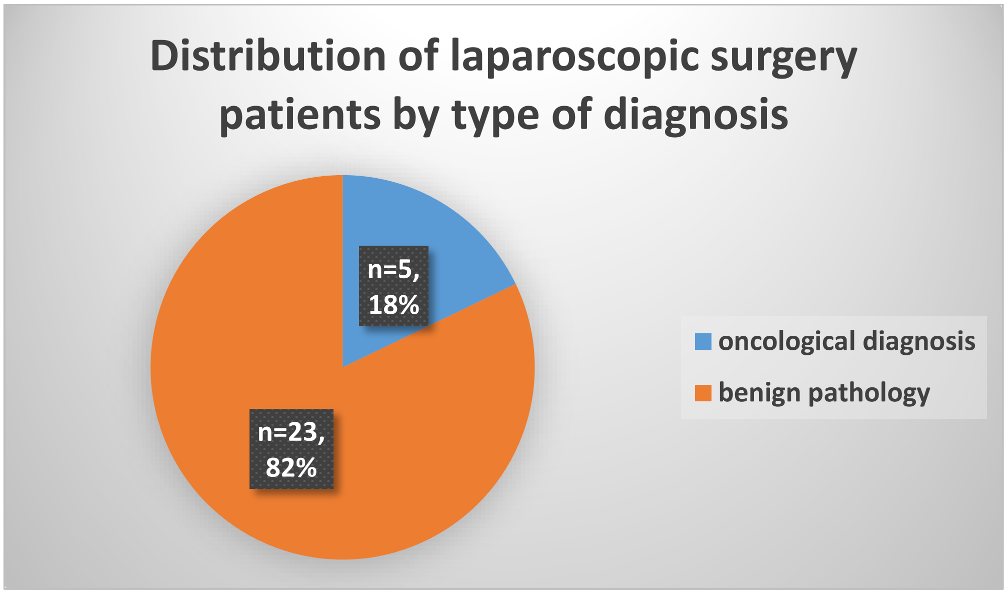


Figure 4. Distribution of patients (n=28) undergoing laparoscopic surgeries by type of diagnosis

Table 4. Diagnoses in patients with laparoscopic gynecologic surgery (n=28)

Diagnosis	**Number of patients**
Endometrioid carcinoma (EIN)	5
Myoma	6
Endometrial polyps	1
Ovarian androblastoma	1
Ovarian cyst	10
Chronic pelvic inflammatory disease (PID)	1
Hydro-/ Pyosalpinx	2
Tubo-ovarian unilateral abscess	2
Total	28

The distribution of patients operated by laparoscopic technique according to the type and volume of the surgery is presented in Table 5.

Table 5. Operative procedures in patients (n=28) with laparoscopic surgery (LAVH – Laparoscopically assisted vaginal hysterectomy)

Type of operation	Number of patients
LAVH with bilateral adnexectomy	11
LAVH without the adnexa	2
Laparoscopic cystectomy	10
Adhesiolysis	1
Laparoscopic salpingectomy	2
Unilateral adnexectomy	2

The distribution of patients operated on by laparoscopic gynecologic surgery, by type of surgery and diagnosis, is presented in Figure 5.

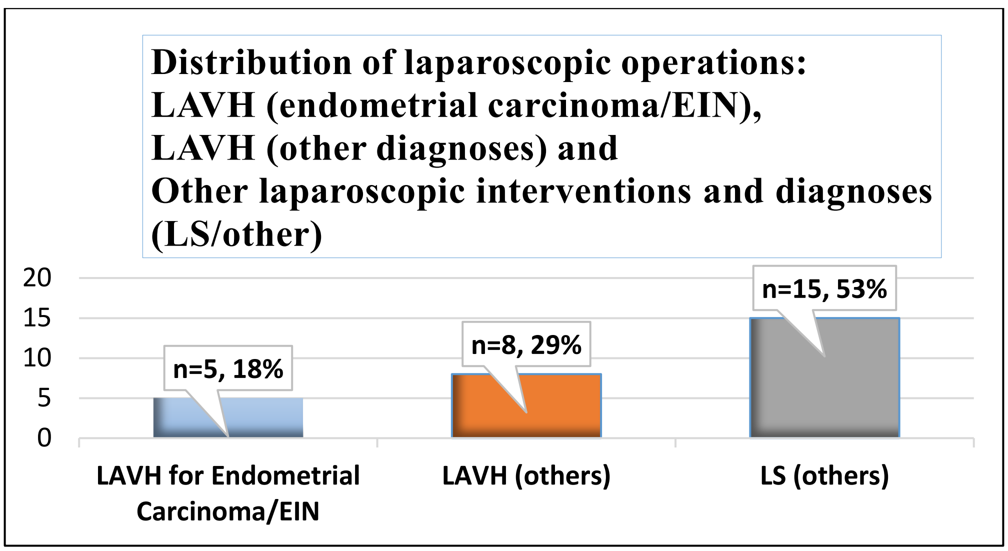


Figure 5. Distribution of patients operated on by laparoscopic gynecologic surgery, by type of surgery and type of diagnosis (LAVH – Laparoscopically assisted hysterectomy, EIN – Endometrial intraepithelial neoplasia, LS – laparoscopic surgery)

For the indicated time interval, 10 patients who underwent vaginal gynecologic surgery with different indications, shown in Table 6, were also included in the prospective study.

Table 6. Diagnoses in the patients operated by vaginal surgeries

Diagnosis	Number of patients
Paget's disease	1
Uterine prolapse	4
Vaginal descensus	2
Cystocele	2
Enterocele	1

The distribution of patients operated on by vaginal gynecologic surgery by type of surgery is shown in Table 7.

Table 7. Types of surgeries in patients with lower access

Type of operation	Number of patients
Simple vulvectomy	1
Vaginal hysterectomy with bilateral adnexectomy	3
Vaginal hysterectomy without adnexectomy + anterior and posterior colporrhaphy	1
Anterior and posterior colporrhaphy	2
Anterior colporrhaphy	3

The patients with benign pathology included in the prospective study were 78. Their distribution by type of gynecologic surgery is illustrated in Figure 6.

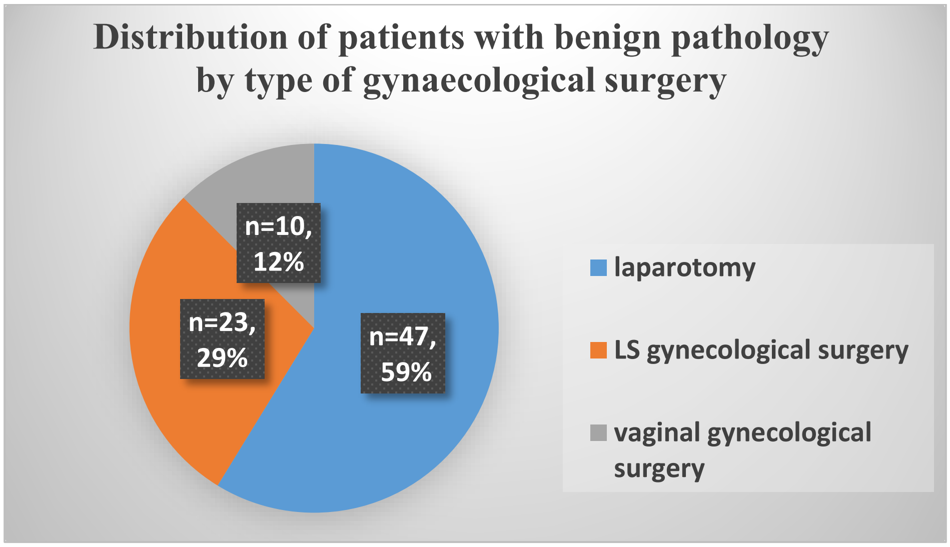


Figure 6. Distribution of patients with benign pathology by type of gynecologic surgery (LS – laparoscopic)

The patients with an oncological diagnosis included in the prospective study were 43. Their distribution according to the gynecologic oncologic diagnosis – ovarian carcinoma or others is shown in Figure 7.

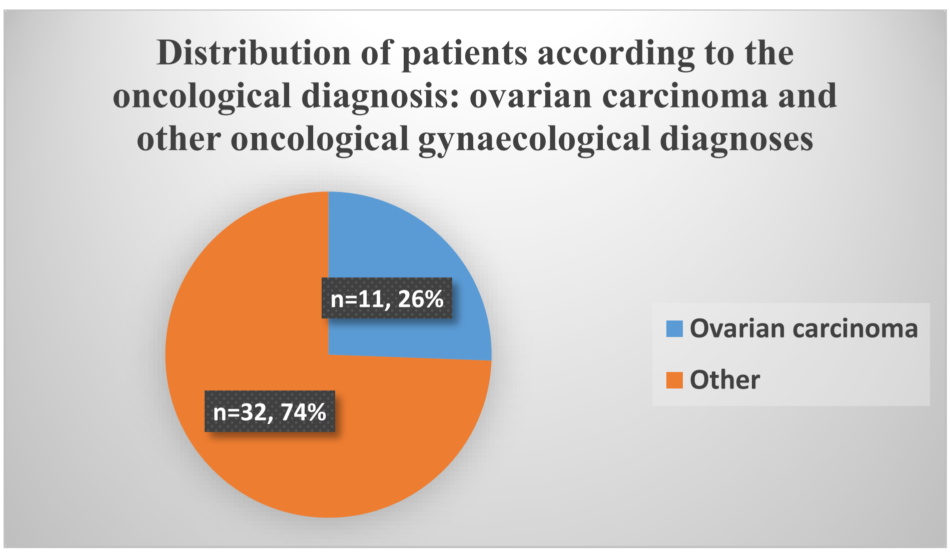


Figure 7. Distribution of patients with an oncological diagnosis of ovarian carcinoma and other gynecologic oncology diagnoses

2. Restoration of bowel function (prevention of ileus, subileus, gastroparesis, nausea, vomiting)

One of the limitations of faster discharge after gynecologic oncology surgeries is the delayed recovery of normal bowel function. Prolonged dysfunction of the gastrointestinal tract can be multifactorial and lead to respiratory, renal, and infectious complications as a consequence of aspiration, dehydration, and deterioration of nutritional status. Despite early oral intake, the ERAS protocol reduces the risk of gastrointestinal complications (Bisch SP et al., 2018) and is associated with a shortened recovery time of intestinal peristalsis and gas release, as well as a minimal risk of paralytic ileus (Sanches-Iglesias JL., 2020; Kalogera E., 2013; Yi HC., 2020; Agarwal R., 2019; Boitano TKL, 2018). In a 2018 study of 376 patients undergoing gynecologic oncology surgery, Boitano et al. (2018) found a significantly lower incidence of ileus following the ERAS protocol compared to a control group (2.8% vs. 15.7%). Kalogera et al. (2013) reported outcomes following the implementation of ERAS guidelines in patients who underwent surgery for gynecologic oncology diagnosis and genital prolapse. The authors found that bowel function recovery (defined as gas release) occurred 1 day earlier in the group following the ERAS system guidelines than in the control group (historical control). Notably, patients in the ERAS protocol group experienced a higher percentage of nausea but not vomiting on the 2^{nd} postoperative day compared to the control group (55.6% versus 38.5%).

One of the most important, if not the most important, factors in recovery after any surgical intervention is the return of normal bowel function. This becomes possible due to several components: early (on the day of the surgical intervention) oral (enteral) fluid intake; avoiding the phenomena of postoperative nausea and vomiting; early verticalization and mobilization; achieving a state of euvolemia; application of opioid-sparing analgesia in the early postoperative period, thereby avoiding the adverse effects of opioid analgesics – nausea and vomiting (gastrostasis).

A) Early feeding – early oral intake of liquids and food

Figure 8 shows the feasibility of early (on the day of surgery) oral fluid intake. Of the 121 patients included in the prospective study, rapid initiation of oral fluids was not possible in only 1 patient.

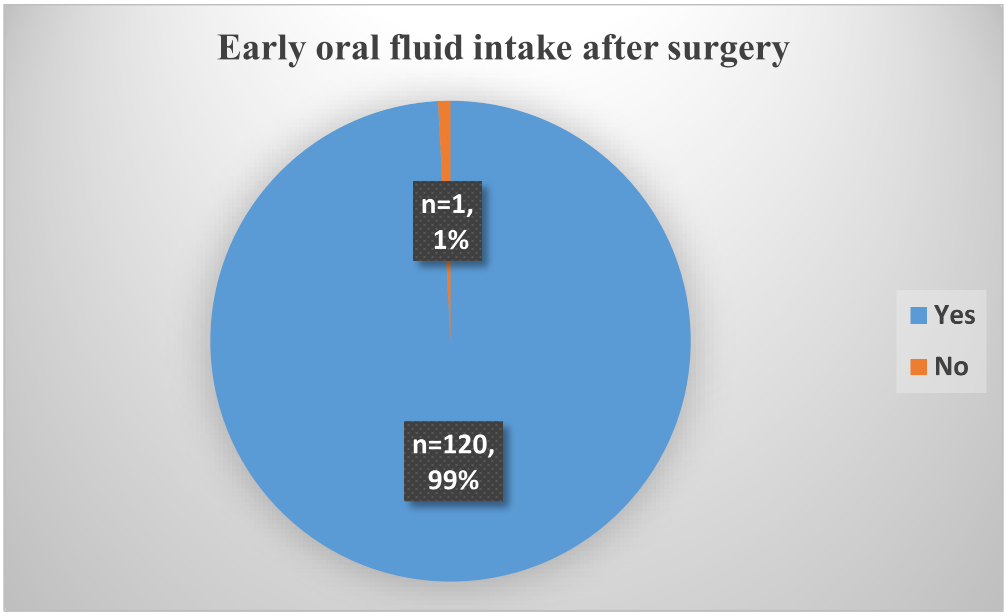


Figure 8. Distribution of patients according to the indicator "early oral fluid intake"

This component aims to replenish the water-electrolyte balance enterally, and not through infusions (targeted infusion therapy, i.e., a restrictive regimen of infusions during and after surgery – 40 mL/hour) and achieving a euvolemic state. Early oral intake of fluids and food avoids catabolic processes in the early postoperative period, loss of muscle strength, and delayed verticalization and mobilization. It also avoids insulin resistance and postoperative hyperglycemia – factors increasing the risk of wound infections and delayed mobilization, hence recovery. Early feeding is the basis of the rapid return of bowel function (gas release) and prevention of paralytic ileus and subileus. The gradual and accelerated transition to normal nutrition regimens strengthens the motor activity and self-esteem of the patients.

Early postoperative nutrition is defined as the resumption of oral fluid intake on the day of surgery and the inclusion of a normal diet on the first postoperative day (de Groot JJ., 2014). Several randomized trials have evaluated this approach in postoperative recovery after gynecologic surgeries (KrausK., 2000; Pearl ML., 2002). They unequivocally demonstrate that early feeding leads to a significantly enhanced return of bowel function (intestinal passage and gas release) and tolerance when returning to a normal diet. A large review states that early feeding after major gynecologic oncologic surgeries, except for cases with intestinal resections, is associated with rapid recovery of the intestinal passage without the occurrence of gastrointestinal complications (Charoenkwan K., 2014). ERAS guidelines for perioperative care in gynecologic/oncology include returning to a normal diet within 24 hours after surgery (Nelson G., 2016). Delivery of postoperative nutrition on postoperative day 1 has been reported as an independent prognostic factor for 5-year survival in colorectal surgery (Wischmeyer PE., 2018; Gustafsson UO., 2011; Lewis SJ., 2009). In many gynecologic oncology centers, a standard diet and oral intake are practiced immediately after surgery without increasing complications (Weimann A., 2017). The content of the postoperative diet is still a matter of debate. According to some studies, a high-protein postoperative diet can reduce the incidence of complications (Wischmeyer PE., 2018). Several guidelines state that daily protein and calorie needs in the postoperative period are 2 grams and 25 – 30 kcal/kg, respectively (Weimann A., 2017; McClave SA., 2016). The ERAS Society USA has also confirmed these recommendations (Wischmeyer PE., 2018).

In conclusion, nutrition in the perioperative period is one of the main components of the ERAS program. It is essential to assess patients' nutritional status preoperatively and screen those patients for malnutrition. Patients should be prepared at least 7 – 14 days before surgery with enteral and parenteral protein supplementation. Fasting and the state of starvation before surgeries should be avoided by carbohydrate loading twice – the evening before the surgery and 3 hours before the surgery. Postoperative feeding should begin on the day of surgery and be increased gradually. In this whole process, it is advisable to include, in addition to, gynecologists and anesthesiologists, nurses and nutritionists.

B) Symptoms of nausea and vomiting

The absence of nausea and vomiting immediately after surgery and coming out of anesthesia is the main goal and prerequisite for enhanced recovery. In the absence of these conditions, early feeding becomes possible, i.e., the early oral intake of liquids and food (drinks rich in proteins and carbohydrates – Fresubin 200 mL).

Figures 9 and 10 illustrate the incidence of postoperative nausea and vomiting in the study population. The reporting of nausea and vomiting phenomena in the operated patients, registered between 18:00 and 19:00 hrs. on the day of the surgery, has the following distribution:

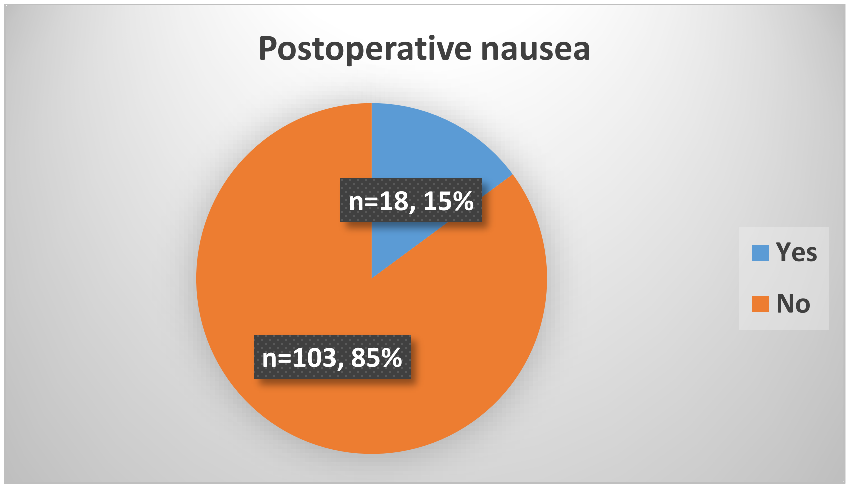


Figure 9. Postoperative nausea

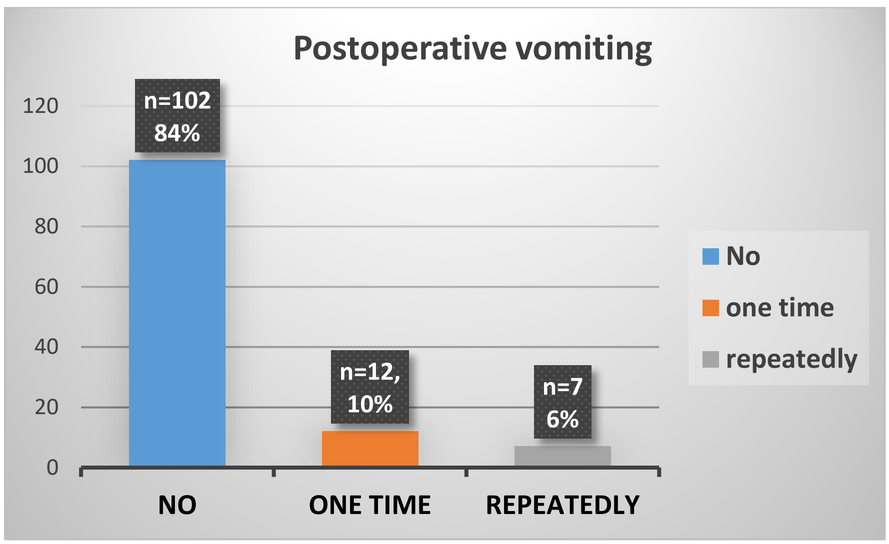


Figure 10. Postoperative vomiting

The presented results: absence of vomiting in 84% of the operated patients and absence of nausea in 85% of the operated patients is due to compliance with the protocol for postoperative analgesia without opioid analgesics and prevention of nausea and vomiting described in the study methodology. This, in turn, is a prerequisite for early oral fluid intake on the day of surgery.

C) Early verticalization and mobilization

Early verticalization and mobilization around the bed and within the room for active monitoring on the day of surgery is a core element of the ERAS protocol. For this essential step to take place, the patient should be well analgesized, in a euvolemic and euglycemic state, free of nausea and vomiting, and oral fluid intake restored.

Of the 121 patients included in the prospective study, only 6 could not be mobilized early – 95% applicability or compliance with this protocol element. The results for this indicator are shown in Figure 11.

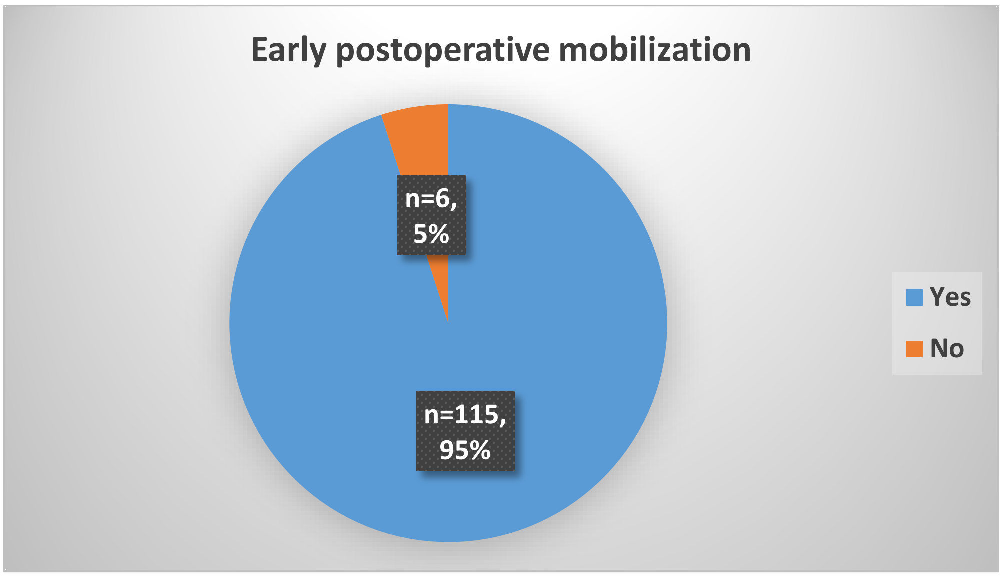


Figure 11. Results for the "Early postoperative mobilization" indicator

The applicability of this components of the ERAS protocol requires an audit and direct participation by a surgical team member, as well as prior application of other elements – analgesia, prevention of nausea and vomiting, and early nutrition (oral fluid intake). All this proves that a separate component of the protocol cannot be implemented independently, i.e., it concerns a continuum of events. Another critical point in early mobilization is the prevention of thromboembolic complications, primarily through so-called mechanical prevention (elastic bandages or stockings).

D) Euvolemia

This condition is an essential prerequisite for early recovery of bowel function and avoidance of early postoperative complications such as paralytic ileus and subileus. It is achieved through 3 components of the ERAS protocol: 1.) avoidance of mechanical bowel preparation, 2.) targeted infusion therapy, and 3.) early oral fluid intake.

1.) Preoperative bowel preparation

Regarding bowel preparation, all 121 patients received a cleansing enema at 6 a.m. before surgery, without prior mechanical action with medicinal laxatives – Mannitol, X-Prep (Senna), or Dufalac (lactulose), i.e., 100% compliance was achieved on this indicator.

ERAS protocols in gynecologic surgery do not recommend preoperative oral mechanical bowel preparation with laxatives (Nelson G, 2016). These recommendations also apply to patients who are about to undergo intestinal resections. This opinion is based on extensive clinical studies demonstrating that avoiding oral mechanical bowel preparation does not increase the risk of infections and compromised anastomoses after bowel resections (Gǘenaga KF., 2011). In addition, this measure increases patient satisfaction and reduces the risk of electrolyte imbalance and dehydration (Arnold A., 2015). In a randomized French study, patients with rectal carcinoma were divided into two groups – with and without mechanical preoperative bowel preparation for rectal resection with low colorectal anastomosis. Although they found no difference between the two groups in terms of mortality, non-infectious complications, leakage of intestinal anastomoses, or severe postoperative morbidity, they found significantly higher morbidity in the group without mechanical bowel preparation at the expense of infectious postoperative complications. The authors recommend mechanical bowel preparation for upcoming rectal resection and low anastomosis due to the high incidence of infectious complications in these patients (Bretagnol F., 2010).

Further studies in this direction are needed in patients with advanced ovarian carcinoma, in whom, due to anatomical considerations, resection of a part of the rectum or the sigmoid and a colorectal anastomosis is often necessary. Implementing this element of the ERAS guidelines in gynecologic/oncology surgery undergoes modifications in different clinics and centers (Forsmo HM, 2016). Bowel preparation is considered the standard in Germany, while a Dutch study reported avoidance of mechanical bowel preparation in 90% of gynecologic oncology surgeries (de Groot JJ., 2014; Muallem MZ., 2016). In Australia and New Zealand, 55% of oncologists do not perform bowel preparation regardless of whether a bowel resection is planned, including when a low rectal resection is planned (Lindemann K., 2017).

2.) Perioperative infusion therapy

A restrictive regimen of postoperative infusion therapy, the so-called "Targeted infusion therapy", was administered to all 121 patients. Targeted infusion therapy means a rate and volume of infusions of 50 mg/h (about 1 L by the following day). We report 100% applicability on this indicator as well. Such a regimen of infusions is possible due to early oral fluid intake, which contributes to the euvolemic state of operated patients.

Optimal infusion therapy is vital for rapid recovery after surgery (Holte K., 2006). Targeted infusion therapy or restricted volume of infusions – "restricted fluid therapy", is an approach in the postoperative period that is an essential component of the ERAS protocol but has been studied to the greatest extent in colorectal surgery. There are solid arguments for the physiological and pathophysiological aspects on which the concept of restrictive infusion therapy is built. The optimal infusion therapy, hemodynamic parameters, and infusion monitoring strategies in the perioperative period are not sufficiently specified for patients with ovarian carcinoma. Data from colorectal surgery suggest that excess infusions (infusion overload) may delay recovery of bowel function and prolong hospital stay (Lobo DN., 2002). On the other hand, restrictions in the volume of infusions aim to reduce cardiopulmonary complications (MacKay G., 2006). Due to the variety of surgical procedures, duration of surgeries, and tumor burden in advanced ovarian carcinomas on the one hand, and shorter interventions in early carcinoma stages, on the other, there is still no precise algorithm for targeted infusion therapy in ovarian carcinoma patients in general.

E) Opioid-sparing analgesia

The effect of opioid-sparing analgesia is not limited to postoperative analgesia. The main goal of opioid-sparing analgesia is the reduction and prevention of the phenomena of nausea, vomiting, gastrostasis, intestinal paresis, and paralytic ileus, thereby helping restore the gastrointestinal tract function quickly.

All 121 patients received opioid-sparing anesthesia and intraoperative infiltration of the surgical incision with Bupivacaine for the laparotomy patients – 100% applicability of the ERAS procedure.

Our experience with applying the ERAS protocol in gynecology surgery shows that the recovery of intestinal function can be accelerated by applying the measures mentioned earlier.

3. Opioid-sparing analgesia - analgesia in the early postoperative period

In the Methods section, the method of analgesia, as described for the early postoperative period, calls into action the synergistic analgesic effect of the regional blockade with bupivacaine in the area of the surgical incision and analgesics excluding opioid analgesics. Thus, the side effects of opioids, which are described above, are spared. Such analgesia was administered to all open surgery patients included in the study – 100% applicability of this protocol component. In patients with laparoscopic and vaginal surgeries, no blockade was applied in the surgical incision area due to the minimally invasive approach. The results of the indicator "analgesia in the early postoperative period" reported according to the visual analogue scale (VAS) are illustrated in figure 12.

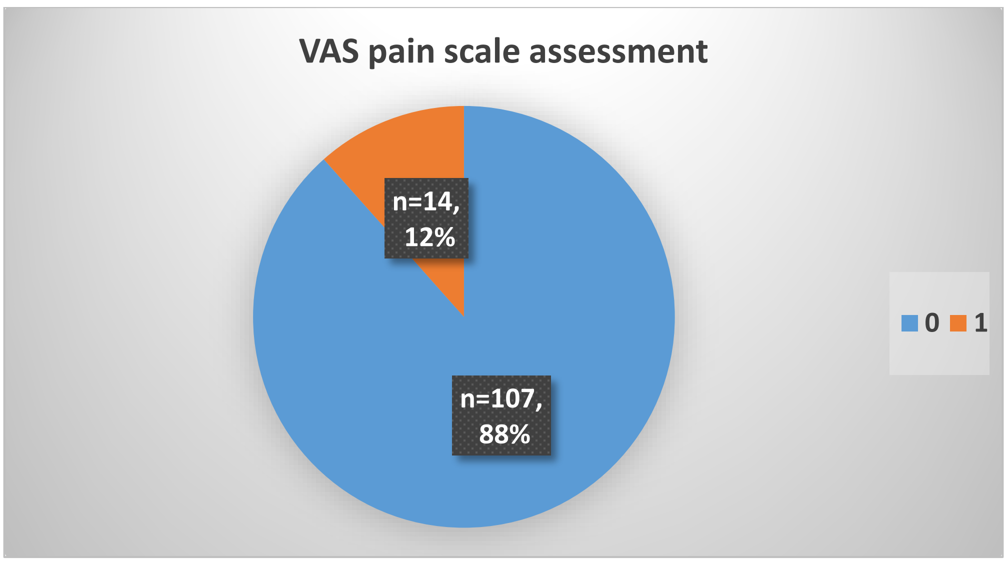


Figure 12. Results according to the "analgesia in the early postoperative period" indicator.

VAS – visual analogue pain assessment scale

These results indicate that in 88% of the patients, there is no pain, and in 12%, it is mild and tolerable. Therefore, analgesia adhering to the described methodology is fully applicable, feasible, and effective. This factor allows the early verticalization and mobilization of the operated patients on the day of the surgical intervention.

Current strategies in perioperative anesthesia according to ERAS protocols

In order to limit the overuse of opioid analgesics and their associated side effects, some surgical and anesthetic techniques and new models in perioperative care, especially in postoperative analgesia, have been mainstreamed in the last decade. ERAS protocols aim to optimize perioperative care and postoperative outcomes (complications, readmissions, patient satisfaction) (Fearon KC, 2005). In 2007, anesthesiologists and surgeons formed the PROSPECT (PROcedure-SPEcific Postoperative Pain ManagemenT) Working Group. The PROSPECT initiative aims to provide practical procedure-specific pain management recommendations for anesthesia for various surgical procedures based on evidence-based medicine (Lee B., 2018, Joshi GP., 2019; Kehlet H., 2007). Guidelines have been created with recommendations on perioperative care that have proven successful in reducing complications, opioid use, length of hospital stay, and financial costs in several surgical specialties (Madani A., 2015; Gotlib CL., 2015; Nelson G., 2014; Meyer LA., 2018). Multimodal opioid-sparing analgesia is the basis of perioperative analgesia according to ERAS protocols. This concept includes various pharmacological agents as well as regional analgesia techniques.

The most commonly used systemic pharmacological agents are NSAIDs and acetaminophen (paracetamol). NSAIDs are routinely and widely used in postoperative analgesia in ERAS programs because of their strong analgesic effect without the side effects of opioids, such as nausea, vomiting, somnolence, and intestinal paralysis. With the introduction of selective COX-2 inhibitors (celecoxib), the risk of postoperative gastrointestinal bleeding and compromised anastomoses associated with nonselective NSAIDs has significantly decreased. These analgesics are recommended for analgesia in the perioperative period of a large part of non-cardiac surgical interventions, incl. in orthopedics and spine surgery (Hyland SJ., 2021; Chou R., 2016).

Infiltration of liposomal bupivacaine into the abdominal wall along the laparotomy incision is used in ERAS protocols for postoperative analgesia and synergism with NSAIDs and acetaminophen. Abdominal wall infiltration with bupivacaine (AWIB) has a similar effect to the epidural catheter in pain control and opioid consumption. Kadam et al. (2011) compared the infiltration with bupivacaine (IB) and a thoracic epidural catheter, and Niraj et al. (2011) compared the analgesic effect of bilateral subcostal IB and epidural catheter in upper abdominal surgery. Ganapathy et al. (2015) compared IB and thoracic epidural analgesia in laparotomy patients. All studies concluded that bupivacaine infiltration and epidural anesthesia have similar efficacy, with IB patients having a greater need for opioids.

Besides the analgesic effect and the avoidance of opioids, the associated complications (nausea, vomiting, paralytic ileus/subileus) and regional analgesia techniques are associated with the length of hospital stay and financial costs.

There is not much data in the literature on the effect of epidural anesthesia on the length of hospital stay. A 2011 study pointed out that, on the one hand, the length of hospital stay can be shortened as a result of the absence of pain and ileus/subileus, and on the other hand, hospitalization can be prolonged due to hypotension or urinary retention (Spanjesberg WR., 2011). Another source states that epidural patients have 2 days longer hospital stay compared to those with IB, which is also associated with increased hospital costs (Wesson AJ., 2012).

ERAS protocols in several specialties, including gynecologic oncology, include components limiting the use of opioids. Meyer et al. (2018) studied the use of opioid analgesics in gynecologic oncology patients and reported a 72% reduction in their use after the introduction of ERAS. The same publication highlighted that 16% of the operated patients did not take an opioid analgesic in the first 3 postoperative days, without this leading to a significant difference in the pain score. In addition, patients following the ERAS protocol have shown faster mobilization, recovery to regular activity, and a lack of fatigue (Meyer LA., 2018). Several randomized controlled trials in gynecologic oncology have demonstrated reduced use and need for opioid analgesics following ERAS protocols. In the PROFAST trial, better pain control and less opioid use were reported in the ERAS group compared to the control group (Sanchez-Iglesias JL., 2020). The study by Ferrari et al. (2020) demonstrated a reduction in pain at the 12th and 24th hours postoperatively and found that 37% of patients following the ERAS protocol required parenteral analgesic postoperatively versus 74% in the control group with conventional postoperative care. In this and two other randomized trials, the authors recommend an epidural catheter in addition to multimodal postoperative analgesia for better analgesia (Sanchez-Iglesias JL., 2020; Dickson EL., 2017; Ferrari F., 2020). In a 2021 publication, Joshi et al. reported a 50% reduction in opioid analgesic use following the ERAS multimodal analgesia protocols.

The optimal postoperative analgesia regimen for patients with ovarian carcinoma has not been established and varies between institutions. Routinely used epidural analgesia after major gynecologic oncological surgeries were not launched in the ERAS protocol (Nelson G., 2016). Generally, epidural analgesia is an effective method for controlling postoperative pain after laparotomy and large-volume surgeries, which are also associated with more significant surgical trauma. However, some publications point out that this type of analgesia delays early discharge and may lead to urinary retention and infusion overload (Nelson G., 2016). Instead of this mode of analgesia, different approaches for postoperative analgesia are proposed, which can be mutually combined. These are oral analgesics, spinal anesthesia, non-opioid analgesics, NSAIDs, and bupivacaine infiltration of the abdominal wall (Modesitt SC., 2016; Kalogera E., 2016). According to the recommendations of the ERAS society, the medications that can be administered are acetaminophen, celecoxib, and gabapentin (Nelson G., 2019).

4. Prophylaxis of surgical site infections

Surgical site infections and fever in the early postoperative period are the main factors that negatively affect the length of hospital stay, quality of life, and hospital costs—the latter results from delayed discharge and increased use of medications and consumables. Wound infections are part of the complications of the surgical incision, along with hematomas, seromas, and dehiscences/eventrations. These complications are typical for open surgeries, regardless of the type of incision (Pfannenstiel or lower median laparotomy), and some of the measures in the ERAS protocol are aimed at limiting them. These are complex measures that include: ensuring normothermia during the operative intervention; prevention of postoperative hyperglycemia and insulin resistance by preoperative intake of carbohydrates; antibiotic prophylaxis, and targeted infusion therapy.

A) Normothermia

Ensuring normothermia in our study population through the measures and activities described in the Methods section was achieved in all 121 patients. According to this indicator, 100% applicability of this protocol component was reported. The course of the surgery in normothermia conditions has an impact, both in terms of the prevention of surgical site infections and in reducing intraoperative blood loss and the rapid recovery from general anesthesia.

Surgical site infections are a significant risk factor in reporting postoperative outcomes and are among the leading causes of nosocomial infections in surgical patients (Esnaola NF., 2011). Even mild hypothermia is an independent and significant risk factor, increasing 6-fold the possibility of SSI (Flores-Maldonado A., 2001). Perioperative hypothermia is associated with an increased incidence of infectious complications, even after 8 weeks of surgery (Wong PF., 2007). Hypothermia-related SSIs can prolong hospital stays and increase hospital costs in the postoperative period (Mahmoud NN., 2009). A recently published meta-analysis found that active rewarming during surgery reduces the risk of SSIs by 70% (Balki I., 2020). Perioperative hypothermia suppresses the immune system by reducing oxygen supply, thereby reducing protection against various pathogens (EdwardsSW., 1984; Allen DB., 1997; Jonsson K., 1988). Another effect of hypothermia is peripheral vasoconstriction, which leads to reduced blood flow and reduced tissue oxygenation of the surgical wound. Tissue hypoxia disrupts healing processes by altering protein metabolism, which can lead to surgical wound dehiscence (Carli F., 1989).

B) Carbohydrate intake before surgery and control of postoperative hyperglycemia – avoiding insulin resistance and catabolic processes induced by fasting

The ERAS protocol recommends an oral intake of carbohydrate-rich beverages up to 2–3 hours before surgery to avoid postoperative hyperglycemia. Postoperative hyperglycemia is defined as blood sugar values above 11.1 mmol/L. Carbohydrate intake before surgery is associated with blood sugar values below the above, and thus glycemic control is ensured. Our experience is reduced to carbohydrate drinks intake (200 mL of Fresubin) as late as possible in the evening before surgery, and not 2 hours before surgery, a requirement set by anesthesiologists. In this way, the applicability of carbohydrate intake before surgery was achieved in 92% (111 patients), and in 10 patients, oral intake of Fresubin was not carried out the evening before surgery. Notably, postoperative glycemic control (blood sugar below 11.1 mmol/L) was achieved in the same percentages, which proves the role of preoperative carbohydrate load. In 10 patients, control of postoperative hyperglycemia was not achieved (>11.1 mmol/L) due to a lack of carbohydrate intake before surgery (Figure 13).

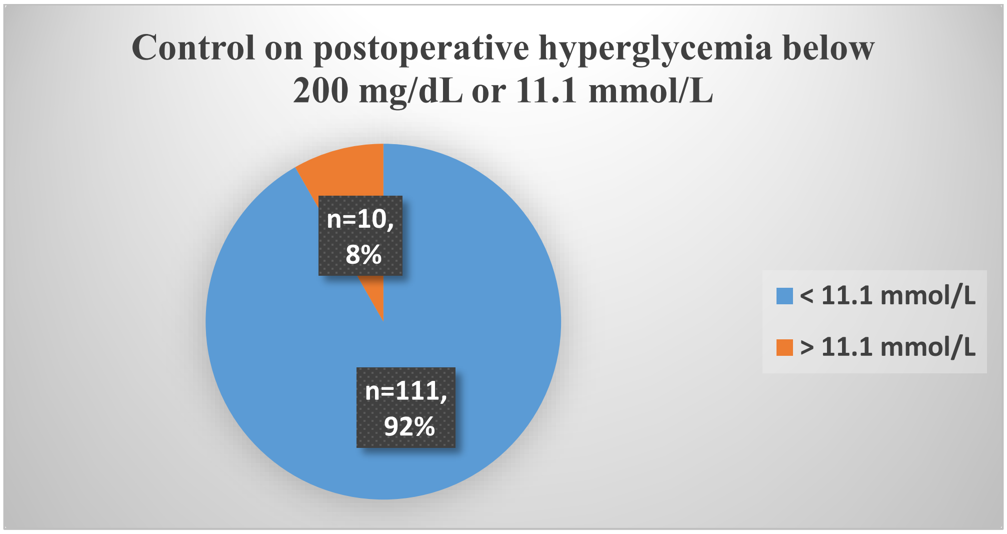


Figure 13. Control on postoperative hyperglycemia in the study population

Preoperative fasting and intake of carbohydrate-rich liquid drinks

In elective abdominal surgery, it is routinely recommended to stop eating and drinking 8 hours before surgery. However, some publications report that oral intake of clear liquids up to 2 hrs. before surgery does not increase gastric contents, does not decrease its pH, and does not increase complications (Smith I., 2011). As a result of these studies, recommendations were made for the intake of liquids and solid foods, respectively, up to 2 and 6 hours before anesthesia induction, unless there is documented evidence of gastrostasis/gastroparesis, previous esophageal, stomach, and small bowel surgeries (Smith I., 2011). Several studies have shown that preoperative intake of carbohydrate-enriched fluids reduces insulin resistance and leads to rapid recovery of bowel function (Smith MD., 2014). In a randomized controlled trial in patients with colorectal cancer, it was demonstrated that those who took 50 grams of a carbohydrate product dissolved in 400 mL of water 3 hours before surgery had significantly faster recovery of bowel function and a shorter hospital stay compared to the control group undergoing preoperative fasting (Noblett SE., 2006). Based on these studies, some clinics and centers have adopted and enforced these recommendations in patients with colorectal cancer. Although these data were not obtained in patients with gynecologic diseases, the ERAS society, in its first recommendations (2016), ruled on the use of carbohydrate preoperative intake in patients with gynecologic pathology (Nelson G., 2016). Still, most gynecologic oncology centers are cautious and do not introduce this measure in patients with ovarian carcinomas due to the specificity of tumor spread in the abdominal cavity and the possibility of influencing gastrointestinal motility ((Muallem MZ., 2016).

Nutritional aspects of the application of ERAS in gynecologic oncology surgery

• Preoperative fasting

The original concept of preoperative fasting was based on the hypothesis of preventing regurgitation and aspiration of gastric contents. The aim is for the stomach contents before surgery to be below 200 mL of liquid. This concept of preoperative fasting, however, leads to some negative phenomena: increased insulin resistance, hyperglycemia, catabolic phenomena in metabolism, and muscle strength decrease (Pogatschnik C., 2015). Although the risk of aspiration pneumonia is low (Landreau B., 2009; Saki T., 2006), the recommendation of "nothing by mouth" has remained valid for decades. In recent years, attention has been paid to the fact that preoperative fasting negatively affects the electrolyte balance and leads to dehydration and insulin resistance (Scott MJ., 2014). Preoperative fasting reduces glycogen reserves in the liver, increases insulin resistance, and puts the body in a postoperative period of stress. Postoperative hyperglycemia is an independent factor for increased morbidity and mortality (Gustafsson UO., 2008; Kotagal M., 2015).

Many publications have pointed out that oral fluid intake 2 hours before surgery does not affect the amount of gastric contents, gastric pH, and possible complications compared to those who do not take anything by mouth (Brady MC., 2003). Gastroparesis, peritonitis, and conditions associated with delayed emptying of gastric contents (pyloric stenosis) have not been sufficiently studied and need further investigation. Increased attention should be paid to conditions such as functional dyspepsia, increased concentrations of ovarian hormones, and autonomic neuropathy until sufficient clinical data are accumulated. An increased concentration of estrogens has been found to suppress gastric emptying (Chen TS., 1995) and, therefore, in estrogen-producing tumors (granulosa cell tumors of the ovary), this fact should be taken into account. Except for the considerations mentioned above, most anesthesia guidelines recommend fluids for 2 hours and solid food 6 hours before induction of anesthesia (Weimann A., 2017; Merchant R., 2016; Scott T., 2014; Smith I., 2011).

• Preoperative intake (loading) of carbohydrate drinks

A fasting state that triggers some metabolic processes (postoperative insulin resistance and hyperglycemia) can be produced 4 hours after the last meal. This increases the risk of postoperative complications – prolonged hospital stay, infections, kidney failure, resurgery, myocardial infarction, and even death (Pogatschnik C., 2015; Frisch A., 2010; Kwon S., 2013). The fasting state causes insulin resistance by disrupting mitochondrial function (Awad S., 2009). Carbohydrate loading before surgery is recommended in order to reduce inflammatory reactions, increased insulin sensitivity, postoperative improvement of muscle function, and improved patients' overall experiences (Hausel J., 2001; Yildiz H., 2013; Fawcett WJ., 2017). At the same time, it does not affect the time for gastric emptying (Weimann A., 2017). In recent years, a number of studies, systematic reviews, and meta-analyses have been published on this topic, specifically in colorectal surgery. They show that carbohydrate loading should be routinely applied because it improves insulin resistance caused by operative trauma and reduces the length of hospital stay (Smith MD., 2014; Scott T., 2014; Yagci G., 2008; Bilku DK., 2014; Ljunggren S., 2014; Webster J., 2014; Awad S., 2013). Furthermore, carbohydrate loading improves patients' self-esteem and satisfaction by reducing feelings of hunger and anxiety. Although these data were not derived from a series of patients undergoing major gynecologic oncology surgeries, they may also be valid for them, as gynecologic oncology interventions, such as extensive dissections and resections, cause significant surgical and physiological stress.

There are few studies analyzing the preoperative carbohydrate load in people with diabetes. Gustafsson et al. (2008) compared 25 women with type 2 diabetes to 10 women without diabetes. Despite the differences in the time of occurrence of the glucose concentrations peak, the authors did not find a negative influence on gastric emptying (Hausel J., 2001)]. Diabetic women are at higher risk of delayed gastric emptying, but on the other hand, they benefit most from avoiding postoperative hyperglycemia by preoperative carbohydrate loading (Gustafsson UO., 2008). Current guidelines for perioperative care recommend the intake of carbohydrates in uncomplicated type 2 diabetes, while patients with type 1 diabetes and those with poor long-term control require an individualized approach (Gustafsson UO., 2008).

The introduction of preoperative carbohydrate loading into routine practice has been limited and resisted by the staff due to logistical reasons – anesthetists, nurses, midwives, and clinicians ((Scott

MJ., 2014). To overcome these problems, a multidisciplinary approach in preoperative education and counseling of patients is required.

C) Antibiotic prophylaxis

All 121 patients from the study population were given antibiotic and antiemetic prophylaxis with a first-generation cephalosporin (Cefazolin 2 grams) and Dexamethasone. 100% compliance was achieved on this indicator. Prophylaxis was carried out according to the methodology described in the Methods section. Metronidazole (1 or 2 vials according to the patient's weight) was added to the antibiotic in patients undergoing gynecologic oncology surgeries.

As mentioned earlier, febrility (over 37.8ºC) after the 2nd postoperative day is an unfavorable factor for rapid recovery and early discharge. Figure 14 shows the incidence of this deviation from average postoperative recovery.

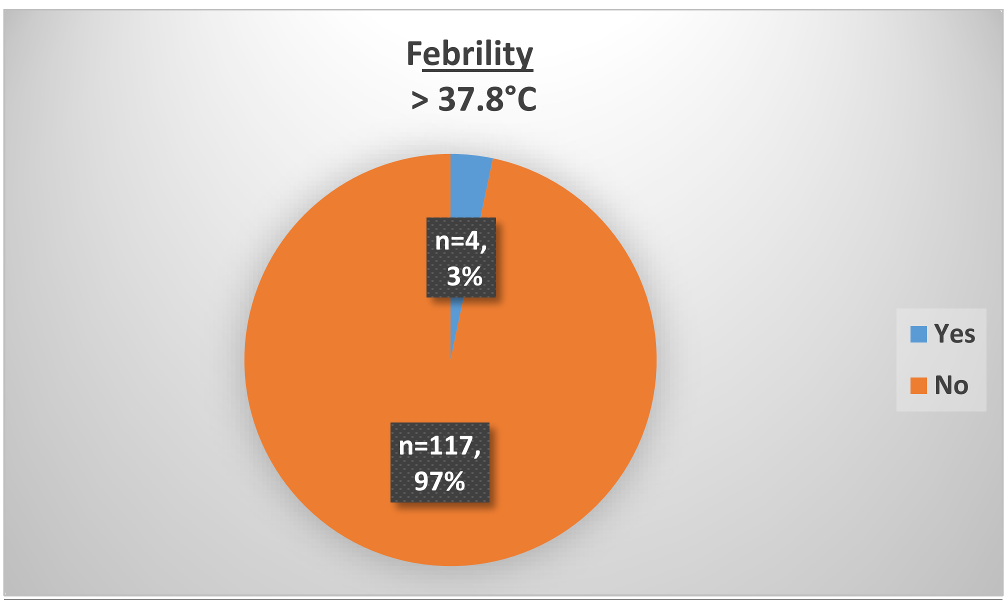


Figure 14. Frequency of febrility above 37.8°C

The figure shows that 4 of the patients had a fever above 37.8 °C after the 2nd day of surgery, while 97% of the patients in the study were afebrile or had a resorptive temperature < 37.5 °C, proving the applicability and benefit of the measures for prevention of SSIs.

ERAS recommendations in gynecology include the intravenous administration of antibiotics 60 minutes before skin incision (Nelson G., 2016). A total hysterectomy is performed in most gynecological interventions, including gynecologic oncology ones. This surgery is considered noncontaminating, and antibiotic prophylaxis prior to skin incision is recommended (ACOG practice Bulletin N195). According to a large-scale study in most European countries, second-generation cephalosporins are the most commonly used antibiotics, sometimes in combination with metronidazole (Piovano E., 2019). According to this study, antibiotics were administered prophylactically at a dose of 1 gram dissolved in 50 to 125 mL of saline over a 15-minute intravenous infusion. A repeated dose intraoperatively is required in patients undergoing long-time surgery, obese patients, and in cases of significant blood loss (Piovano E., 2019).

D) Infusion therapy

Balanced infusion therapy, the so-called restrictive or targeted infusion therapy, is based on the concept of avoiding fluid overload. The most significant adverse consequences of infusion overload are difficult surgical incision healing and the slow recovery of intestinal function (MacKay G., 2006; Abraham-Nordling M., 2012). Surgery is associated with disorders in the body's immune defense mechanisms with suppression of lymphocyte number and function (Kawasaki T., 2007; Evans C., 2009; Tartter PI., 1988; Utah J., 1988). Targeted infusion therapy counteracts these disorders and has a role in preventing SSIs. For all patients in the study (n=121), this component of the ERAS protocol – infusing up to 1 liter of saline solutions in the first 24 hours of surgery has been followed. The possibility of early feeding favors this.

5. Normothermia and intraoperative blood loss

One of the consequences of hypothermia during surgery is increased intraoperative blood loss. Therefore, one of the tasks set in the study was to determine the blood loss in conditions of normothermia. A blood loss of 200 mL was defined as the boundary between minimal and increased. All 121 patients underwent surgical treatment under normothermic conditions. Intraoperative blood loss > 200 mL was observed in 6 patients (Figure 15).

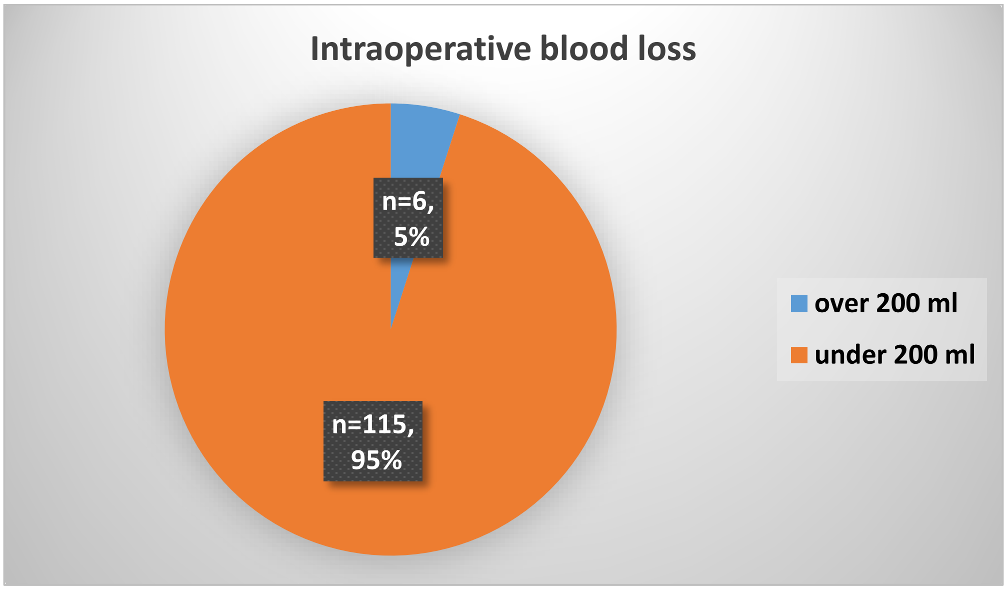


Figure 15. Intraoperative blood loss

Consequences of perioperative hypothermia can occur in several directions:

a) Consequences on the pharmacokinetics and pharmacodynamics of anesthetic medications

Hypothermia can affect drug pharmacokinetics by disrupting enzyme activity. In hypothermia conditions, the body redistributes blood from the intestines, extremities, kidneys, and liver to the vital organs. This reduces the plasma bioavailability of the drugs used. In addition to the above effects, as the body temperature decreases, blood saturation with carbon dioxide increases, leading to a decrease in pH. When the pH changes, drugs are ionized, which changes their bioavailability (van den Broek MPH., 2010). This way, the metabolism is reduced and slowed down, and the effect of the drugs used to introduce and maintain anesthesia is prolonged accordingly. A decrease in body temperature increases propofol plasma concentration, resulting from reduced blood flow to the liver (Ruetzler K., 2018). Perioperative hypothermia affects the activity of volatile anesthetics by reducing the minimum alveolar concentration of sevoflurane and isoflurane by 5% per 1-degree drop in the body temperature. In addition, hypothermia increases the tissue solubility of volatile anesthetics and thus delays recovery from anesthesia (Riley C., 2018). The concentration of fentanyl, an opioid analgesic commonly used during anesthesia, increases by 5% for every 1-degree drop in body temperature (Fritz HG., 2005). Hypothermia affects the action of muscle relaxants through a change in metabolism and excretion, respectively, their bioavailability. A decreased body temperature by 2 degrees can double the duration of neuromuscular blockade (Heier T., 2006). All these perioperative hypothermia effects are associated with delayed recovery from anesthesia (Ruetzler K., 2018).

b) Hypothermia and recovery from general anesthesia

One of the consequences of perioperative hypothermia is delayed recovery from anesthesia. Patients subjected to hypothermia during major abdominal surgery require 40 min longer to be removed from the so-called postanesthesia care unit compared to normothermic patients. Complete recovery takes 90 min longer than for patients with a body temperature above 36 ºC, which affects perioperative costs (Lenhardt R., 1997; Bock M., 1998).

c) Hypothermia-associated coagulopathy

Hypothermia is associated with significant coagulation disorders. Like other enzymes, plasma coagulation factors require a temperature optimum to function correctly. Hypothermia reduces enzyme activity and thus leads to coagulopathy. The associated blood loss reduces the clotting factors, further increasing blood loss. Suppression of the synthesis of thrombin and fibrinogen explains increased bleeding risk at a temperature below 36 ºC (Shenaq SA., 1986; Watts DD., 1999; Winkler M., 2000). In addition to the effect on plasma coagulation factors, hypothermia affects platelet counts and function. Platelet sequestration in the liver and spleen and a decrease in their number in the peripheral circulation is reached. This is the cause of thrombocytopenia with a maximum drop in the number of platelets at a temperature between 25 and 30 ºC (Van Poucke S., 2014). This hypothermia-induced thrombocytopenia is reversible with rewarming and restoration of normal body temperature. Hypothermia causes a reversible disorder in platelet aggregation by inhibiting the release of thromboxane A2, which plays a key role in platelet activation and aggregation (Valeri CR., 1992). A systematic review showed that even a 1-degree drop in body temperature could lead to increased blood loss by 16% and an increased risk of blood transfusion by 22% (Rajagopalan S., 2008). Another study provides evidence that maintaining normothermia during surgery reduces the risk of blood transfusion by 40% (Balki I., 2020). Hypothermia may also be responsible for hypercoagulability due to various coagulation and vasculature changes, such as increased viscosity, hemoconcentration, and activation of the inflammatory cascade, comparable to the effect of disseminated intravascular coagulopathy that occurs in patients with septic shock (Sun Z., 2016).

6. Management of drains, probes, and catheters

All 121 patients of the study population had urethral catheters placed, which were removed in the evening after surgery (except for radical hysterectomy cases). In 1/3 of the cases, drains were placed, which were removed on day 0 of the surgery (after verticalization and early mobilization). The presence of drains, probes, and catheters creates discomfort for the patients and delays their recovery. After the introduction of the ERAS protocol, we do not leave nasogastric tubes, as a rule, even after supracolic omentectomy. Abdominal drains signaling early postoperative bleeding are removed sooner – after the early mobilization to avoid discomfort to the patient. Our tactics are the same with regard to urethral catheters, which are removed as early as possible in the postoperative period.

Avoidance of nasogastric decompression (tube)

According to a meta-analysis, nasogastric intubation during elective surgery increases the risk of postoperative pneumonia (Cheatham ML., 1995). Avoiding nasogastric tubes reduces cardiovascular and respiratory complications (TeeuwenPH., 2010; Greco M., 2014). Early removal of the nasogastric tube is associated with significantly faster recovery of bowel function and fewer subjective complaints (Pearl ML., 1996). It was established that routine nasogastric decompression did not reduce the incidence of paralytic ileus or improve bowel function recovery (Nelson R., 2007). In the ERAS protocols, for the stated reasons, the insertion of a nasogastric tube after gynecologic oncology surgeries is not recommended (Nelson G., 2019).

Rapid removal of the urethral catheter

The ERAS Society recommendations include the removal of the urethral catheter before the 24th hour of surgery (Nelson G., 2016). Although there is a lack of randomized controlled trials on this topic in patients with ovarian carcinoma, some publications point out that early removal of the urethral catheter is associated with a lower incidence of uroinfections and shorter hospital stays without leading to re-catheterizations (Griffiths R., 2005, Ahmed MR., 2014).

7. Minimally invasive surgery (MIS) and ERAS

Although the primary purpose of the ERAS protocol is to shorten the length of hospital stay in open and complex surgeries and thereby reduce hospital costs, in recent years, elements of this protocol have been introduced in minimally invasive surgery. ERAS protocol for MIS is not as much to shorten the hospital stay but to improve the quality of life and patient satisfaction. Protocol components such as early mobilization, early feeding, removal of catheters and drains (especially after LAVH) on the day of surgery, control of postoperative hyperglycemia, opioid-sparing postoperative analgesia, and minimal infusion loading are the basis of quality quick recovery after minimally invasive surgeries and patients' readiness for discharge on the day of the surgery.

The term MIS includes laparoscopic and vaginal surgeries, i.e., interventions avoiding trauma and the possibility of complications associated with laparotomy.

In the presented study, MIS was performed on 31% of the patients included in the study – 38 patients with laparoscopic and 10 patients with vaginal surgery (Fig. 2). The components of the ERAS protocol (except bupivacaine injection into the surgical incision) were applied to all patients (100% applicability). Of the laparoscopic surgeries, 18% were performed for oncological diseases and 82% for benign pathology (Fig. 4). Patients with oncological disease underwent LAVH in 18%, and patients with benign pathology underwent LAVH in 29%. Other laparoscopic surgeries (mainly on adnexa) without LAVH were performed in 53% (Fig. 5). Of the 10 vaginal surgeries, 4 were vaginal hysterectomies. In endometrial carcinoma, MIS becomes the standard. Applying the ERAS protocol in MIS for oncological and benign diseases (with or without hysterectomy) is applicable, improving the quality of recovery, satisfaction, and self-esteem of the operated patients.

Scientific data on the effects of ERAS procedures in minimally invasive surgery (MIS) in gynecologic practice is increasing. Weston et al. (2020) reported reduced use of opioid analgesics in oncology patients treated by the ERAS program and MIS involving hysterectomy. Wong et al. (2018) concluded that by applying the ERAS guidelines in the postoperative period of patients operated on by minimally invasive techniques, pain could be controlled without opioid analgesics. Ljungqvist et al. (2017) and Helou et al. (2020) concluded that implementing ERAS protocols in gynecology improved postoperative outcomes and patient satisfaction and reduced costs. According to Helou et al. (2020), a modification of part of the protocol measures is necessary when applying it to some specific groups of patients – patients with chronic pelvic pain, opioid dependence, and psychiatric diseases.

a) Minimally invasive surgery in oncologic surgeries

Minimally invasive surgery in gynecologic oncology includes laparoscopic, robotic, and vaginal surgery and the introduction of sentinel biopsy of the lymph nodes. The first ERAS guideline in gynecologic oncology (2016) launched the concept of more frequent application of MIS. For this reason, there is a discrepancy in the number of minimally invasive procedures in the groups before and after the introduction of the ERAS protocol (Nelson G., 2016). Given the fact that MIS independently affects the reduction of postoperative pain, complications, and hospital stay, opponents of ERAS point out that the benefits in postoperative outcomes in many of the studies are due to MIS as a stand-alone factor and not contributed by the introduction and adherence to the ERAS guidelines. Although such detection bias is possible in study analysis due to the widespread introduction of MIS in gynecologic oncology following ERAS protocols, other studies have accounted for this influence in their design and analysis of outcomes. Lambaudie et al., in 2017, published an analysis of the effect of the ERAS protocol in a specialized MIS center, where 85% of the procedures were performed minimally invasively. The authors prove that when performing MIS, the employing measures and procedures of the ERAS protocol after laparoscopic surgeries reduces LOS from 3 to 2 days. In the patients who underwent open surgery (only 25), the study did not establish a difference in the postoperative results due to the introduction of the ERAS protocol. The randomized trial by Ferrari et al. (2020) compared perioperative outcomes in laparoscopy, Pfannenstiel laparotomy, and median laparotomy with and without ERAS procedures. The authors found LOS shortening in the laparoscopy subgroup from 4 to 2 days, as well as in the laparotomy subgroup from 6 to 3 days after following the ERAS protocol.

b) MIS in benign pathology involving hysterectomy

ERAS after minimally invasive gynecologic surgery

A systematic review by Kalogera et al. (2019) reviewed 12 studies reporting outcomes after the employing ERAS in MIS and 1 study of MIS and bowel resections [390]. All studies analyzed the impact of adherence to the ERAS guidelines in laparoscopic hysterectomies. With reference to the effect on open gynecologic surgery, compliance with the ERAS elements leads to a shorter hospital stay (i.e., discharge on the day of the surgical intervention), improves patient satisfaction, and significantly reduces costs without an increase in the frequency of complications and rehospitalizations.

In a retrospective study aimed at evaluating the effect of the ERAS protocol on minimally invasive gynecologic procedures excluding hysterectomy, Peters et al. (2020) found that implementation of ERAS procedures was associated with increased discharges on the day of surgery and improved perioperative outcomes, including opioid avoidance, without affecting 30-day postoperative morbidity. Based on these results, the authors conclude that the ERAS protocol can be recommended for all laparoscopic gynecologic surgeries, not only for laparoscopic hysterectomies.

In a randomized trial, Yilmaz et al. (2020) investigated the ERAS impact on patients undergoing minor surgery (laparoscopic and hysteroscopic). One hundred and four patients were randomized into two groups: a group with an applied ERAS protocol and a group with conventional perioperative care. The reported results showed that ERAS care resulted in significantly shorter hospital stays, early mobilization, and reduced infusions without increasing complications.

Role of ERAS in patients after laparoscopic hysterectomies

In a recently published study, Inania et al. (2022) analyzed recovery time and possible early discharge after a total laparoscopic hysterectomy. Following adherence to ERAS procedures, the patients were discharged within 24 hours of laparoscopic hysterectomy versus 2 days for the control group. The researchers also found reduced opioid analgesic requirements and less nausea and vomiting in the early postoperative period in patients following the ERAS protocol compared to the control group. Preoperative education and psychological preparation of patients for early discharge from the hospital play a vital role in the good results of the ERAS system. One of the significant advantages of following the ERAS protocol is the avoidance of opioids, which are associated with multiple adverse effects—decreased intestinal motility, nausea, vomiting, sedation, delirium, constipation, and ileus.

There are publications confirming the arguments and considerations mentioned above regarding the beneficial role of the ERAS protocol in gynecologic minimally invasive interventions, including hysterectomies. In these studies, patients' rapid mobility (verticalization and mobilization), early discharge from the hospital, avoidance of opioid analgesics, good postoperative analgesia, shortened hospital stay, and reduced financial costs are highlighted (Chapman JS., 2016; Lee J., 2018; Abdelrazik AN., 2020). Keil et al. (2019) investigated the factors delaying early discharge after minimally invasive gynecologic surgery and adhering to the ERAS protocol. According to them, urinary retention, postoperative pain, nausea, and vomiting are at the root of delayed discharge. Besides the possibility of early hospital discharge, an essential indicator of the effectiveness of ERAS programs is the frequency of rehospitalizations due to complications. The studies by Inania et al. (2022), Sheyn et al. (2018), and Keil et al. (2019) showed that early discharge did not increase readmissions in patients after total laparoscopic hysterectomy for benign pathology.

c) MIS in benign pathology not necessitating hysterectomy

Applying the ERAS protocol to patients undergoing laparoscopic non-hysterectomy gynecologic surgeries may result in the possibility of discharge on the day of surgery. Discharge from the hospital on the day of laparoscopic surgery, without increasing the incidence of complications and rehospitalizations, would significantly reduce hospital costs, especially for private hospitals. Discharge from the hospital on the day of surgery would also improve patient satisfaction.

Due to implementing a series of measures laid down in the ERAS protocol, the paradigm for 24-hour monitoring of operated patients after medium-volume laparoscopic surgeries has changed. This makes possible de-hospitalization on the day of the surgery and the performance of this type of surgical intervention in outpatient centers (Modesitt SC., 2016; Ljunggqvist O., 2017; Carter-Brooks CM., 2018). In some countries, such as the US, surgeries of this volume are performed in outpatient centers, and the discharge is on the day of surgery. This approach aims to save money from hospital costs from the so-called postanesthesia care unit. A paper by Peters et al. (2020) pointed out that patients undergoing non-hysterectomy laparoscopic procedures following elements of the ERAS protocol had a 19-minute shorter stay in the postoperative observation unit compared to other patients, resulting in financial savings of $693 per patient. For the entire patient cohort (n=410) in this study, the cost savings were $284,335 over a 2-year period. In addition, the authors of the study reported a significant reduction in postoperative pain, opioid requirement, nausea, vomiting, and spontaneous micturition time in patients treated according to the ERAS system. The impact of pain management in the early postoperative period is significant, considering that most patients who underwent surgery had chronic pelvic pain and/or pelvic endometriosis.

8. ERAS and gynecologic oncology surgery

Of all 121 patients included in our study, 43 patients (36%) were operated on for gynecologic oncology disease. Due to the specificities of patients with ovarian carcinoma, we divided this population into patients with ovarian carcinoma (n=11) and those with other gynecologic oncology diseases (n=32) (Fig. 7). The results regarding the applicability of the ERAS protocol show that patients with gynecologic oncology diseases can be a target for the implementation of procedures and measures reducing the stress of complex surgical intervention, without additional risk of complications and rehospitalizations.

The concept of enhanced recovery after surgery initially referred to as "fast-track surgery", was published by Engelman et al. in the field of cardiac surgery in 1994. Kehlet published the first results regarding the effectiveness of this concept in 1995. Subsequently, in 2000, a group of European surgeons created the Enhanced Recovery After Surgery Society, whose mission is to improve the recovery process through training, research, auditing, and implementation in practice of the achievements of evidence-based medicine by preparing guidelines and protocols. These protocols aim to reduce surgical morbidity (postoperative complications) by introducing evidence-based measures to regulate physiological processes in the perioperative period. Initially, the studies were on colorectal surgery. In 2003 Marx et al. demonstrated the validity of this concept in gynecologic oncology. This study presents the application of ten ERAS elements in patients with ovarian carcinoma who have undergone surgery. The ERAS protocol was applied to 69 patients, and standard perioperative care – to 72 patients. The authors found a demonstrable benefit of implementing this protocol in shortening the hospital stay and reducing the incidence of severe complications. Since this seminal publication by Marx et al., by 2022, 31 comparative studies dedicated to ERAS in gynecologic oncology surgery have been published, of which 5 were controlled and randomized.

In its final form, the first ERAS guideline in gynecologic oncology was published in 2016 (Nelson G., 2016 (Part I, II)). It includes 21 guidelines in 13 sections regarding the preoperative and intraoperative period and 19 guidelines in 9 sections regarding the postoperative period. In the preoperative period, the guidelines focus on patient counseling and education and optimizing the patient's general condition before surgery. The latter is achieved by encouraging to stop or reduce smoking and alcohol intake and avoiding dehydration and fasting before surgery. According to the ERAS protocol, prevention of VTE, antimicrobial prophylaxis, preemptive administration of antiemetics, and multimodal opioid-sparing analgesia are the cornerstones of perioperative care. Intraoperative ERAS guidelines aim to maintain normovolemia and normothermia and avoid the placement of drains and tubes. In the postoperative period, applying the principles of normalizing physiological processes continues, along with reducing body stress associated with the surgical intervention through oral intake of liquids and food and rapid removal of catheters and catheters continues. Prevention of ileus is achieved by early mobilization, stimulation of intestinal peristalsis by oral liquid and food intake, and multimodal opioid-sparing analgesia.

In 2019, the latest and most updated version of ERAS protocols in gynecology was published (Nelson G., 2019). This protocol provides further evidence and adds new guidelines to reduce SSIs, for rehabilitation and interventions applied to complex surgical procedures such as exenteration and cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. In addition, attention is paid to patient compliance, control, and reporting the results of implementing the guidelines (Nelson G., 2019). In 2020, the guidelines regarding hyperthermic intraperitoneal chemotherapy and GIT surgical interventions were detailed (Hü̈bner M, 2020 (Part I, II)). The specifics of patient recovery after vulvar and vaginal surgery were published (Altman AD, 2020).

A) ERAS in different gynecologic oncology localizations

Gynecologic oncology includes a wide range of malignant tumors that can affect various anatomical areas. Given this feature, the existing ERAS protocols were updated and included specific guidelines regarding surgery in the vulvar and vaginal areas and cytoreductive surgery in the upper abdomen (Hü̈bner M, 2020; Altman AD, 2020). The first ERAS guideline in gynecologic oncology addressed patients undergoing major abdominal and pelvic surgery for endometrial carcinoma, CC, and primary ovarian carcinoma (Nelson G., 2019). Although, by now, scientific literature presents incontrovertible evidence of the beneficial effect attributable to the employing ERAS guidelines in gynecologic oncology surgery, little is still known about the effect of these protocols in rarer malignant sites, such as carcinoma of the vulva and vagina. Most of the comparative studies on ERAS have focused on major pelvic surgery (Bisch SP., 2021). Hence, there is an uneven accumulation of data regarding surgery for breast cancer and ovarian and endometrial carcinoma. The ERAS guidelines for vulvar and vaginal carcinoma were published in 2020, with evidence of their applicability and benefits expected to accumulate in the near future (Altman AD, 2020).

B) ERAS in ovarian carcinoma

Ovarian carcinoma is mainly diagnosed at an advanced stage, and the surgical treatment of these patients is of the highest complexity and risks of complications. The applicability of the components of the ERAS protocol is a significant challenge for the surgical team. This includes early mobilization and oral nutrition, degree of analgesia, targeted infusion therapy, and removal of catheters, drains, and tubes. In all 11 patients from our population, we achieved 100% applicability of the protocol, favorably affecting the recovery process and potentially shortening the hospital stay, respectively, costs. This is the target group that will benefit the most from the implementation of measures for enhanced recovery after surgery.

9. Complications

Of the 121 patients included in our study, complications were observed in 4 patients (Fig. 16)

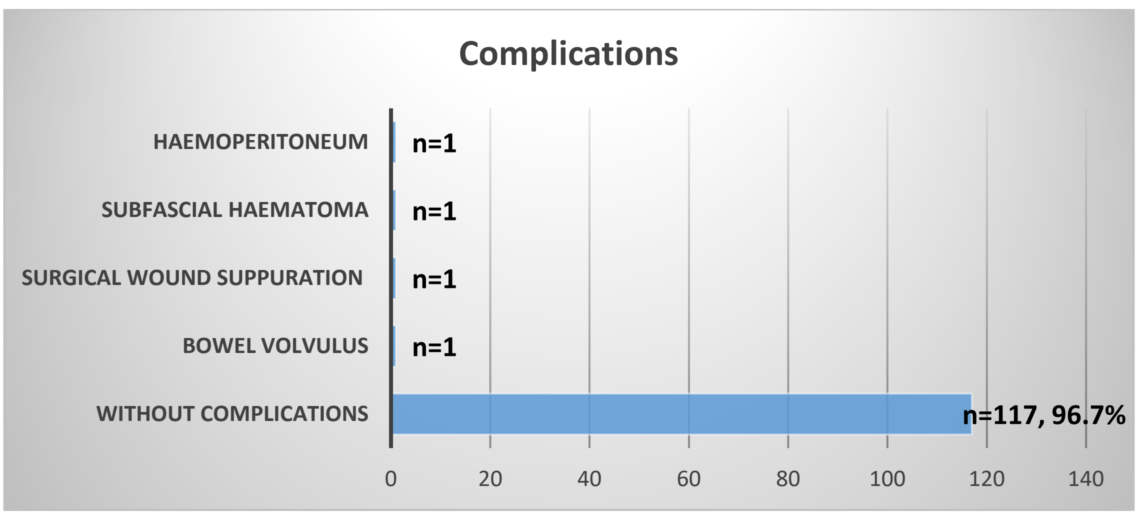


Figure 16. Complications

The absence of complications in 96.7% of the patients included in the study confirms that ERAS measures do not increase the frequency of complications in the perioperative period, although some are revolutionary. The applicability of these measures and components of the ERAS protocol in gynecology requires a shift in thinking regarding basic principles of behavior in preoperative preparation and care in the early postoperative period. Alternatively, it is worth analyzing the 4 cases with postoperative complications. In the patient with volvulus of the small intestine, the complication occurred on the 15th postoperative day and resulted in rehospitalization. The patient's initial surgery was due to an ovarian tumor formation, which, after histological verification, was specified as a carcinosarcoma. Pelvic and para-aortic lymph metastases were detected on preoperative imaging and intraoperatively. Therefore, pelvic and para-aortic lymph node dissection was performed in order to achieve optimal cytoreduction. After a smooth postoperative period, the patient was discharged from the hospital on the 10th postoperative day according to the requirements of the National Health Insurance Fund. On the 15th postoperative day, complaints of nausea, vomiting, and abdominal distension were reported.

The examination revealed evidence of peritoneal irritation and acute abdomen, requiring rehospitalization. An abdominal x-ray showed hydro-aerial shadows. The patient underwent a relaparotomy, with a surgeon also participating in the team. Intraoperatively adhesions of small bowel loops in the bed of the para-aortic dissection were observed, causing small bowel volvulus. The patient recovered normally after the relaparotomy and has been disease-free for almost 2 years since then, having undergone postoperative chemotherapy and, in the meantime, another surgery for ileus.

The hemoperitoneum case also raises questions for discussion. The patient had advanced ovarian carcinoma, proven histologically at a previous laparotomy, had undergone 6 courses of chemotherapy, and was admitted for secondary optimal cytoreduction. During surgery, optimal cytoreduction was achieved through pelvic and diaphragmatic peritonectomy, supracolic omentectomy, and total hysterectomy with the remaining from the previous surgery ovary. All components of the ERAS protocol have been implemented and adhered to. The abdominal drain and urethral catheter were removed in the morning of the 1st postoperative day; as a complex and prolonged surgery, the mobilization was on the day of surgery in and around the bed. The patient continued with mobilization, feeding, and recovery with normal blood, biochemical and hemodynamic parameters until the late afternoon of the 1st postoperative day. A worsening of the general condition followed, accompanied by a fall in blood pressure and a progressive fall in hemoglobin. At 9 pm on the 1st postoperative day, a relaparotomy was performed, and hemoperitoneum with clots was found in the diaphragmatic and pelvic peritonectomy areas. Blood loss was estimated at nearly 2 liters. Lavage, hemostasis, bilateral ligation of the hypogastric vessels, pelvic and diaphragmatic drainage, and adequate hemo- and plasma transfusions and infusion therapy were performed. The patient continued her normal postoperative recovery. The case raises questions for discussion regarding compliance with the recommendation to refrain from drain placement. We consider early removal of the pelvic drain and failure to remove a drain from the diaphragmatic peritonectomy area as an error. In large-volume surgeries (especially in patients with ovarian carcinoma), we recommend bilateral ligation of the hypogastric arteries above the posterior branch to prevent postoperative bleeding from the small pelvis.

The other two cases of complications – hematoma and suppuration of the surgical wound, represent complications from the side of the surgical incision and raise questions for discussion. Both patients underwent Pfannensteil laparotomy. The transverse incision of the abdominal wall is burdened with a high risk of subfascial hematoma in the postoperative period, and therefore the placement of a subfascial drain for 1–2 days is recommended. Interesting in one of the cases is the time of appearance of the subfascial hematoma -– on the 4th postoperative day. In this regard, the subject of discussion is whether, in this case, the administration of low molecular weight heparins does not cause this hematoma and secondary bleeding.

Surgical wound suppuration occurred in a patient with diabetes and obesity.

Although the frequency of these complications (3.3%) is low, we believe that complications from the surgical wound can be avoided by increasing the minimally invasive laparoscopic and vaginal approaches instead of performing laparotomy. We developed an algorithm to limit SSIs and complications in this regard. The algorithm is based on our clinical experience and data from the literature.

Algorithm for limiting SSIs and complications

1. Selection and screening of high-risk patients for surgical incision complications who have the following characteristics:

• Obesity;

• Diabetes, especially poorly controlled diabetes;

• Hypertension;

• Smokers;

• Pelvic inflammatory disease and its varieties: pyosalpinx, acute adnexitis with pelvioperitonitis, tubo-ovarian abscess, Douglas abscess, acute parametritis;

• Elderly patients (over 75 years).

2. In these patients, if surgical intervention is required, it should be performed through minimally invasive access (laparoscopy or vaginal access), i.e., avoid laparotomy.

3. Prevention of SSIs (antibiotic prophylaxis, control on postoperative hyperglycemia, normothermia during surgery, targeted infusion therapy).

4. In patients who require a Pfannenstiel laparotomy, a subfascial drain should be placed, and low molecular weight heparin should not be administered. Prevention of PTE should be carried out by mechanical means (elastic stockings).

Since the ERAS guidelines in surgical gynecology include new, somewhat revolutionary for traditional surgery procedures, the risks of various complications have been discussed for their safe introduction into practice. Skeptics' concerns regard early feeding after surgery and the risks of aspiration syndrome because of the fluid intake up to 2 hours before induction of anesthesia. The presumption of shortening hospital stays when following the components of ERAS protocols raises concerns about rehospitalizations due to premature discharge of operated patients. Concerning these risks, some researchers have focused on evaluating the frequency of rehospitalizations and the occurrence of complications after implementing ERAS guidelines in surgical gynecology. According to literature data, 21 publications report and analyze the occurrence of complications when applying ERAS protocols. Depending on the studied group of patients, the type of surgery, and the severity of complications, the frequency of complications before the introduction of the ERAS guidelines varied from 5% to 70% (Bisch SP., 2018; Gerardi MA., 2008; Heathcote S., 2019). The PROFAST study looked at the occurrence of specific complications in the conventional care group and the ERAS protocol group. No statistically significant difference in the occurrence of severe complications between the two groups was established, despite a 10% reduction in the incidence of postoperative ileus in the ERAS group (Sanchez-Iglesias JL., 2020). These results are similar to the ones reported by another non-randomized study on operated patients with ovarian carcinoma. No statistical difference in the occurrence of severe postoperative complications between the compared groups (with and without the application of the ERAS protocol) was found (Gerardi MA., 2008).

Ferrari et al. (2020) reported a significantly lower rate of postoperative complications in the ERAS group compared to the standard perioperative care group. A meta-analysis of 21 studies that reported complications after gynecologic oncology surgeries when applying the ERAS guidelines, including 4974 patients, showed a statistically significant reduction in postoperative complications of 32% after introducing the ERAS measures (Bisch SP., 2021). The risks of rehospitalization in the first 30 days after surgery were reduced by 20% (OR 0.80) in the ERAS cohorts compared to those with conventional care. The randomized PROFAST study presented similar data – 20% of rehospitalizations in the group with conventional care versus 6% in the group following ERAS guidelines (p=0.033) (Sanchez-Iglesias JL., 2020). The meta-analysis found no significant difference for rare complications such as leakage of anastomoses (OR 0.93) as well as for postoperative mortality (OR 0.61) between the two groups (with and without ERAS) (Bisch SP., 2021). Patients with gynecologic oncology diseases require postoperative adjuvant treatment such as chemotherapy, radiotherapy, or a combination of these therapies. Enhanced and optimal recovery after surgery is of great importance for the timely implementation of this treatment. A study by Tankou et al. (2021) showed that implementation of ERAS perioperative procedures was the strongest predictor of timely continuation of therapy in patients undergoing interval cytoreductive surgery with a 10-fold higher chance of chemotherapy continuation within 28 days after surgery compared to those operated without following the ERAS protocol.

10. Prevention of PTE

All 121 patients from the present study underwent two-component thromboprophylaxis – mechanical with elastic bandages or elastic stockings and medication prophylaxis – by applying low molecular weight heparin (LMH). The method of PTE prophylaxis is described in detail in the Methods section. According to this indicator, 100% applicability was achieved. As a result of this prophylaxis, no thromboembolic complication was registered, both in the early and late postoperative period. In patients with ovarian carcinoma, LMH is administered until the 28th postoperative day due to the high risk of VTE. As described above, two cases of postoperative bleeding were recorded in our sample – hemoperitoneum and subfascial hematoma.

One of the significant risks for patients after gynecologic oncology surgeries is venous thromboembolism (VTE). Some studies report a 38% incidence of this complication in patients with ovarian carcinoma (Levitan N., 1999). The ERAS guidelines in surgical gynecology assess the risk of this complication and recommend using venous thromboembolism prophylaxis in all patients undergoing gynecologic oncology surgery. Specific guidelines include the administration of low-molecular-weight heparins and mechanical prophylaxis with elastic bandages or stockings prior to surgery. These measures should continue in the postoperative period, with early mobilization being an essential component (Baykal C., 2001; Lyman GH., 2013). Pharmacological regimens consisted of subcutaneous administration of 40 mg Enoxaparin or 5000 U Dalteparin 2 hours before surgery and 8–12 hours postoperatively. Thromboembolic prophylaxis should be continued daily for 1 month after gynecologic oncology surgery (Bergqvist D., 2002).

11. Compliance with the components of the ERAS system

Successful implementation of the ERAS protocol in daily practice is related to adherence to the procedures and patient tolerability (Gustafsson UO., 2011). It has been established that the clinical benefits of the protocol are directly proportional to the degree of implementation of the various components of the ERAS program (ERAS compliance group, 2015). It is not always possible to objectively assess the degree of protocol adherence. For example, a patient who has adhered to the preoperative and intraoperative elements of the protocol may develop a surgical complication that prevents the performance of postoperative procedures. The complication and non-adherence to the rest of the protocol (the postoperative elements in the specific example) can subsequently influence clinical outcomes. Therefore, some researchers exclude postoperative components of the protocol when analyzing the impact of compliance on clinical outcomes (Wijk L., 2019). Preoperative and intraoperative components are under the control of the subject (physician/team) applying them, while postoperative components can be affected and result from the previous ERAS procedures (Gustaffson UO., 2011). Thus, the concept of continuity and connectivity (continuum) of the specific components of the protocol is confirmed, i.e., one measure or a group of measures affects the following measures. Therefore, the protocol is not a mechanical set of independent actions (Wijk L., 2019). Successful adherence to one component of the ERAS protocol facilitates adherence to the next, thus exerting a synergistic effect toward improving and enhancing patients' recovery.

A study of the applicability of the individual components of the ERAS protocol by oncologists in Australia and New Zealand found that prevention of hypothermia, thromboembolic and wound complications, and avoidance of drains was widely implemented in daily practice. At the same time, the measures and procedures related to other elements of the protocol (preoperative fasting, early postoperative nutrition, postoperative analgesia, infusion target therapy, and prevention of nausea and vomiting) show a different degree of applicability between individual centers (Lindemann K., 2017). Active and organized efforts to implement the measures concerning specific components will increase patients' tolerance and adherence to them. This goal is feasible only through a multidisciplinary approach, i.e., the involvement and participation of the entire team responsible for patients' perioperative care. The organized and systematic audit can assess patients' compliance with the respective elements of the ERAS protocol in operative gynecology, incl. in gynecologic oncology surgery.

The most extensive study of compliance with the ERAS procedures and their effect on outcomes in gynecology included an international network of hospitals using the ERAS Interactive Audit System – a centralized database of patient outcomes (Wijk L., 2019). This study analyzed 2,101 patients at 10 hospitals in Canada, the United States, and Europe between January 2011 and November 2017. The study showed that each department that achieved high compliance in implementing ERAS components reported a shortening hospital stay by 8% after minor and moderate surgeries and 12% after major surgeries (Wijk L., 2019). Iniesta et al. (2019) examined the effect of adherence to components of the ERAS protocol. They found that when the compliance rate reached 80% of the 21 components of the ERAS protocol, complications were statistically significantly less (38% vs. 58%), and hospital stay was shorter (2 vs. 3 days) compared to patients with less than 80% compliance. In the group with a complete implementation of the protocol and adherence to some specific components, such as avoiding infusion overload, early mobilization, early feeding, and early removal of the urethral catheter, there were fewer postoperative complications (Iniesta MD., 2019). A secondary analysis of the PROFAST study found that an increase in compliance led to a shorter hospital stay, and this dependence was more pronounced after complex surgical interventions (Sanchez-Iglesias JL., 2021).

The primary objective of the present prospective study was to determine the applicability and adherence rates for the specific components of the ERAS protocol. The presented results for the respective tasks of the thesis show the following percentages of compliance.

Compliance with:

• Bowel preparation – all 121 patients underwent bowel preparation receiving a cleansing enema at 6 am before surgery –100%;

• Targeted infusion therapy – all 121 patients were administered targeted infusion therapy: 50 mg/h (about 1 liter until the following day) – 100%;

• Prevention of thromboembolic complications – all 121 patients underwent two-component thromboprophylaxis: mechanical (elastic bandages or stockings) and medication prophylaxis by applying LMH – 100%;

• Antibiotic and antiemetic prophylaxis – all 121 patients were given antibiotics with first-generation cephalosporins ± metronidazole and antiemetic prophylaxis with dexamethasone – 100%;

• Analgesia – all 121 patients were given opioid-sparing anesthesia, and intraoperative infiltration of the surgical incision with Bupivacaine (for laparotomy patients) – 100%;

• Normothermia – all 121 patients underwent surgical treatment in conditions of normothermia – 100%;

• Oral fluid intake – only one patient was unable to take oral fluids after surgery - 99% compliance;

• Mobilization – only in 6 patients early mobilization was not carried out postoperatively – 95% compliance;

• Carbohydrate intake the evening before the surgery – in 10 patients Fresubin intake of 1 vial p.o. was not carried out – 92% compliance;

• Drains, catheters, probes – all 121 patients had urethral catheters inserted, which were removed the evening after surgery (except for radical hysterectomy cases), and 1/3 of the cases had drains inserted, which were also removed on day 0 of the surgery – 66% compliance.

12. Hospital stay

The main idea in implementing specific components of the ERAS protocol is to speed up the recovery process and reduce the stress of the operative intervention on the whole organism. ERAS measures have their effect not as separate procedures but in a complex continuum. Enhanced recovery aims to shorten the hospital stay without increasing the frequency of complications and rehospitalizations. This, in turn, would lead to tangible (reduced costs to health systems) and intangible (patient satisfaction and improved quality of life) benefits. The latter, in turn, can lead to additional benefits by directing patient flow to clinics implementing this protocol. As a result of the application of particular components of the ERAS protocol in our study, the following recommendations for length of hospital stay (LOS) can be made:

• In open surgeries due to benign pathology – 2 days LOS and discharge from hospital on the 1st postoperative day;

• In open surgeries for oncological diseases, except for ovarian carcinoma – 3 days LOS and discharge from hospital on the 2nd postoperative day;

• In open surgeries for ovarian carcinoma – 5 days LOS and discharge from hospital on the 4th postoperative day;

• In laparoscopic surgeries without hysterectomy, as well as in vaginal surgeries without vaginal hysterectomy –1 day LOS and discharge from hospital on the day of surgery (day 0);

• In laparoscopic surgeries, including hysterectomy, as well as in vaginal hysterectomies –2 days LOS and discharge from hospital on the 1st postoperative day.

Since the hospital stay of health-insured patients is determined for each clinical pathway funded by the National Health Insurance Fund, the shortening of the hospital stay after the implementation of the measures and procedures for enhanced recovery after surgery may have a recommendatory nature and be taken into consideration by the Expert Council of Obstetrics and Gynecology for future updates in the Obstetrics and Gynecology Standard, respectively in case of revisions of the minimum hospital stay for the specific clinical paths of treatment. For this, our experience of 121 patients will not be sufficient. Our results, which show the feasibility and safety, as well as scientific evidence of the benefits of the ERAS protocol for enhanced recovery after surgery and the possibilities of shortening the hospital stay, can serve as a model and a prerequisite for the implementation of this complex of measures in clinics and health facilities in charge of surgical gynecology and gynecologic oncology.

Length of hospital stay (LOS)

LOS is the most frequently studied performance indicator of the ERAS system in gynecology: in a meta-analysis, 27 of 31 studies reported results on LOS (Bisch SP., 2021). Hospital length of stay is related to clinical patient outcomes and financial resources. This metric is attributable to a significant part of the surgical treatment cost in most centers. Many studies on LOS after ERAS in gynecologic oncology are based on comparison with control groups using the historical control methodology. The number of patients enrolled in these studies ranged from less than 100 to more than 500, and the reported LOS shortening ranged from 0 to 3 days. Kalogera et al. (2013) analyzed the effect of applying the ERAS guidelines in staging and cytoreductive surgery in gynecologic oncological patients as well as patients with urogynecologic procedures. This retrospective study compared 241 patients with 235 historical controls, finding a LOS shortening after cytoreductive surgery of a median of 4 days and a median of 1 day in staging surgery. Two extensive, similar studies were published in 2018 and reported a reduction in hospital stay following compliance and employing ERAS measures in gynecology oncology (Meyer LA., 2018; Bisch SP., 2018). In one of them, Meyer et al. (2018) examined adherence to the ERAS protocol at a single US clinic from 2014 to 2016, comparing every patient who underwent open gynecologic surgery according to this protocol to historical control. Six hundred-seven patients were included, and 80% had gynecologic oncology diseases. The authors found that ERAS implementation reduced the average hospital stay from 4 to 3 days. Bisch et al. (2018) reported that in 519 patients with suspected or histologically proven female genital malignancy, application of the ERAS protocol reduced LOS from 4 (pre-protocol) to 3 days. In the case of milder surgeries, the LOS was shortened from 3 to 2 days. A more pronounced tendency to shorten the hospital stay was observed in the more complex surgeries – from an average of 5 to 3 days. After considering the factors of age, smoking, alcohol consumption, accompanying diseases, and the type and complexity of surgery performed, the application of the ERAS system remains a statistically significant factor responsible for an average decrease in hospital stays of 31.4%.

The promising initial results of these comparative cohort studies in gynecologic oncology only assert the growing need for randomized controlled trials to support these data and their applicability in daily practice. Five such studies have so far evaluated the effect of ERAS on the length of hospital stay after gynecologic oncology surgeries (Yi HC., 2020; Dickson EL., 2017; Ferrari F., 2020; Sanchez-Iglesias JL., 2020; Cheb L., 2020). The first was published in 2017 (Dickson EL., 2017), and the remaining 4 in 2020 (Yi HC., 2020; Ferrari F., 2020; Sanchez-Iglesias JL., 2020; Cheb L., 2020). Although the first study did not demonstrate a statistically significant difference in LOS, patient compliance data on 9 elements of ERAS protocol prompted another study (Nelson G., 2017). The subsequent two studies proved a shortening of the hospital stay from 3 to 2 days (Ferrari F., 2020; Sanchez-Iglesias JL., 2020). The PROFAST study randomized 99 patients undergoing open surgery for suspected or proven ovarian carcinoma in two groups – with applied ERAS recommendations and conventional care. Results showed 92% compliance with 15 elements of the ERAS protocol and a shortening of median LOS from 9 to 7 days in the ERAS group (Sanchez-Iglesias JL., 2020). Another randomized controlled trial by Ferrari et al. (2020) analyzed patients undergoing complex gynecologic surgeries with or without adherence to an ERAS protocol comprising 18 elements. Approximately 60% of 168 patients included in the study had proven gynecologic oncology disease by the final histological result. The patients randomized to the ERAS protocol group had a shorter hospital stay (2 days) compared to the control group (4 days). This statistically significant difference in adherence to the ERAS protocol was maintained when open (LOS reduction of 6 to 3 days) and laparoscopic surgery (LOS reduction from 4 to 2 days) were examined and compared.

In 2021, Bisch et al. published a meta-analysis of cohort and randomized controlled trials on the application of ERAS in gynecologic oncology (Bisch SP., 2021). This analysis included 6 345 patients from 27 studies and reported a mean reduction in hospital stay of 1.64 to 2.10 days compared with historical controls. Since then, at least 2 cohort studies have been published in this regard, demonstrating a significant shortening of LOS (Joshi TV., 2021; Bernard L., 2021).

Length of hospital stay after surgery for benign pathology following the ERAS protocol

In a case-control study, adherence to the ERAS protocol after a vaginal hysterectomy resulted in a 23.5-hour reduction in hospital stay (Yoong W., 2014). In a randomized clinical trial, the authors reported that following the ERAS protocol resulted in a shorter hospital stay of 1.18 days after an open hysterectomy and 0.42 days after a laparoscopic hysterectomy (Abdelrazik AN., 2020). Another study pointed out that employing ERAS shortened hospital stay by 0.3 days (from 2.6 to

2.3 days) in patients after an open hysterectomy (Wijk L., 2014). Generally, compliance and adherence to ERAS procedures shorten hospital stay after surgery by an average of 40% (Huang J., 2017). The authors of all these studies agree that to achieve a real effect on the length of hospital stay after surgery, compliance with all components of the ERAS protocol with an emphasis on control of infusions (infusion therapy) and postoperative analgesia is necessary.

13. Treatment costs

We did not aim to calculate the cost savings from implementing the enhanced recovery after surgery protocol. Reflecting the accelerated recovery on hospital length of stay is not feasible due to NHIF's minimum hospital stay requirements. However, some studies on this topic are of interest.

Costs after gynecologic oncology surgery following the ERAS protocol

Employing ERAS protocols in the daily practice of a number of surgical specialties shortens LOS and reduces complications, which is associated with cost savings (Thanh N., 2020). The cost-effectiveness associated with the implementation of ERAS guidelines in gynecologic oncology practice was investigated in 7 studies, with cost savings ranging from $950 to $8,500 (Bisch SP., 2018; Chapman JS., 2016; Gerardi MA., 2008; Wijk L., 2019, Gentry ZL., 2020; Mendivil AA., 2018). A meta-analysis of these studies established an average of $2,128 cost savings per patient after implementing the ERAS protocol (Bisch SP., 2021). According to the secondary analysis of the randomized PROFAST study published in 2021, the ERAS protocol brings savings of 1145 euros per patient ((BebiaConesa V., 2021).

Financial analysis of the savings after ERAS implementation shows significant cost savings for some surgical interventions such as colorectal resections, cystectomy, and pancreatic and liver surgeries ((Nabhani J., 2016; Joliat GR., 2016).

Regarding cost reduction after gynecologic surgery, in addition to the studies cited above, a retrospective analysis by Pache et al. (2019) compared the perioperative costs of three groups of patients: operated on before, immediately after ERAS implementation and three years after the implementation (Pache B., 2019). The authors conclude that the costs decreased significantly in the first 3 years after implementing the ERAS protocol.

14. Patient satisfaction and quality of life

As already noted, the benefits of enhanced recovery after surgery can be tangible, related to reduced costs due to shortened hospital stay, and intangible. The latter is due to patient satisfaction and quality of life.

Patient satisfaction is an essential element of the successful implementation of ERAS programs. Initial studies evaluated patient satisfaction without using quantitative means (Ghosh K., 2001), while more recent studies demonstrate an improvement in satisfaction indicators with the introduction of ERAS protocols in gynecologic oncology. Philp et al. (2015) evaluated the satisfaction of 106 patients with the implementation of ERAS procedures in gynecologic oncology practice using the IN-PATSAT32 questionnaire with 32 questions. The authors found a high degree of satisfaction with the implemented measures according to the ERAS protocol. However, fewer points were attributed to access to healthcare facilities and the availability of nursing staff. Thangavel et al. (2021) also reported high satisfaction (92.2 points for laparoscopy and 92.4 points for laparotomy) in implementing ERAS guidelines using IN-PATSAT32. Modesitt et al. (2016) assessed patient satisfaction before and after the introduction of ERAS in 145 patients undergoing large gynecologic oncology surgeries using a centralized patient satisfaction database (Press Ganey info EDGE). Data from this study show improved outcomes in postoperative pain management, patient perception of team-centered care, and patient awareness of the steps in the surgical process. Patient satisfaction with minimally invasive surgical techniques in gynecologic oncology was assessed by Ferraioli et al. (2020) via the EVAN-G survey. This survey included 26 questions related to staff-to-patient care, comfort in the clinical setting, awareness, postoperative pain, discomfort, and waiting time for surgical procedures. In the 92 patients included in this study, the highest mean score of 81.9 out of 100 was obtained in patients following the ERAS protocol. The randomized controlled trial by Ferrari et al. (2020) on ERAS in gynecologic oncology assessed patient satisfaction through 15 questions regarding the quality of the rehabilitation process. It included 168 patients, and those recovering according to ERAS guidelines showed a significantly higher degree of satisfaction than those with conventional perioperative care (123.1 points vs. 91 points).

VI. CONCLUSIONS

1. Early verticalization and mobilization on the day of surgery (day 0) were achieved in 95% of patients included in the study.

2. Early oral fluid intake on the day of surgery (day 0) was achieved in 99% of patients included in the study without complications. This is possible due to the prevention of nausea and vomiting and is a prerequisite for achieving euvolemia, early feeding, and return of bowel activity.

3. Preoperative intake of carbohydrate-rich fluids is central to the control of postoperative hyperglycemia. The applicability of this component of the ERAS protocol was 92% and fully correlated with the incidence of postoperative hyperglycemia < 11.1 mmol/L (control of postoperative hyperglycemia and insulin resistance).

4. Antibiotic prophylaxis as a measure to limit SSIs is applicable in 100% of the cases. The frequency of fever over 37.8 ºC after the 2^{nd} postoperative day was 3.3% (4 patients). Despite antibiotic prophylaxis, 1.6% (2 patients) had complications from the surgical wound, which necessitated the development of an "Algorithm for limiting SSIs and complications".

5. All patients (n=121) included in the study received opioid-sparing analgesia and antiemetic prophylaxis in the early postoperative period. Laparotomy patients (n=83) had Bupivacaine infiltration into the surgical incision. As a result of this methodology, 88% of patients had no postoperative pain, 85% had no nausea, and 84% had no vomiting. These results are a prerequisite for early mobilization and early feeding.

6. In 4 out of 121 patients (3%) included in the study, early postoperative complications were found – small bowel volvulus (15^{th} postoperative day); hemoperitoneum (2^{nd} postoperative day); subfascial hematoma (4^{th} postoperative day); surgical wound suppuration (4^{th} postoperative day).

7. The applicability of the ERAS protocol components (early oral intake, early agitation, opioid-sparing analgesia, euvolemia, avoidance of mechanical bowel preparation, targeted infusion therapy) comprises the basis of bowel function rapid recovery in all patients without cases of ileus, intestinal paresis, and gastrostasis.

8. Maintenance of normothermia (using warmed infusion solutions and normal temperature in the operating room) during the surgical intervention was achieved in all patients (100% applicability).

Avoiding hypothermia during surgery is associated with minimal intraoperative blood loss (up to 200 mL) in 95% of cases.

9. Minimally invasive gynecologic surgery was performed in 31% (n=38) of the patients in the study (in 28 patients – laparoscopic, and in 10 patients – vaginal surgery). In all, the elements of the ERAS protocol were applied (no Bupivacaine infiltration due to the minimally invasive approach) – 100% applicability.

10. In 36% (n=43) of the patients in the study, surgeries were performed due to gynecologic oncology diseases. Compliance with the various elements of the ERAS protocol in these patients was 92% – 100%.

11. As a result of applying the specific elements of the ERAS protocol in our study of 121 patients, ERAS audit, reporting, and control, the following recommendation can be made for the length of hospital stay:

• In open surgeries for benign pathology –2 days LOS, hospital discharge on the 1st postoperative day;

• In open surgeries for oncological diseases, except for ovarian carcinoma –3 days LOS, hospital discharge on the 2nd postoperative day;

• In open surgeries for ovarian carcinoma –5 days LOS, discharge from hospital on the 4th postoperative day;

• In laparoscopic surgeries without hysterectomy, as well as in vaginal surgeries without vaginal hysterectomy –1 day LOS, hospital discharge on the day of surgery (day 0);

• In laparoscopic surgeries, including hysterectomy, as well as in vaginal hysterectomies – 2 days LOS, hospital discharge on the 1st postoperative day.

VII. CONTRIBUTIONS

Original and applied/practical contributions

1. For the first time in Bulgaria, a prospective single-center study of 121 patients was performed on the applicability of the ERAS protocol in surgical gynecology, and perioperative results were reported.

2. The frequency of complications after introducing measures and procedures for enhanced recovery after gynecologic surgeries was studied.

3. An "Algorithm for limiting SSIs and complications" was developed and implemented in daily practice.

Confirmative and applied/practical contributions

1. **The ERAS (Enhanced recovery after surgery) system survey template** was introduced into daily practice.

2. The applicability and/or compliance with the specific elements of the ERAS protocol in surgical gynecology was investigated through audit and control.

3. The applicability of the ERAS protocol in gynecologic oncology surgeries was studied.

4. The applicability of the ERAS protocol in minimally invasive gynecologic surgery (laparoscopic and vaginal surgeries) was studied.

5. Minimum hospital stay in days after various gynecologic surgeries was calculated – open, laparoscopic (with and without hysterectomy), vaginal (with and without vaginal hysterectomy), gynecologic oncology (including optimal cytoreduction) after applying the elements of the ERAS protocol.

VIII. Dissertation-related publications and reports

Dissertation-related publications

1. Slavchev S, Yordanov A. Measures limiting surgical site infections after gynecologic surgeries. Varna Medical Forum. 2022; 11(1). ISSN 1314-8338

2. Slavchev S, Yordanov A. Methods to prevent bowel dysfunction following gynecologic and gynecologic oncology surgery. Varna Medical Forum. 2022; 11(1). ISSN 1314-8338

3. Slavchev S, Yordanov A. The evolution of the ERAS (Enhanced Recovery After Surgery) concept in gynecologic surgery. Varna Medical Forum. 2022; 11(2). ISSN 1314-8338.

4. Kornovski Y, Malkodaski I, Ivanova Y, Slavchev S, Kostov S, Yordanov A. The role of intestinal preparation, preoperative carbohydrate intake, and early postoperative nutrition for accelerated recovery after gynecologic surgeries Anaesthesiology and Intensive Care. 2022; LI (3): 17-21.

5. Kornovski Y, Ivanova Y, Kostov S, Slavchev S, Marinov M, Yordanov A. ERAS (Enhanced Recovery After Surgery) - philosophy, concept, and general principles of implementation in open gynecologic surgery. Anaesthesiology and Intensive Care. 2021; 1: 10-13. ISSN:1310-4284 Scopus (SJR – 0.1)

6. Kornovski Y, Malkodaski I, Ivanova Y, Slavchev S, Kostov S, Yordanov A. ERAS (Enhanced Recovery After Surgery) protocols and their implementation in gynecologic surgery - first outcomes. Anaesthesiology and Intensive Care. 2022; 2:16-18 ISSN:1310-4284 Scopus (SJR – 0.1)

7. Slavchev S, Yordanov A. Basic principles of anesthesia and postoperative analgesia in patients operated within an enhanced recovery after surgery (ERAS) protocol. J. Med. P'ceutical Allied Sci. 2022; 11(2): 4752 – 4756. doi: 10.55522/jmpas. V11I2.3088. SCOPUS (SJR) ISSN: 2320-7418

8. S. Slavchev, Ya. Kornovski, Y. Ivanova, S. Kostov, A. Yordanov. Measures for rapid recovery after gynecologic surgeries on the day of the surgery. Obstetrics and Gynecology. 2022; 1: 26-31. ISSN: 0324-0959

9. S. Slavchev, Ya. Kornovski, Y. Ivanova, S. Kostov, A. Yordanov. Non-opioid (opioid-sparing analgesia) analgesia after gynecologic surgeries in the early postoperative period. Obstetrics and Gynecology. 2022; 1: 22-25. ISSN: 0324-0959

10. Slavchev S. The Enhanced Recovery After Surgery (ERAS) program in gynecologic practice – socioeconomic benefits (first announcement). Social Medicine. 2022; 28 (1) DOI: http://dx.doi.org/10.14748/sm.v28i1.8545

Dissertation-related reports:

1. S. Slavchev, Ya. Kornovski, Y. Ivanova, S. Kostov, A. Yordanov. Non-opioid (opioid-sparing analgesia) analgesia after gynecologic surgeries in the early postoperative period. XV National Congress of Obstetrics and Gynecology. 24-27.03.2022, Marinella Hotel, Sofia

2. S. Slavchev, Ya. Kornovski, Y. Ivanova, S. Kostov, A. Yordanov. Measures for rapid recovery after gynecologic surgeries on the day of the surgery. XV National Congress of Obstetrics and Gynecology. 24-27.03.2022, "Marinella" hotel, Sofia.

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