SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

3100.

TÓTH RICHÁRD GÁBOR

A szöveti adaptáció mechanizmusai

című program

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Investigation of Determinants in Quality of Life of Gynaecologic Patients

PhD thesis

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Budapest
2024

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LIST OF ABBREVATIONS

AE	adverse event
AMPK	adenyl-monophosphate activated protein kinase
ART	assisted reproductive technique
BC	bladder cancer
cAMP	cyclic adenyl-monophosphate
CC	cervical cancer
CR	complete response
CRC	colorectal cancer
CT	computed tomography
DEX	dexamethasone
EC	endometrial cancer
ECOG	Eastern Cooperative Oncology Group
ECP	emergency contraceptive pill
EEC	endometrioid endometrial cancer
EHA	endometrial hyperplasia with atypia
FIGO	The International Federation of Gynaecology and Obstetrics
GLP-1	glucagon-like peptide-1
GLP1RA	GLP-1 receptor agonist
Gyn	gynaecologic malignancy
HAL	haloperidol
HB	hyoscine butylbromide
HPV	human papilloma virus
im.	intramuscular
IQR	interquartile range
IUD	Intrauterine device
iv.	intravenously
LAR	lanreotide
LNG	levonorgestrel
MA	megestrol acetate

MBO	malignant bowel occlusion
MCP	metoclopramide
MD	median
MEEC	Motivation and Epidemiology of Emergency Contraceptive Pill
MN	mean
MPA	medroxyprogesterone-acetate
MRI	magnetic resonance imaging
MS	morphine sulphate
mTOR	mammalian target of rapamycin
NGT	nasogastric tube
NR	not reported
NSAID	non-steroid anti-inflammatory drug
OC	ovarian cancer
OCT	octreotide
OR	overall response
OS	overall survival
Pan	pancreatic cancer
PC	peritoneal cancer
pCR	pathological complete remission
PD	progressive disease
PEG	percutaneous endoscopic gastrostomy
PR	partial response
QoL	quality of life
RCT	randomised controlled trial
SB	scopolamine butyl-bromide
sc.	subcutaneous
SD	stable disease
SOP	standard operation procedure
TVUS	transvaginal ultrasound
UC	uterine cancer
WHO	World Health Organisation

1. INTRODUCTION

1.1. Quality of Life in Gynaecology, Determinants of Quality of Life.

Medical treatments traditionally focused on the therapeutic effect. As with the development of medicine the rates of curability rose and chronic disease became more frequent, interest was slowly directed towards quality of life. According to the WHO definition, Quality of life is "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns".(1) Under medical circumstances, this general definition is easier to manage if we reduce it only to health-related quality of life (further: quality of life (QoL)) which is a multidimensional construct with domains related to mental, physical, emotional and social functioning and provides insight into the patient experience of illness including the effects of treatment. (2) The main domains of QoL are: (a) physical domain; (b) psychological domain; (c) level of independence; (d) social relationships; (e) environment; and (f) spirituality/religion/personal beliefs. (3)
These domains are often affected by gynaecological conditions.

Surgical procedures for gynaecological cancer frequently result in several adverse physical and psychosocial effects. Research consistently highlights immediate post-operative issues, such as pain, fatigue, and reduced mobility, which can negatively affect overall quality of life.(4) Additionally, long-term outcomes, including changes in body image, sexual dysfunction, and infertility, underscore the lasting impact of these treatments. (5) Family planning has a significant impact on the QoL of the patients, short and long term equally. To diminish the potential negative effects, multidisciplinary care, including physical, psychological, sexual, and social support, is accepted as integral part of care of gynaecological cancer patients.(6)

For this thesis we aimed three conditions in different fields of gynaecology which do have a great impact on QoL. To understand these studies, we have to get familiar with the background of each.

1.2. Retrospective Observational Study- Sociodemographic and Medical Characteristics of Women Applied for Emergency Contraception

Unintended pregnancies continue to pose a significant global public health challenge, highlighting the necessity for accessible and effective emergency contraception (7). Emergency contraceptive pills (ECPs) offer a quick and efficient solution to prevent unintended pregnancies, yet in Hungary, they are only available by prescription (8). The use of ECPs is linked to increased fertility awareness (9) and is influenced by various factors, making it a compelling area of study (10). Despite this, approximately 61% of unwanted pregnancies result in abortion (11). Abortion rates vary considerably across Europe (12). Although education has led to some progress, unintended pregnancy rates remain a challenging public health issue, underscoring the need for accessible and effective emergency contraceptive options (7).

Contraceptive methods have been thoroughly proven for their safety and efficacy (13). ECP options include Levonorgestrel, a progestin-only pill taken either as a single 1.5 mg dose or two 0.75 mg tablets 12 hours apart, and ulipristal acetate, a progesterone receptor modulator effective up to 120 hours after intercourse (14). These pills are only available by prescription in Hungary (8). Other emergency contraception methods include the Yuzpe method, which involves taking two doses of an oestrogen/progestin combined oral contraceptive 12 hours apart which is effective within 3 days (15), and the use of IUDs, which can serve as emergency contraception up to 5 days after the event (16, 17).

Lifestyle is defined by daily behaviours and routines, professional commitments, recreational activities, and dietary habits (18). Recently, there has been a growing focus on the role of lifestyle in determining health. According to the World Health Organization (WHO), lifestyle choices account for about 60% of the factors influencing individual health and quality of life (19). Lifestyle choices impact a wide range of health issues, including metabolic disorders, musculoskeletal conditions, cardiovascular diseases, hypertension, obesity, and interpersonal violence, illustrating the complex and multifaceted nature of these choices. While awareness of the harmful effects of smoking and drinking is widespread, individual choices in these areas are often shaped by diverse social, cultural, and personal influences, despite the health risks (20, 21). Smoking and excessive alcohol consumption harm both general and reproductive health (22). Smoking increases the risk of infertility and cervical cancer (23, 24), while excessive alcohol

consumption can disrupt hormonal balance and impair reproductive functions, affecting fertility. Both smoking and excessive alcohol consumption can also negatively impact the outcomes of assisted reproductive techniques (ARTs) (25).

In recent decades, there has been a notable increase in women's interest in understanding and actively monitoring their menstrual and reproductive cycles (26, 27). This trend coincides with the rapid growth of mobile health applications, with hundreds of apps dedicated to cycle tracking emerging in recent years (27). The rising awareness of sexual health issues, including human papillomavirus (HPV) and cervical screening, along with the detailed tracking of ovulation, further emphasizes the contemporary focus on fertility awareness.

1.3. Protocol for a Prospective Randomized Interventional Trial- Comprehensive Evaluation of a Levonorgestrel Intrauterine Device, Metformin, and Liraglutide for Fertility Preservation in Endometrial Cancer

Endometrial cancer (EC) is a significant concern in developed countries, being the most common gynaecological cancer globally and the sixth most common cancer overall (28, 29). Projections estimate a 50% increase in global cases by 2040, underscoring the urgency for updated management strategies (30). Most EC histotypes are oestrogen-dependent, linked to aromatase in body fat, which increases oestrogen production as body fat levels rise. Consequently, women classified as obese or severely obese have a 2.6-to-4.7-fold higher risk of developing EC compared to those of normal weight (31, 32).

Traditional treatment, even in early stages, impacts QoL as it typically involves removing the uterus, adnexa, and sentinel lymph nodes, thereby preventing future childbearing. This affects about 14% of premenopausal EC patients, including 5% who are younger than 40 (32). Therefore, the demand for fertility-preserving therapies is significantly rising (33), although these methods deviate from standard guidelines and require a holistic, multidisciplinary approach with active patient involvement (34, 35). Fertility preservation decisions must consider the desire for childbearing and reproductive capability.

To meet this critical need, progesterone preparations, particularly IUDs, containing levonorgestrel (LNG), have gained popularity. These devices provide continuous high-dose progesterone release within the uterine cavity and have a favourable

side effect profile (36). Additionally, aggressive weight-loss therapy is essential to counteract excess oestrogen dominance and reduce tumour growth.

Metformin and glucagon-like peptide-1 (GLP-1) agonists offer promising strategies to reduce the risk of endometrial cancer by affecting molecular and metabolic pathways. Metformin activates AMP-activated protein kinase (AMPK) and inhibits the mTOR pathway, suppressing cell proliferation and inducing apoptosis in endometrial cancer cells (37, 38). It also improves insulin sensitivity and reduces insulin levels, addressing a key driver of endometrial cancer (39). GLP-1 agonists inhibit inflammatory processes associated with cancer progression, activate intracellular cAMP pathways leading to cell cycle arrest, and inhibit cell proliferation and invasion, thus counteracting cancer growth and metastasis (40, 41). Additionally, their impact on weight loss and metabolic parameters offers extra protection against endometrial cancer in high-risk populations. Combining these medications could provide a multifaceted approach to reducing endometrial cancer risk by targeting both molecular and metabolic pathways (42).

While studies have examined the role of LNG-IUDs in managing early-stage endometrial cancer and hyperplasia, there is a noticeable gap in research on the impact of metabolic interventions (43). This highlights the need for further investigations to understand how the combination of weight loss and LNG-IUDs affects complete pathological response rates, emphasizing the importance of exploring fertility preservation and tumour regression further.

1.4. Systematic Review on The Management of Malignant Bowel Obstruction in Gynaecological Cancer Patients

Gynaecological malignancies caused 680,000 deaths worldwide in 2022, with incidence rates projected to rise to 1.1 million cases annually by 2040 (44). Despite various preventive measures and advancements in targeted therapies (45) extending survival rates, clinicians frequently face complex palliative care decisions. While protocols for administering antitumor therapy or performing surgeries are well-established, palliative care decisions often rely on individualized clinical judgment due to the lack of robust evidence (46).

A key area of focus is the management of malignant bowel obstructions (MBO). MBO is a clinical syndrome caused by malignant disease, antitumoral treatment, or its

complications, and it tends to recur. Therefore, some authors describe it as an occlusive state rather than a single event (47).

Studies show that MBO occurs in 25-60% of patients with gynaecological cancers (48, 49). The consequences of the occlusion cause severe symptoms, significantly impair quality of life, and can be life-threatening

1.4.1. Pathomechanism of Malignant Bowel Obstruction

Bowel obstructions can be categorized into mechanical and functional types, each requiring different management strategies. Mechanical obstructions include intraluminal causes like faecal impaction or intraluminal tumour growth and extraluminal causes like tumours or adhesions that physically block the intestines. Functional obstructions, such as paralytic ileus or pseudo-obstruction, involve impaired intestinal motility without a physical blockage. Additionally, obstructions can be partial or complete and may occur in the small or large bowel, each presenting distinct symptoms and clinical challenges. Accurate differentiation of these types is crucial for effective treatment and improving patient outcomes.

MBOs typically develop gradually, though symptoms can appear suddenly, and the causes are often multifactorial (50). Mechanically, bowel occlusion can result from the infiltration of the bowel, mesentery, or from a bulky tumour exerting external pressure on the bowel (51). In colorectal cancer, the primary cause of occlusion is intraluminal tumour growth (52). Conversely, intraluminal occlusion is less common in gynaecologic tumours.

Functional bowel obstruction, such as adynamic ileus, represents another mechanism of transit disorder contributing to bowel occlusion (53). These disorders can arise from the infiltration of the muscular layer, nerves of the bowel, or the celiac plexus, leading to decreased motility, or can be the side effects of chemotherapy or pain medications. Although rare in gynaecology, paraneoplastic syndromes can also contribute to functional obstructions. Furthermore, intra-abdominal adhesions, which may form after surgery, chemotherapy, or radiotherapy, play a significant role in the development of bowel occlusions (54). Summary of the pathogenetic pathway is presented in Figure 1.

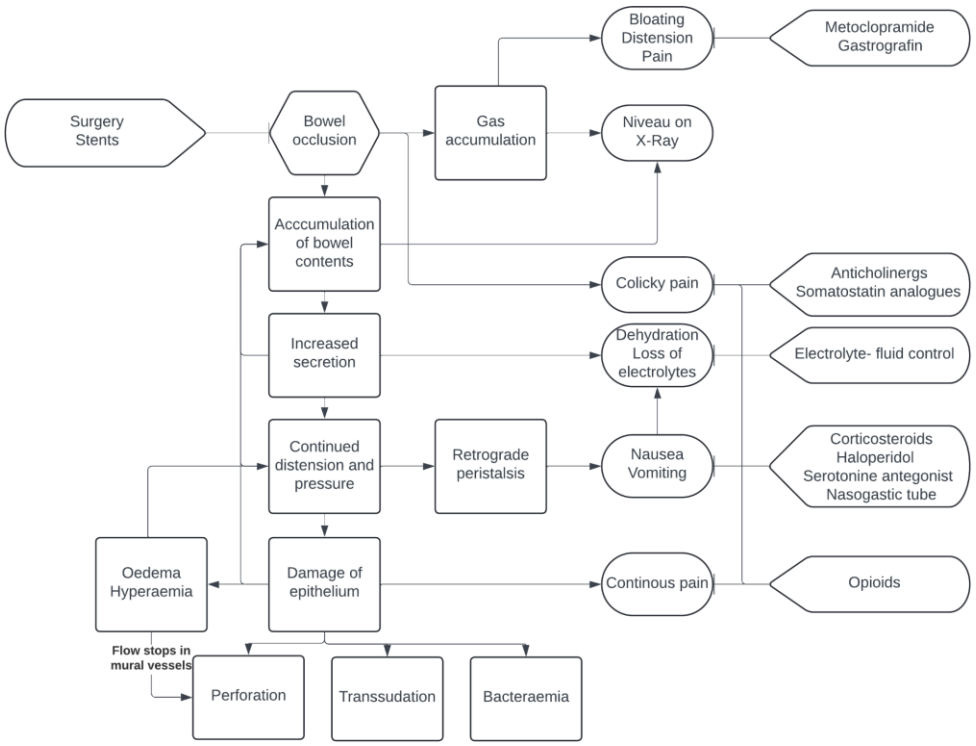

Figure 1. Pathogenesis and Points of Intervention in MBO (55)

1.4.2. Diagnosis of Malignant Bowel Obstruction

The diagnosis of MBO is based on clinical symptoms and the patient's history of a malignant disease. Key signs include nausea and vomiting, abdominal pain and distension, and constipation. In 10-20% of cases, bowel obstruction is the initial presentation of the malignant disease, which is linked to a poorer prognosis (56, 57).

In addition to clinical symptoms and physical examination, X-rays or CT scans are essential for diagnosis. Indicators such as intraluminal fluid levels, pre-occlusive distension, and post-occlusive normal bowel diameter are pathognostic (58).

1.4.3. Management of Malignant Bowel Obstructions (MBOs)

In the management of MBO, various treatment options are available. Diatrizoate meglumine plays a crucial role in the diagnostic process and can also be therapeutic, potentially speeding recovery (59). Due to its high osmotic activity and mild laxative effect, diatrizoate meglumine draws fluid into the bowel lumen, reducing wall oedema and stimulating peristalsis (60). For patients who do not respond to diatrizoate

meglumine, the next step typically involves conservative methods, often combining opioids, corticosteroids, and anti-secretory drugs (61).

Given that the primary pathogenic event is the accumulation of bowel content, therapeutic efforts focus on reducing it. Somatostatin analogues (such as octreotide and lanreotide) and anticholinergics like hyoscine butylbromide decrease bowel motility, bowel and pancreatic secretion (62). Pain, often severe and colicky, requires opioids, which provide both analgesia and decreased bowel motility.

Corticosteroids, with their anti-inflammatory and anti-secretory properties, effectively reduce intraluminal content and wall oedema by promoting water and salt absorption (63).

The placement of a nasogastric tube offers temporary relief by decompressing the stomach, thereby alleviating symptoms like abdominal distension, pain, and nausea caused by fluid accumulation. This intervention reduces the risk of aspiration, which can be fatal if vomiting occurs, and allows for medication and nutrition administration in patients unable to tolerate oral intake (64).

Percutaneous endoscopic gastrostomy (PEG), the placement of a feeding tube directly into the stomach through the abdominal wall, is used for long-term enteral nutrition, but it also aids in gastric decompression, relieving symptoms and preventing complications associated with gastrointestinal obstructions (65).

Stent placement in the obstructed bowel, a minimally invasive procedure usually performed endoscopically, provides immediate symptom relief and improves quality of life. However, it can have complications such as stent migration, perforation, and re-obstruction, necessitating careful patient selection and expert execution (66).

Surgical interventions for MBOs are often complex and challenging for both the surgeon and the patient. Focus must be kept on the goal that is not cytoreduction but rather the resolution of the obstructions. Surgical options include bowel resection, bypass, or stoma formation, depending on the obstruction sites' location and multiplicity.

In gynaecological cancer patients, managing MBOs is particularly challenging due to the lack of clear guidelines and standardized protocols, complicating decision-making for clinicians striving to improve patients' QoL. While surgical interventions offer the most definitive solution, providing prolonged symptom-free periods and potentially more effective relief from obstruction, they are associated with higher morbidity and mortality rates (48). Conversely, conservative treatments, while having lower morbidity, do not

significantly extend survival, necessitating a careful, individualized approach to patient care (67, 68).

Recently, the Multinational Association for Supportive Care in Cancer (MASCC) emphasized the need for a multidisciplinary approach to manage MBO in cancer patients and support their families (61).

2. OBJECTIVES

Increasingly, studies and investigations emphasize the importance of QoL, its measurement, and improvement. In the last decade, it has become essential to include patient-reported outcomes in clinical trials. When discussing QoL, all its aspects must be considered. Healthcare providers often prioritize health issues, but it is equally important to address and manage the impact of interventions on other dimensions of QoL.

This is particularly pronounced in gynaecologic practice, where improving QoL interventions is crucial for addressing the multifaceted aspects of women's health. These interventions focus on physical, psychological, sexual, and social well-being. Integrating such approaches into routine gynaecologic care not only alleviates symptoms but also enhances overall life satisfaction and wellness.

In our research, we aimed to address various important aspects of a woman’s life, integrating multiple layers of QoL. This ranges from contraception and health consciousness to cancer diagnosis, fertility preservation, and end-of-life decisions in the symptomatic therapies of palliative care.

The relationship between sexual health and lifestyle or general health awareness is evident, although less researched. In recent years, there has been a heightened focus on the role of lifestyle as a determinant of health. The WHO underscores its significance, attributing a noteworthy 60% of factors influencing individual health and quality of life to the intricacies of lifestyle choices (19). The impact of lifestyle choices extends across a broad spectrum of health issues, underscoring the intricate and multifaceted nature of these choices. Awareness of the deleterious effects of smoking and drinking is widespread, yet individual choices are shaped by diverse social, cultural, and personal influences, irrespective of the potential health hazards (20, 21).

We hypothesized a similar effect of sociocultural environmental and contraceptive responsibility on emergency contraception use.

In this study we aimed to:

1) assess reproductive health awareness among women using emergency contraceptive pills, to see if healthier patients seek medical advice earlier.
2) to investigate which factors influence reproductive health awareness among women using ECP.

The ability of conception is influenced by a plenty of environmental and lifestyle factors. Some of them can even lead to the development of malignant diseases. In the case of EC this progress is quite well known. High carbohydrate intake, sedentary lifestyle and obesity through insulin resistance and relative hyperestrogenism play a crucial role in the pathogenesis of EC. Unfortunately, these cases tend to occur more and more frequently impacting around 14% of premenopausal women, 5% younger than 40 years old (32, 69). Therefore, the demand for fertility-preserving therapies is markedly amplified (33), although these methods mean a diversion from standard guidelines, which needs a holistic, multidisciplinary approach in every single patient's case (34, 35). We conducted robust research in the literature to find potential targets of intervention over the standard fertility treatment of early-stage endometrial cancer in the hope of delivering higher success rates both in cancer and fertility treatment.

To answer this question, we

3) set a trial for the investigation of quality of life enhancing, fertility-preserving cancer treatment option with higher fertility success rates.

Dealing with oncologic patients it is inevitable to face those cases where no curative option is left. For these patients it is extremely important to provide the best QoL achievable. In the case of gynaecologic cancer patients, a potential life-threatening and QoL deteriorating syndrome is the MBO.

We made a systematic review on the literature to

4) examine the potential therapeutic interventions to improve QoL in end-stage gynaecologic cancer patients, suffering from MBO, without resulting major morbidities.

3. METHODS

3.1. Retrospective Observational Study- Sociodemographic and Medical Characteristics of Women Applied for Emergency Contraception

3.1.1 Patients

As this study is part of the Motivation and Epidemiology of Emergency Contraceptive Pill (MEEC) initiative our data is originated form a Hungarian database of 447 women. (10). A total of 447 individuals were enrolled from July 2021 to September 2021, on the telemedicine consultation platform: https://esemenyutan.hu. This service was available to patients, having a valid Hungarian health insurance looking for emergency contraceptive prescriptions following consultations with gynaecologists. The aim of this service was to offer a prompt consultation and to send prescription of the contraceptive within an hour. Patients were asked to fill a form of standardized set of questions investigating their sexual behaviours and lifestyle.

3.1.2. Characteristics

Our investigation involved a comprehensive analysis of patient records, exploring numerous factors. These comprised sociodemographic details such as age, prior pregnancy history, and lifestyle elements like smoking, alcohol use, and sexual behaviour, including partner consistency and protection during intercourse. Health-related information, like cervical cytology screening in the preceding two years, former HPV screening, and preferences for future contraceptive methods, were taken into consideration. The time since first the sexual activity was also taken into consideration.

The study was approved by the Institutional Review Board of Semmelweis University (SE RKEB: 125/2022).

3.1.3. Reproductive Awareness Score

The collected data underwent rigorous quality control procedures, thus repeated consultations were eliminated, and data entry errors were rectificated.

The scoring was determined by the participants' lifestyle choices, reproductive health practices, and preferences for future contraceptive methods.

This comprehensive assessment analysed various lifestyle factors, such as smoking and alcohol consumption patterns or the participants' relationship statuses. It also evaluated participants' engagement with preventive health measures, including cervical screening history within the past two years and previous HPV screenings. Ovulation status, a crucial aspect of reproductive health, was also considered. Additionally, the study investigated contraceptive practices during intercourse, like the use of condoms or withdrawal methods. Finally, it explored participants' preferences for future contraceptive methods, focusing on their inclination towards oral contraceptives or IUDs.

The following table (Table 1) shows the scores that participants could receive: evaluated based on their smoking and alcohol consumption patterns, relationship status, recent cervical cancer screening history within a two-year period, ovulation status, contraceptive use during intercourse (condom or withdrawal), previous human papillomavirus screening, and their preferences regarding future use of oral contraceptives or IUDs. Scores could range from 0 to 13, higher score suggest higher level of health-consciousness.

Table 1. Health Awareness Score (70)

Category	Points	
Smoking (0–3)	1 pack daily	0
	1 pack weekly	1
	Occasionally	2
	No smoking	3
Alcohol consumption (0–2)	Every few days	0
	Occasionally	1
	No alcohol consumption	2
Partner consistency (0–1)	None	0
	Yes	1
Pap smear in the last 2 years (0–1)	None	1
	Yes	2
Ovulation awareness (0–2)	Non-fertile period	0
	Fertile period edges days (12 or 16 days of menstrual cycle)	1
	Fertile period (13–15 days of menstrual cycle	2
Protection used (0–2)	No protection	0
	Other, e.g., withdrawal	1
	Condom	2
Previous HPV screening (0–1)	No	0
	Yes	1
Further contraception desired (0–1)	No	0
	Yes	1

3.1.4. Statistical Analysis

The Shapiro‑Wilk test was used to test the normality of continuous variables. The Mann‑Whitney test was used to analyse the relationship between awareness score and history of pregnancies. Pearson correlation was performed to assess the correlation between the awareness score and time or age. Statistical significance was set at $p < 0.05$. Prism9 GraphPad (ver. 8. GraphPad Software, Inc., San Diego, CA, USA) software was used for data management and analysis, and for creating figures.

3.2. Protocol for a Prospective Randomized Interventional Trial- Comprehensive Evaluation of a Levonorgestrel Intrauterine Device, Metformin, and Liraglutide for Fertility Preservation in Endometrial Cancer

This protocol was developed in harmony with the guidelines outlined in the Standard Protocol Recommendations for Interventional Trials (SPIRIT) reporting template (71). Our multi-centred randomized 1:1:1 open-label interventional phase III clinical trial consists of three treatment arms: LNG-IUD; LNG-IUD with metformin; and LNG-IUD with metformin and with liraglutide therapy.

The study protocol was approved and registered by the Ethics Committee of Semmelweis University (SE RKEB 63/2024).

3.2.1. Study Setting

Women between 18 and 45 years, with histologically proven endometrial hyperplasia with atypia (EHA) or early-stage endometrial cancer can be involved under the following circumstances: 1) existent wish of further childbearing, 2) obesity (BMI>30).

Early-stage endometrial cancer is meant to be FIGO stage I, grade 1 disease with no lymphovascular space invasion and no myometrial invasion, according to MRI or transvaginal ultrasound (TVUS) findings. We plan to enrol 264 patients.

3.2.2. Eligibility Criteria

3.2.2.1. Inclusion Criteria

- Women in their reproductive years (18–45);
- Females with a body mass index (BMI) > 30 kg/m2;

- Histologically confirmed EHA or low-grade EEC;
- Lack of myometrial invasion (confirmed by expert TVUS, or MRI);
- No hypersensitivity or contraindications to LNG-IUD, MPA (medroxyprogesterone-acetate), or metformin, or liraglutide;
- No use of metformin before inclusion at least for 2 years;
- Understanding the study design, risks and benefits, providing informed consent, and the ability to comply with the study protocol;
- Negative pregnancy test 7 days before starting the treatment.

3.2.2.2. Exclusion Criteria

- Previous treatment for endometrial cancer;
- Advanced endometrial cancer (FIGO IA<);
- Non-endometrioid, or high-grade histology;
- Known allergies or intolerances to LNG-IUD, or diabetic medications;
- Inability to comply (exercise and attend on regular visits);
- Disorders other than diabetic endocrine disorders (renal disorder, liver failure);
- Lactation;
- Previous thrombosis, stroke, or acute myocardial infarction in the anamnesis.

Clinical characterization besides demographic information and clinical observation includes laboratory and histology testing as well. To obtain the most secure sample samples are harvested during hysteroscopy. Women, previously undergone dilatation and curettage (D&C) for diagnosis, were not required to undergo a second sampling, but the previous pathology specimen should be evaluated expert gynaecologic pathologist.

3.2.3. Objectives

The primary objective of this study is to assess the efficacy of combined LNG-IUD and metformin and liraglutide therapy on achieving complete pathologic remission and to define the role of metformin and liraglutide in the pathological response. To conduct a thorough analysis, we will monitor glucose and insulin levels and track weight loss over 12 months. This detailed assessment aims to investigate the effect of these interventions on metabolic processes, providing valuable insights into their influence on physiological markers and overall health outcomes.

3.2.3.1. Primary Outcome

The primary outcome is the rate of complete pathological remission of EHA or early-stage EEC in response to the therapy of LNG-IUD with metformin and with liraglutide.

3.2.3.2. Secondary Outcome

The secondary outcomes include:
Assessment of histological changes compared to baseline after 3, 6, 9, 12 months;
Monitoring changes in glucose and insulin levels for 12 months;
Tracking weight changes for 12 months;
Comparing the effectiveness between study groups.

3.2.4. Study Assessments and Procedures

The study assessments and procedures performed at baseline and at 3-, 6-, 9-, and 12-month visits are summarized in Table 2.

Table 2. Schedule of Patient Assessments (72)

* Months; D&C: dilatation and curettage

TIMELINE	Screening	Baseline	2*	3*	6*	9*	12*
Investigator meetings	X						
Informed consent and eligibility criteria	X						
Demographics and medical history	X						
Histology assessment by hysteroscopy/D&C/Pipelle	X						
MRI/Ultrasound of the pelvis	X						
Urine Pregnancy test		X					
LNG-IUD insertion		X					
Oral glucose tolerance test		X					X
Blood test		X					
Education by dietitian and physiotherapist		X					
Instructions for maintaining diet and exercise diary		X					
Medical consultation on diabetic medication		X	X				
Hysteroscopy sampling				X	X	X	X

3.2.5. Sample Size

For both EHA and EEC groups, a parallel, 3-group design will be used to assess whether there is any difference in the rates be-tween the groups. The two-sided hypotheses will be evaluated with the chi-square test, with an overall Type I error rate (α) of 0.05. For the sample size calculations, the response rate for arm A (LNG-IUD) is expected to be 58.9%, while the response rates for both arms B and C (LNG-IUD plus metformin and LNG-IUD plus metformin plus liraglutide) are expected to be 86.7% based on the results of (73). To reach at least 80% power with equal group size, the sample size needed is 33/group. Additionally, 24% of the participants are expected to be drop out (74), resulting in a target sample size of 44 participants/group (total sample size = 264).

3.2.6. Statistical Methods

Where applicable, baseline participant characteristics will be presented as frequencies and proportions (%) for categorical data and the mean, standard deviation, median and interquartile range (IQR) for continuous data. As the study interventions are considered low-risk interventions, no interim analysis is planned. The statistical tests for the primary outcome variable will be two-tailed, and a value of $p < 0.05$ will be considered to indicate statistical significance. All analyses will be performed using R version 4.4.1.

3.2.7. Recruitment and Implementation

Eligible patients will be recruited from gynaecological oncology centres, coordinated by Semmelweis University, Hungary. Written and oral information will be provided by examining physician.

The principal investigator or a designated sub-investigator will input the required data into the web-based allocation system for eligible patients. Subsequently, the system will allocate participants to one of the treatment arms.

3.3. Systematic Review on The Management of Malignant Bowel Obstruction in Gynaecological Cancer Patients

The study's protocol was registered on PROSPERO under the reference number CRD42024543407. We declare that no Preferred Reporting Items for Systematic Reviews

and Meta-Analyses (PRISMA) registration was performed for this study, however our systematic review adheres to the guidelines outlined in the PRISMA 2020 Statement. Furthermore, we adhered to the recommendations provided in Version 6.3 of the Cochrane Handbook for Systematic Reviews of Interventions.

3.3.1. Eligibility Criteria

Our analysis included research on gynaecologic cancer patients with malignant bowel obstruction, identified by clinical symptoms or radiological examination.

3.3.2. Information Sources

Systematic literature search was conducted in four medical databases: MEDLINE (via PubMed), Embase, CENTRAL, and Scopus, from inception to 10 May 2024.

3.3.3. Search Strategy

We applied the following search key: (gynaecological cancer OR gynaecologic oncology OR gynaecological tumour) AND (malignant bowel obstruction OR MBO OR intestinal obstruction OR malignant gastrointestinal obstruction) for all fields in the given search engines. No language or other restrictions were imposed.

3.3.4. Selection Process

Following a systematic search of databases and subsequent duplication removal, selection was conducted according to the PICO criteria. (Figure 2.) EndNote X9 reference manager software (Clarivate Analytics, Philadelphia, PA, USA, year) facilitated this process. Two independent authors individually screened publications for title, abstract, and full text. To ensure the reliability of the selection process, Cohen's kappa was calculated after both the title and abstract selection, and again after the full-text selection. This statistical measure quantified the interrater agreement beyond chance, adhering to Cochrane's rigorous standards for conducting systematic reviews and meta-analyses.

3.3.5. Selection Protocol

3.3.5.1. Clinical Questions:

The primary question guiding our review was: What is the most effective treatment for MBO in gynaecological malignancies?

3.3.5.2. Title and Abstract Selection:

Both randomised and non-randomized studies were included, provided they involved adult women with MBO who underwent any kind of treatment. Publications without original research data like, reviews, letters, commentaries, and protocols, were excluded.

3.3.5.3. Full-Text Selection:

Studies were included if they used the same measurement units for outcomes. Studies not matching the PICO framework or with inappropriate values were excluded.

3.3.5.4. Data Collection Process

Two authors independently extracted data into an Excel spreadsheet (Office 365, Microsoft, Redmond, WA, USA, year).

3.3.5.5. Data Items

We collected the following data from the eligible articles: first author, year of publication, study type, study design, demographic data, details of treatments received, and data on outcomes for statistical analysis. The relief of the bowel obstruction symptoms can be measured through various methods, including improvements in symptoms such as abdominal pain, nausea, vomiting, and constipation. A third reviewer resolved the discrepancies.

3.3.6. Assessment of Bias and Assessment of Grade

The aim of this review was to extract, analyse and compare outcome reports, counting their frequency, to determine the outcomes most used in the evaluation of MBO. This review did not intend to draw conclusions about treatment effectiveness, nor the research design of the included studies.

To ensure the reliability of the included studies, we followed the NHS Executive's guidelines from the Reviews on Commissioning Cancer Services. These guidelines categorise evidence quality by study design, from randomised controlled trials (Grade I) to cross sectional studies (Grade IV). We assessed each study's design, methodological quality (including sample size and follow-up duration), and potential biases (such as

selection, performance, and drop-out biases). Outcome measures' appropriateness and consistency were also reviewed. Two authors independently reviewed each study, with discrepancies resolved by a third reviewer, ensuring the inclusion of only high-quality studies (75).

3.3.7. Calculation of Cohen's Kappa

In accordance with Cochrane's rigorous standards for conducting systematic reviews and meta-analyses, Cohen's kappa was calculated to protocolize the selection process and guarantee its systematic and comprehensive nature. The first calculation was made after the title and abstract selection, and the second after the full-text selection. Cohen's kappa (κ) is calculated using the formula:

$$\kappa = \frac{p_0 - p_e}{1 - p_e},$$

where Po is the observed agreement, which is the proportion of agreement between the two raters, and Pe is the expected agreement, which is the proportion of agreement that would be expected by chance alone. The observed agreement is calculated by summing the counts of items where the raters agree (the diagonal elements) and dividing by the total number of items.

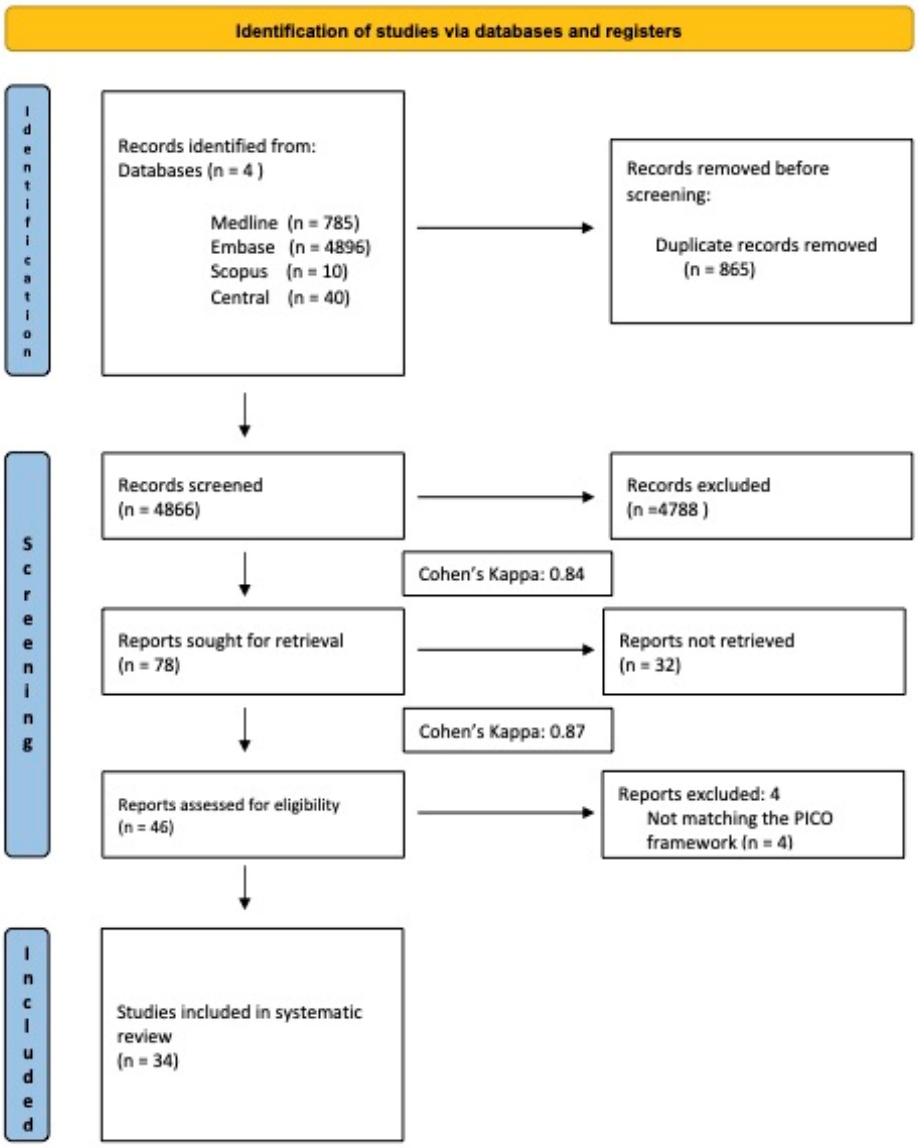

Figure 2. PRISMA Flow Diagram of the Screening and Selection Process (55)

4. RESULTS

4.1. Retrospective Observational Study- Sociodemographic and Medical Characteristics of Women Applied for Emergency Contraception

4.1.1 Patient Characteristics

Table 3 shows the distribution of patients in different health categories such as smoking, alcohol consumption, partner consistency, pap smear in the last 2 years, ovulation awareness, protection used, previous HPV screening, and further contraception desired.

Table 3. Patient Characteristics (70)

Categorical parameters are presented as n. Continuous data are presented as median with interquartile range

Total	447	
Median age with 95% CI (years)	30 (29–31)	
Place of living	Countryside 258	Capital City 189
Category	**Subcategory**	**Range of percent**
Smoking	1 pack daily 1 pack weekly Occasionally No smoking	9.0% 12.3% 9.8% 68.9%
Alcohol consumption	Every few days Occasionally No alcohol consumption	13% 50.8% 36.2%
Partner consistency	None Yes	29.5% 70.5%
Pap smear in the last 2 years	None Yes	33.6% 66.4%
Ovulation awareness	Non-fertile period Fertile period edges days (12 or 16 days of menstrual cycle) Fertile period (13–15 days of menstrual cycle	70.9% 9.0% 20.1%
Protection used	No protection Other, e.g., withdrawal Condom	29.8% 10.3% 59.9%
Previous HPV screening	No Yes	84.6% 15.4%
Further contraception desired	No Yes	67.1% 32.9%

Figure 3 shows in detail the distribution of the sample according to the reproductive health awareness scores obtained. The maximum score was 13, which was not reached by any of the participants. The lowest score achieved was 2. The calculated scores are distributed according to a Gaussian curve, with the highest and lowest scores being obtained by a few, 1–2%, while the average score of 7 or 8 was obtained by 19 and 20% of the participants, respectively.

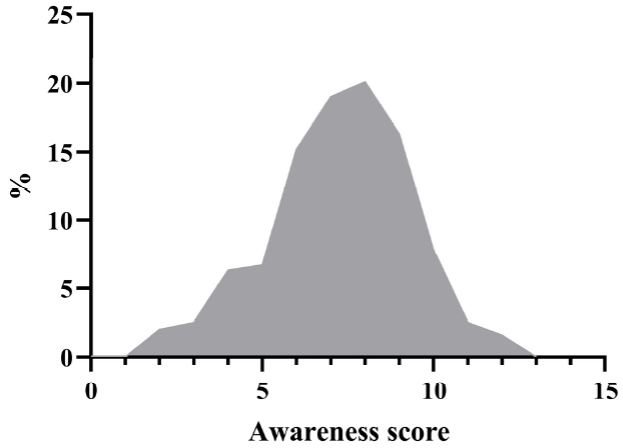

Figure 3. Reproductive Health Awareness Score Distribution (70)

4.1.2. Reproductive Health Awareness Score and Elapsed Time

Linear regression analysis showed that the average time elapsed before requesting a medical consultation was inversely correlated with the reproductive awareness score. The more health-conscious women were, the faster they made a phone call (Figure 4).

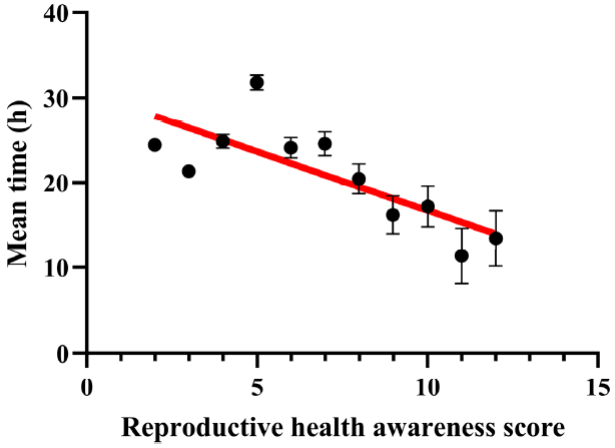

Figure 4. Mean Time and Reproductive Health Awareness Score Correlation (70)

The time to call and the awareness score show a significant negative association. Data are presented as mean + SEM. Pearson correlation: r = −0.7755; R2 = 0.6014; p value = 0.005

4.1.3. Reproductive Health Awareness Score and Previous Pregnancy and Age

Women who had previously been pregnant had a significantly higher number of awareness points compared to those who had not been pregnant (Figure 5). Furthermore, the reproductive health awareness score increased significantly with age (Figure 6).

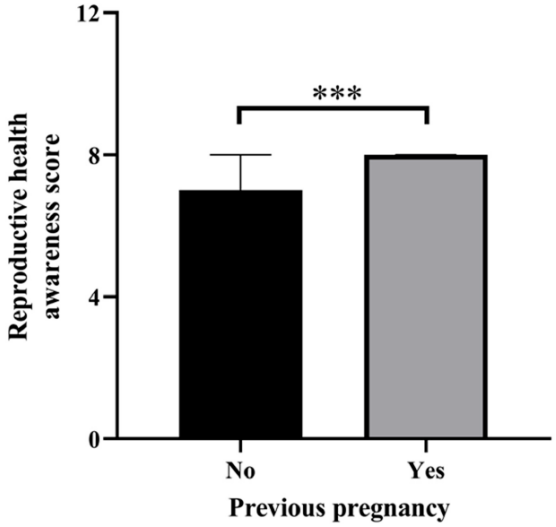

Figure 5. Previous Pregnancy and Reproductive Health Awareness Score (70)

The awareness score is significantly higher for women who have been pregnant before. Data are presented as median with 95% confidence interval confidence interval. Mann–Whitney test, *** p = 0.0007.

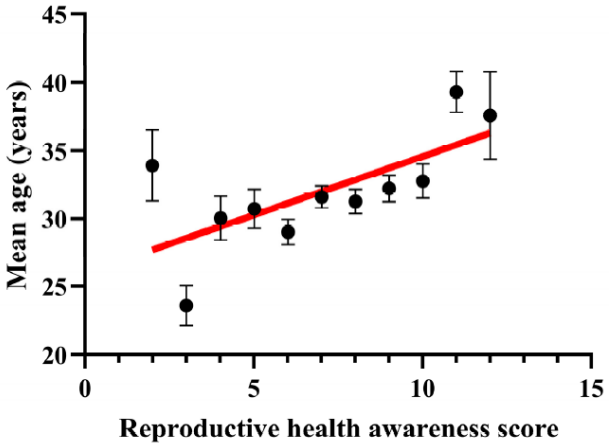

Figure 6. Age and Reproductive Health Awareness Score (70)

With age, the awareness score showed a positive correlation. Data are presented as mean + SEM. Pearson correlation: r = 0.6823; R2 = 0.4655; p value = 0.0207.

4.2. Protocol for a Prospective Randomized Interventional Trial- Comprehensive Evaluation of a Levonorgestrel Intrauterine Device, Metformin, and Liraglutide for Fertility Preservation in Endometrial Cancer

As this study was performed to create a trial design, the study protocol itself represents the result of our preliminary investigation, as further detailed.

4.2.1. Intervention

The levonorgestrel intrauterine device has been approved as a standard therapy in case of fertility-sparing procedures (76). Compared to systematic progesterone therapy, adverse effects do not include nausea, thromboembolic complication, or weight gain (77).

3000 mg (or maximum tolerated dose) of metformin will be administered to the study participants. To avoid gastrointestinal side effects such as diarrhoea, bloating, and pain, dosage will be built up carefully, but final dose must be reached within 2 months (78).

Liraglutide, a long-acting GLP-1 agonist, will be administered via subcutaneous injection once daily, irrespective of mealtimes or time of day. To enhance gastrointestinal tolerability, an initial dose of 0.6 mg will be used. After a minimum of one week, this dose should be escalated to 1.2 mg. For certain patients, further titration up to the maximum recommended dose of 1.8 mg daily may be beneficial (79).

Since selection criteria is BMI over 30 kg/m2, medication of all groups includes inositol (2×2 g), a diet plan comprising 160–200 g carbohydrates, and introduction of 40–60 min of walking. Exercise levels are measured using the Active Australia Survey (80).

4.2.2. Randomisation

Patients will be randomly allocated in a 1:1:1 ratio to one of three groups: arm A (LNG-IUD), arm B (LNG-IUD plus metformin), or arm C (LNG-IUD plus metformin and liraglutide). This randomization will be conducted by an internet-based, remote third-party statistician who is blinded to the study and participant details. The recruiting physician will be trained and provided with detailed instructions on the recruitment protocol. The objective of randomization is to eliminate selection bias. Trial design is summarized in Figure 7.

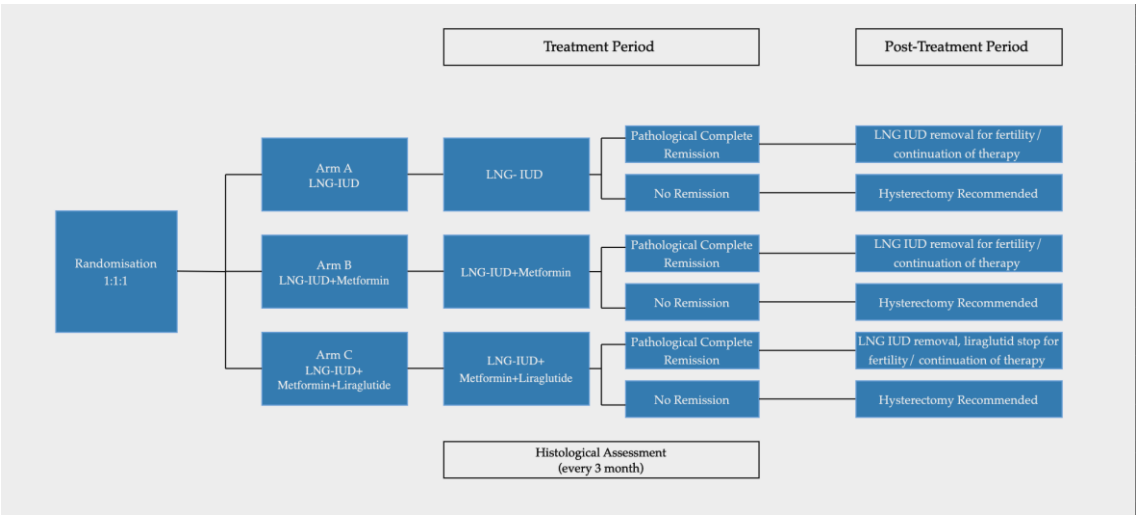

Figure 7. Trial Design (72)

4.2.3. Treatment of Adverse Events

Local investigators will handle any adverse events (AE) in accordance with current good clinical practice guidelines. Each AE will be documented in a case report form, detailing its nature, onset and resolution times, severity, treatment, and outcome. Follow-up examinations may be conducted as needed to ensure patient safety. If a participant shows signs of harm or ineffectiveness, they will be removed from the study by the overseeing physician. These participants' results will be analysed separately as a non-pathological complete remission (non-pCR) group.

4.2.4. Criteria for Discontinuing or Modifying Allocated Interventions

The criteria for the discontinuation of trial medication are as follows.

1. A participant chooses to withdraw from the study or revokes their consent. Participants may leave the study at any time for any reason without consequences.
2. Cancelation of the entire study.
3. Discontinuation of the protocol treatment if it fails to achieve remission based on the following criteria: no treatment response or pCR within one year; disease progression at any time; or relapse after remission.
4. Occurrence of severe AEs, potentially related to the medication (e.g., haemorrhagic shock due to massive vaginal bleeding, severe allergic reaction, thrombosis, liver function impairment), or the diagnosis of a new malignancy

(e.g., breast cancer). These AEs will be assessed by two chief physicians before discontinuing the trial.

5. Any circumstance where the physician determines that treatment with LNG-IUD, metformin, or liraglutide cannot be continued.

4.2.5. Discontinuation of the Study

The study will be terminated early if the Institutional Review Board (IRB) identifies any of the following: serious adverse drug effects (e.g., unresponsive abnormal liver function, thrombosis, haemorrhagic shock due to massive bleeding, severe allergic reaction); diagnosis of a new malignancy; participants encountering unexpected, significant, or unacceptable risks (such as death); or the determination of treatment in-effectiveness.

4.2.6. Baseline Assessments

Baseline assessments will adhere to the trial's standard operating procedure (SOP). During the visit, a urine pregnancy test will be conducted, if negative, LNG-IUD insertion will be performed following protocol guidelines. Blood tests and oral glucose tolerance tests will be administered at 0–60–120 min intervals to assess glucose and insulin levels. Education provided by a dietitian and physiotherapist will emphasize the importance of adopting healthy dietary habits and regular physical exercise. Participants will be encouraged to maintain an exercise diary. Medical consultation and the initiation of diabetic medications will also commence during this phase.

4.2.7. Efficacy Assessments

Medical consultations regarding diabetic medication will occur in the second month to evaluate the tolerance of metformin or liraglutide. At 3, 6, 9, and 12 months following treatment initiation, a series of assessments will be conducted, including histologic and TVUS assessments to rule out disease progression. If pCR is attained, patients will receive guidance to remove the LNG-IUD and discontinue liraglutide if pregnancy is desired. Metformin may be continued without restrictions if tolerated.

4.2.8. Follow-Up Evaluations

During the 3-month follow-up, patients with progressive disease (PD) will be withdrawn from the trial. Those showing complete response (CR), partial response (PR), or stable disease (SD) will continue to be monitored and undergo further evaluation after 3 months. At the 6-month follow-up, patients demonstrating PD or recurrence in endometrial pathology will be withdrawn from the trial, while those with CR, PR, SD will undergo another 3-month follow-up. Similarly, at the 9-month follow-up, patients exhibiting PD or recurrence will be withdrawn, while those with CR, PR, or SD will be followed up again after 3 months. During the 12-month follow-up, patients with PD, recurrence, PR, SD in endometrial pathology will be withdrawn from the trial and recommended for hysterectomy. Although the study duration is one year, treatment and patient follow-up will be long-term. Hysterectomy will be advised for patients who do not achieve pCR within one year. Patients with fertility requirements or those unwilling to undergo hysterectomy will be closely monitored for signs of recurrence.

4.3. Systematic Review on The Management of Malignant Bowel Obstruction in Gynaecological Cancer Patients

4.3.1. Included Studies

Our systematic search resulted 5731 records. After eliminating 865 duplicates, 4866 articles underwent screening, resulting in the exclusion of 4788 during title and abstract evaluation. Additional 32 articles were excluded during full text assessment, 4 articles were excluded due to data unsuitability, leaving 34 articles selected for systematic review. Inter-reviewer agreement was assessed using Cohen's Kappa (k=0.84 for the first step and k=0.87 for the second step of selection), with any discrepancies resolved by a third reviewer. The characteristics of the studies identified for the systematic review, as well as the patient characteristics of the studies included, providing an overview of the patient demographics and study designs are detailed in Table 4.

2068 Patients were included from 34 studies. Studies identified were mainly observational studies but there were no restrictions in the type of studies included. The inclusion criteria included all studies reporting management of MBO associated with

gynaecological malignancy with no year of publication limitations and with no limitations in the type of treatment and type of management or follow-up.

Table 4. Basic Characteristics of the Studies (55)

Abbreviations: NR: not reported, OS: overall survival, OC: ovarian cancer, EC: endometrial cancer, CC: cervical cancer, PC: peritoneal cancer, CRC: colorectal cancer, UC: uterine cancer, BC: bladder cancer, SB: small bowel, Gyn: gynaecologic malignancy, Pan.: pancreatic cancer

Author, Year, Grade	Population, study design, duration of study, survival	Intervention	Outcome measures	Notes/Side Effects
Castaldo et al. (81); 1981	419 patients with ovarian cc. (between 1968 and 1977); retrospective study; group 1 - mean survival was 16 months; group 2 - mean survival was 18 months	group 1 - intestinal surgery during their initial laparotomy; group 2 - intestinal surgery during re-exploration, no symptoms; group 3 - intestinal surgery during re-exploration, symptomatic	group 1 - pts discharged within 18 days due to infrequent complications; group 2 - infrequent complications but major when occurred; group 3 - major complications	postoperative death; wound infection wound dehiscence; recurrent SBO; sepsis; enterocutaneous fistula; pulmonary embolus; GI bleeding
Malone et al. (82); 1986	10 patients with ovarian cc; retrospective study; between November 1984 and August 1985; mean survival was 35 days	percutaneous gastrostomy	symptom reduction - 10/10 (100%); technical success rate - 10/10(100%)	1 leakage around tube, autodigestion of abdominal wall 1 pain 36 hours 1 pyrexial 24 hours 10/10 (100%)
Larson et al. (83); 1989	33 patients with intestinal obstruction due to ovarian cc. (between 1980 and 1987); retrospective study; median survival time: 92 days without surgery and 102 days with surgery	surgical intervention	survival time significantly related to the prognostic index	N/A
Lee et al. (84); 1991	12 patients with gynaecological cancer: 10 ovarian 1 endocervical 1 endometrial; retrospective study; duration of study - N/A; OS - N/A	interventional radiology	symptom reduction - 12/12 (100%); technical success rate - 12/12(100%)	1 peritonitis, 3 leakage
Cunningham et al. (85); 1995	20 patients with gynaecological cancer: 10 ovarian, 6 endometrial, 3 cervical. 1 peritoneal; retrospective study; Between July 1989 and June 1993 mean OS was 70 days	interventional radiology	symptom reduction - 18/20; technical success rate - 20/20 (100%)	1 sepsis, 2 leakage
Cannizzaro et al. (86), 1995	22 patients - 14 ovarian, 5 endometrial, 3 colon cc.; prospective study; duration of	endoscopy	symptom reduction - 21/21 (100%); technical success rate - 21/22 (95,5%)	1 spontaneous dislodgement, 1 persistent bloating, 1 mild site infection

	study was 1 year; mean OS was 74 days (13-272)			
Mangili et al. (87); 1996	13 patients with gastrointestinal obstruction due to advanced ovarian cancer from January 1992 to May 1994; clinical trial; mean survival from discharge was 15 days (8/13 pts were discharged from the hospital); mean survival from the diagnosis of MBO was 27,1 days	8 pts - nasogastric drainage and 6 received parenteral nutrition/ hydration; Octreotide - a starting dose of 0.3 up to 0.6 mg (mean 0.44 mg) a day by subcutaneous bolus or continuous infusion	Complete relief of symptoms was achieved within 3.07 days (range1±6 days); vomiting stopped within 2±3 days of starting treatment in most patients; in 8 pts with nasogastric tube, drainage decreased from 2000 to under100ml/day after the start of octreotide treatment	no side effects
Campagnutta et al. (88); 1996	34 patients with gynaecological cancer: ovarian cc: 29 patients, endometrial cc: 2, uterine sarcoma in 2, and cervical carcinoma in 1; Prospective study, not feasible for surgery	34 endoscopy PEG	27/32 (84.4%) symptomatic Relief,	4 patients: nausea, vomiting
Hardy et al. (89), 1998	patients with MBO due to ovarian cc.; trial 1: 25 pts; trial 2 : 14 pts; combined: 39 pts; double-blind, placebo-controlled cross-over study; trial 1 : 36 months period; trial 2: 24 months period; median overall survival (diagnosis to death) was 19 months	placebo (normal saline) or dexamethasone 4 mg intravenously (iv), every 6 h for five days	resolution of the bowel obstruction at day 5; response rate: trial 1: 15/22; trial 2: 6/13; combined -> 21/35 (60%)	unpleasant perianal sensation
Gadducci et al. (90); 1998	67 patients with epithelial ovarian cancer (between 1989 and 1997), 50,7% developed intestinal obstruction during the study; retrospective study; between 1989 and 1997; median survival was 23 months	22 patients -> surgical interventions: - gastrostomy; - jejunostomy; - ileostomy; - partial gastric resection; - ileal resection; - right or left colon resection; - Hartman procedure; - Sigmoid colostomy; - transverse colostomy; - ureter resection; - ileo-ileal by-pass;	from the 22 pts 10 underwent further chemotherapy -> died after a median interval of 275 days; the other 12 pts did not receive chemotherapy -> died after a median interval of 45 days; 2 pts underwent further surgery for obstruction-> died within 30 days	cardiovascular complications, bowel perforation, DIC, hematemesis, AML, cachexia

		12 patients -> conservative therapy		
Philip et al. (91); 1999	33 patients with MBO due to gynaecological cc. (mostly ovarian cc.); prospective cohort study; between January 30, 1994 and January 30, 1995; mean survival of the responding pts was 39 days	dexamethasone: 8mg/day iv/sc. 8 mg/day divided doses	9 pts (69%) had a response - decreased pain, nausea, and vomiting and improved oral intake (31 days)	patient 11 -> reduced dose because of mild proximal myopathy affecting the lower limbs
Mercadante et al. (92); 2000	18 patient with inoperable bowel obstruction due to ovarian, vulva, rectum, pancreas, breast, stomach, liver, small bowel cc.; randomized controlled trial (RCT); OS - N/A; duration of study - N/A	octreotide (OCT) 0.3 mg daily vs. hyoscine butylbromide (HB) 60 mg daily	symptom relief within 24 hours - OCT > HB	increased fluid intake correlated with less nausea
Brooksbank et al. (93); 2002	51 patients - 16 ovarian retrospective study; Between 1989 and 1997; median OS was 17 days	46 endoscopy 4 laparotomy 1 interventional radiology	symptom reduction - 47/51 (92%), technical success rate - Endoscopy 46/ 48 (96%), Total 51/51 (100%)	1 hematoma, 6 leakage
Pothuri et al. (94); 2005	94 patients with ovarian cancer; retrospective study; between 1995 and 2002; median OS was 8 weeks (95% CI, 6-10)	92 endoscopy, 2 interventional radiology	symptom reduction - 86/94 (91%), technical success rate - 94/94 (100%)	1 peritonitis, 8 leakage, 3 site infections, 3 blockage, 2 catheter malfunction, 2 bleeding
Matulonis et al. (95); 2005	15 patients with MBO due to recurrent ovarian cancer; clinical pilot study; between 2002 and 2004; mean survival was 226 days, median survival was 89 days	100 μg OCT subcutaneously, followed by 30 mg LAR intramuscularly	complete symptom relief within 3,07 days, vomiting stopped within 2-3 days	no significant toxicities
Mangili et al. (67); 2005	47 patients with intestinal obstruction due to recurrent epithelial ovarian cancer; retrospective study; duration of study - N/A; mean survival from the diagnosis of MBO was 79 days	27 patients - surgery (21 intestinal procedures, 2 gastrostomy tubes, 4 pts inoperable), 20 patients received Octreotide (mean dosage of 0.48 mg/day) from which 1 patient required nasogastric tube	Octreotide - controlled vomiting in all cases (except 1 -> NGT), complete symptom relief within 3 days. Surgery - 16 of 21 pts (76%) tolerated low-residue diet	18% surgical correction not possible (mesentery infiltration); 22% complications: -wound infection -dehiscence -fistula; Oct- 1 patient - fistula

Chi et al. (96); 2009	26 patient with MBO due to ovarian cc.; prospective study; between July 2002 to July 2003 ; survival time: operative procedure -> 191 days, endoscopic procedure -> 78 days	PEG, Colonic stent, Intestinal bypass, Ileostomy, Colostomy	76% symptom relief	3,8% death, 11,5 % major complications
Watari et al. (97); 2012	22 patients with MBO due to cc.; Endometrial or cervical cc. -> 6 pts, Ovarian cc. -> 12 pts, Peritoneal cc. -> 3 pts, Endometrial-ovarian cc. -> 1 pt; prospective study; between 2006 and 2009; OS - N/A	300 μg/d OCT subcutaneously or intravenously as a continuous injection for 7 days + for another 7 days	15 patients (68.2%) had a response of CC and 3 patients (13.6%) had a response of PC, with an overall response rate (CC/PC) of 81.8%	no side effects
Fotopoulou et al. (98); 2013	37 patients with epithelial ovarian cc.; retrospective cohort study; between May 2003 and January 2012; median OS was 5,6 months;	surgical intervention, stent placement, conservative therapy	no significant differences in survival	Any major complications 19 (51%): Sepsis 1 Pulmonary embolism 2 Peritonitis 4, Pleural effusion 3 Relaparotomy 12 Anastomotic insufficiency 5 Abscess, secondary wound healing, Postoperative bleeding; 2 Intestinal perforation 1 Rupture of abdominal wall closure 1; Peritonitis 100% Shor small bowel syndrome
Rath et al. (99); 2013	53 patients with ovarian cc.; retrospective study; between 1/2002 and 12/2010; median OS was 46 days (2-736)	33 surgical, 13 interventional radiology, 6 endoscopy	symptom reduction - 49/53 (93%), technical success rate - 53/53 (100%)	9 blockage, 4 leakage, 5 site infections
Jutzi et al. (100); 2014	32 patient with MBO and gynaecological malignancies (ovarian cc. 75%, uterine cc. 18,8%); retrospective cohort study; between January 2006 and February 2013; median survival time for all patients was 4,1 months	colorectal stent placement	clinical success 47%	complication rate = 42%, 12 stent related complications in 10 pts: - obstruction, stent migration, bowel perforation, rectal bleeding, rectovagina fistula - diarrhea

Perri et al. (101); 2014	62 patients with gastro-intestinal obstruction due to gynaecological (47) malignancies (ovarian (69.1%), primary-peritoneal (8.8%), cervical (11.8%) or uterine (10.3%)); retrospective study; between October. 2004 and January 2013; Median postoperative survival was 106 days	colostomy (26.5%), ileostomy (39.7%), colonic stent (1.5%), gastrostomy (7.3%), gastroenterostomy (5.9%), bypass/resection and anastomosis (19.1%)	18 pts died prior to discharge within 3-81 days; bypass/resection and anastomosis -> improved survival	5 sepsis, 6 leak from anastomosis, 2 necrotizing fasciitis
Peng et al. (102); 2015	97 patients with MBO due to advanced ovarian cancer; randomized controlled trial (RCT); between January 2010 and December 2013; OS - N/A	octreotide (OCT) 0.3 mg/day vs. scopolamine butylbromide (SB) 60 mg/day	symptom relief within 24 hours - OCT > SB	N/A
Daniele et al. (103); 2015	40 patients with MBO due to ovarian cancer; retrospective study; between October 2008 and January 2014; medical treatment group -> median survival from MBO was 5,7 months; surgical treatment group -> median survival from MBO was 13,6 months;	18 pts - medical treatment: Morphine sulphate 60 mg, Haloperidol 1.5 mg, OCT 0.3 mg, Dexamethasone 8 mg /d; 22 pts - surgery	symptom relief within 4 days	no side effects
Zucchi et al. (104); 2016	158 patients - 96 ovarian, 13 colon, 8 endometrial, 41 other cc.; prospective study; between 2002 and 2012; Median OS was 57 days (4-472)	endoscopy	symptom reduction - 110/142 (77%) complete, 12/142 (8%) controlled vomiting, technical success rate - 142/158 (90%)	3 dislodged, 20 site infection, 12 obstruction, 2 leakage, 3 bleeding, 1 catheter failure
Dittrich et al. (105); 2017	76 patients - Ovarian24 (32%), Colorectal 13 (17%) Pancreatic 12 (16%); Small intestine 5 (7%) Gallbladder/biliary tract 5 (7%) Gastric 4 (5%); Breast 3 (4%) CUP 3 (4%),Other 6 (8%); Retrospective study	endoscopy - PEG	significant decrease of vomiting ($p < 0.001$).	112 complications in 56 patients: Stomal leakage (18/75 patients), mild wound pain (17/75) and tube occlusion (13/75) occurred most frequently

Miłek et al. (106); 2017	13 patients with left half colon obstruction due to an inoperable metastatic ovarian cc.; prospective study; 2012-2014	colorectal stent placement	successful decompression in 11 pts (85%)	1 patient with stent migration (7.7%- in 24 hs), 1 outgrowth of the neoplasm beyond the upper edge of the stent and a subsequent stricture of the intestine's lumen. (4 months)
Heng et al. (107); 2018	71 patients (47 women): 24 (33,8%) with ovarian or primary peritoneal neoplasms, 14 (19,7%) bowel, 8 (11,2%) upper gastrointestinal, 5 (7%) pancreatic, 6 (8,5%) intra-abdominal neoplasms, 2 (2,8%) other neoplasms with intra-abdominal/ peritoneal metastases, 12 (16,9%) other neoplasms without intra-abdominal/ peritoneal metastases; Intestinal obstruction in 42 (59,2%) patients; retrospective study; between January 2013 and October 2015 (approximately 34 months), OS - N/A	50 ml Gastrografin - repeated small doses over several days	resolved occlusion in 84% after administration, 75% of these cases improving within the first 24 hours	10 patients (14%) - diarrhoea
Lee et al. (108); 2019	169 patients with MBO due to advanced gynaecological malignancies; retrospective cohort study; baseline program between 2014 and 2016, MBO program between 2016 and 2018; median OS: 141 days MBO program: 141 vs. baseline: 99	surgery, chemotherapy, total parenteral nutrition, and supportive care	shorter hospital length of stay in the MBO program group compared to the baseline group	N/A
Lodoli et al. (109); 2021	76 patients with MBO due to gynaecological (67) GI (19) and other (12) malignancies; retrospective observational cross-sectional study; study time was 5	colostomy 7.2%, ileostomy 62.3%, jejunostomy 30.4%, intestinal bypass, bowel resection, adhesiolysis	Surgery achieved 77.5% 68% p.o. diet, 61.2% NPT, 49% hospice, 51% home	21.4% complication, 9.2% major

	years (between 2014 and 2018); OS - N/A			
Jones et al. (110); 2022	91 patients with epithelial ovarian cancer, partial or complete bowel obstruction; retrospective cohort study; between January 2005 and December 2016; median survival from the diagnosis of MBO was 3,8 months	dexamethasone: median daily dose-> 6-8 mg, twice daily; median total dose was between 26 and 40 mg	89% (137 admissions); 44,8% - adequate symptom resolution	N/A
Armbrust et al. (104); 2022	87 patients with ovarian cc.; retrospective cohort study; between 2012 and 2017; mean OS was 7,8 months	5% colectomy or total colectomy, 46% small bowel resection, 12% primary anastomosis	ECOG Status, platinum sensitivity, ascites < 500 ml, the type of stoma and the number of anastomoses are influencing the results	42% TPN, 26% Grade 3 complication, 13% secondary wound healing, 21% anastomotic leakages, transfusions (17%) or thromboembolic events, 30d mortality - 10% 30d morbidity - 74%
Cole et al. (111); 2023	14 patients - 8 gynaecologic 3 colorectal, 1 bladder, 1 small bowel, 1 peritoneal serous; retrospective study; between November 2019 and July 2021; mean OS was 270 days	endoscopy	symptom reduction - 100%, technical success rate - 100%	N/A
Walter et al. (112); 2024	17 patients (8 women) with MBO due to UG, GI, GYN, Lung cancer; prospective study; between October 21, 2019, and December 1, 2021; overall median survival was 88.8 days; 6 months survival was 20%	“triple therapy”: dexamethasone 4 mg BID, metoclopramide 10 mg Q6 and octreotide 300 mcg TID	10 patients (66,7%) - deobstruction; Resolution of the bowel obstruction or deobstruction was defined as, Introduction of oral intake beyond sips of liquids. With Cessation of vomiting and or ability to remove nasogastric tube (NGT) or Tolerance of clamped venting gastrostomy tube (GT) Resumption of bowel movements	bradycardia in 2 pts, no incidence of bowel perforation

4.3.2. Medical Management

The medical management of MBO remains a significant challenge in clinical practice, particularly due to the limited number of studies available on various treatment options. Among these, the use of diatrizoate meglumine (Gastrografin), somatostatin analogues (octreotide), and dexamethasone has shown promising results in alleviating symptoms and aiding in surgical decision-making. This section reviews the current evidence on these medical treatments, highlighting their efficacy and role in the comprehensive management of MBO.

4.3.2.1. Diatrizoate Meglumine

Limited number of studies are available and comparable on the use of Gastrografin in patients with MBO. Heng's retrospective analysis confirmed the efficacy of diatrizoate meglumine with 84% of occlusions resolving after administration and 75% of these cases improving within the first 24 hours. Notably, no significant complications were reported. The true value of Gastrografin lies in its ability to help determine the optimal timing for surgery. This is crucial because conservative treatment success rates are low in cases of complete bowel obstruction, necessitating timely surgical intervention. Gastrografin's role is highly important in symptom relief, timing and surgical decision-making (107).

4.3.2.2. Somatostatin Analogues

Octreotide emerges as the predominant medication investigated for managing MBO, with eight studies exploring its efficacy. Most patients in these studies were diagnosed with ovarian cancer (OC), and no restrictions were observed based on the type of bowel involvement. Symptom resolution varied across studies, occurring within 24 hours to 4 days, doses ranging from 100 μg/day to 0.9 mg/day. Two studies examined the use of octreotide (OCT) in single doses (67, 87). Additionally, two randomised controlled trials (RCTs) included in the analysis revealed octreotide's significant efficacy in symptom relief within 24 hours compared to butylscopolamine (92, 113).

In a comprehensive evaluation of the long-acting form of octreotide (LAR) in patients with recurrent ovarian cancer, Matulonis et al. administered 30 mg depot injections on Day 1 alongside subcutaneous OCT for 2 weeks, providing sustained relief from bowel dysfunction. This approach demonstrated both safety and utility, with three out of 15

patients experiencing a major reduction in malignant bowel obstruction (MBO) symptoms, and two showing a minor response, while no significant toxicities related to OCT or LAR were reported. Remarkably, some patients remained on LAR Depot for over 9 months, suggesting its potential for long-term symptom management (95). Similarly, Watari et al. investigated octreotide's efficacy in controlling vomiting in patients with advanced gynaecologic cancer and inoperable MBO. OCT, administered via continuous infusion for two weeks, exhibited a high rate of vomiting control, with an overall response rate of 81.8%. Particularly noteworthy was its effectiveness in patients without nasogastric tubes, with an overall response rate of 93.1%. Furthermore, the absence of major AEs associated with OCT underscores its safety profile and potential to enhance the QoL by obviating the need for nasogastric tube placement in these patients (97).

Walter et al. prospectively evaluated a "triple therapy" consisting of dexamethasone, metoclopramide, and OCT in non-surgical management of MBO. Despite the small sample size of 17 patients, the therapy exhibited promising results with complete resolution of nausea and improvement in other symptoms such as pain and constipation. Although AEs such as bradycardia were noted in two patients, there were no incidences of bowel perforation (112).

A study conducted by Daniele et al. suggests that tailored medical protocol, particularly involving antisecretory drugs like OCT, remains the standard of care for frail patients or those with contraindications to surgery (103). While complications are noted in a minority of cases, OCT presents as a valuable adjunct in the management of MBO.

4.3.2.3. Dexamethasone

The use of dexamethasone in managing MBO demonstrates promising outcomes. Our analysis compromising three studies involving 163 patients exclusively diagnosed with OC, highlights its efficacy. The dosage ranged from 4mg/day to 8mg twice a day. The use of dexamethasone is limited specifically in cases of small bowel obstruction, whether administered intravenously or subcutaneously. Dexamethasone achieves resolution of bowel obstruction within 5 to 7 days. While AEs are noted in some cases, overall success rates are encouraging, ranging around 89%. These findings underscore dexamethasone's role as a valuable therapeutic option in managing MBO in gynaecological cancer patients, offering relief and potentially improving their quality of life (89, 91, 110). A summary of the above-mentioned data is presented in Table 5.

Table 5. General Characteristics of the Articles of Medical Treatment (55)

Abbreviations: OCT: octreotide, SB: Scopolamine butylbromide, HB hyoscine butylbromide, LAR: lanreotide, MD: median, MN: mean, sc. subcutanenous, im: intramuscular, DEX: dexamethasone, MCP: metoclopramide, iv: intravenously, MS: morphine sulphate, HAL: haloperidol, CR: complete response, PR: partial response OR: overall response

Author	Study Type	Methods	OS (MD/MN)	Symptom Relief	Notes/side effects
Hardy et al. (89) (1998)	Double-blind, placebo-controlled cross-over	Placebo or DEX 4x 4mg/day iv, for five days n=39	570 days (MD)	CR: 60%	unpleasant perianal sensation
Philip et al. (91) (1999)	Prospective cohort	DEX: 8mg/day iv/sc. n=33	39 days (MN)	OR: 69%	mild proximal myopathy affecting the lower limbs
Mercadante et al. (92) (2000)	Randomised controlled trial	OCT 0.3 m/day vs. HB 60 mg/day n=18	N/A	CR in 24 h: OCT > HB	increased fluid intake correlated with less nausea
Mangili et al. (67) (2005)	Retrospective	OCT n=20	79 days (MN)	CR: 95% in 3 days	1 patient fistula
Matulonis et al. (95) (2005)	Prospective interventional cohort study	0.1 mg OCT sc, + 30 mg LAR im. n=15	226 days (MN)	CR in 3,07 days	no significant toxicities
Watari et al. (97) (2012)	Prospective interventional cohort	OCT: 0.3 mg/ days sc/iv. for 7+7 days n=22	N/A	CR: 68.2% PR: 13.6%	no side effects
Daniele et al. (103)(2015)	Retrospective observational	MS 60 mg/ day, HAL 1.5 mg/day, OCT 0.3 mg/day, DEX 8 mg/day; n=18	171 days (MD)	CR 100% in 4 days	no side effects
Peng et al. (113) (2015)	Randomised controlled trial	OCT 0.3 mg/day vs. SB 60 mg/day n=97	N/A	CR in 24 h: OCT > SB	N/A

Heng et al. (107) (2018)	Retrospective	50 ml Gastrografin – repeated small doses over several days n=71	N/A	CR: 84% 75% in 24 hours	10 patients (14%) - diarrhoea
Jones et al. (110) (2022)	Retrospective cohort	DEX: 2x 6-8 mg/day; n=91	114 days (MD)	CR: 44,8%	N/A
Walter e al. (112) (2024)	Prospective interventional cohort	"triple therapy": DEX: 2x4 mg/day, MCP: 4x 10 mg/day OCT 2x 0.3mg/day n=17	88.8 days (MD)	CR: 66,7%	bradycardia in 2 pts,

4.3.3. Invasive Interventions

4.3.3.1. Percutaneous Gastrostomy (PEG)

PEG procedure used to insert a tube through the abdominal wall into the stomach. This tube provides direct means of feeding or gastric decompression for patients who are unable to take adequate nutrition orally or who need relief from symptoms such as vomiting and nausea due to impaired gastric motility. PEG can be inserted surgically, endoscopically or with radiologic interventions. In the case of MBOs the less invasive method is preferable as the aim of the procedure is highly symptomatic.

Patients treated with this option are usually not eligible for operations because of their general condition, or abdominal status, e.g. multiple sites of occlusion on the small bowel. However, this method is technically feasible with a low rate of intervention failure.

Studies consistently report high technical success rates, often close to 100% (82, 84, 85, 93, 94). The reduction in symptoms, particularly nausea and vomiting, is substantial, with many studies reporting symptom relief in nearly all patients (86). The implantation of gastrostomy has positive effects on QoL (104). Survival times post-procedure vary significantly, with median or mean survival ranging from as short as 17 days to as long as 74 days (86, 93). Despite its effectiveness in symptom relief, PEG procedures are associated with complications, including leakage, peritonitis, site infections, and in some cases, more severe issues like sepsis and autodigestion of the abdominal wall (82, 85). Overall, PEG demonstrates substantial efficacy in palliation for MBO, though the risk of complications necessitates careful patient management and selection (86, 99, 105, 111). Side effects and success rates are described in Table 6.

Unfortunate consequence of this intervention is total parenteral nutrition although the majority of the patients will be able to take sips or drink for comfort after gastric tubing.

Table 6. Studies Evaluating Gastrostomy Outcomes in Gynaecologic Malignancies (55)

Abbreviations: NR: not reported, OS: overall survival, OC: ovarian cancer, EC: endometrial cancer, CC: cervical cancer, PC: peritoneal cancer, CRC: colorectal cancer, UC: uterine cancer, BC: bladder cancer, SB: small bowel, Gyn: gynaecologic malignancy, Pan.: pancreatic cancer

Author	Study Type	Method of Gastrostomy Formation	Number of Cases and Cancer Type	OS	Symptom Relief	Diet	Notes/ Side Effects	Technical Success
Malone et al. (82)(1986)	Retrospective	**Transsectional radiology**	n=10 OC:10	Mean: 35 days (26-56)	10/10 (100%)	NR	OA: 100% Fever: 10 Leakage: 1 Abdominal wall autodigestion: 1 Pain for 36 hours: 1	10/10 (100%)
Lee et al. (84) (1991)	Retrospective	**Interventional radiology**	n=12 OC: 10 CC: 1 EC: 1	NR	12/12 (100%)	NR	OA: 33% Peritonitis:1; Leakage:3	12/12 (100%)
Cannizzaro et al. (86) (1995)	Prospective	**Endoscopy**	n=22 OC:14 EC: 5 CRC: 3	Mean 74 days (13-272)	21/21 (100%)	21/21 (100%)	OA: 14% Dislodgement: 1 Persistent bloating: 1 Mild site infection:1	21/22 (95.5%)
Cunninghanm et al. (85) (1995)	Retrospective	**Interventional radiology**	n= 20 OC: 10 EC: 6 CC: 3 PC:1	Mean 70 days (3-173)	18/20 (90%)	12/20 (100%)	OA: 15% Sepsis:1; Leakage: 2	20/20 (100%)
Campagnutta et al. (88) (1996)	Prospective	**Endoscopy**	n=34 OC: 29 EC: 2 UC: 2 CC:1	Tube in place for median 74 days (5-210)	27/32 (84%)	27/32 (84%)	OA: 6% Mild site infections: 2	32/34 (94%)
Brooksbank et al. (93)(2002)	Retrospective	**Endoscopy/ Laparotomy**	n=51 CRC: 27 OC: 16 Other: 8	Median 17 days (1-190)	47/51 (92%)	NR	OA: 14% Hematoma: 1; Leakage:6	51/51 (100%)
Pothuri et al. (94) (2005)	Retrospective	**Interventional radiology**	n=94 OC: 94	Median 8 weeks (95% CI, 6-10)	86/94 (91%)	89/92 (2 unknown) (97%)	OA: 20% Peritonitis:1 Leakage:8 site Infections:3	94/94 (100%)

							Blockage:3 Catheter malfunction:2 Bleeding:2	
Rath et al. (99) (2013)	Retrospective	**Endoscopy**	n=53 OC: 53	Median 46 days (2-736)	49/53 (93%)	48/53 (91%)	OA: 34% Blockage: 9; Leakage: 4; Site infections: 5	53/53 (100%)
Zucchi et al. (104) (2016)	Prospective	**Endoscopy**	n=158 OC: 96 CRC: 13 EC: 8 Other: 41	Median 57 days (4-472)	110/142 (77%) complete 12/142 (8%) vomiting controlled	110/142 (77%)	OA: 26% Dislodged: 3; Site infection: 20; Obstruction: 12; Leakage: 2; Bleeding: 3; Catheter failure: 1	142/158 (90%)
Dittrich et al. (105) (2017)	Retrospective	**Endoscopy**	n=76 OC: 26 CRC: 13 Pan.: 12 Other: 25	Median 28 days (2-440)	96% (73/75) vomiting 81% (62/75) nausea	59/75 (79%)	OA: 53% Peritonitis: 3 Severe bleeding: 2 Repeated attempts: 7 Fever: 6 Leakage: 18 Wound infection:9	68/76 (90%) primary 75/76 (99%) secondary
Cole et al. (111) 2022	Retrospective	**Endoscopy**	n=14 Gyn: 8 CRC: 3 BC: 1 SB: 1 PC: 1	Mean 270 days	100%	NR	NR	100%

4.3.3.2. Stent Placement

Gynaecological malignancies, especially OC can cause obstruction on the large bowels. It would be evident to use intraluminal colonic stents to restore the lumen of the bowel. Milek et al. investigated a new stent developed by themselves which proved the efficacy and feasibility of the application of large bowel stents. 85% of all patients had the decompression of the obstructed gastrointestinal tract after the first stent implantation (106). In one case 2 stents were implanted due to an insufficient coverage of the stricture. Another study led by Jutzi et al. showed that they had a technical success rate of 75% on their sample of 32 patients, whilst clinical success rate was 47% and 37.5% of the subjects had a complication requiring intervention (100).

Taking all these studies into account, the results are contradictory. Although the intervention is feasible and offers a good option for treatment, there was a meaningful need for intervention because of the complications caused by the stents. There is also a limitation by nature of the disease as it spreads on the peritoneal surface, and it can cause obstructions at different levels while stenting is rather ideal for localised pathologies.

4.3.3.3. Surgical Interventions

Surgery is the treatment option to choose when conservative methods do not seem to be effective in 3-7 days (90). Surgical interventions can be demanding for the patient and sometimes a longer period is needed for recovery, mainly for those patients whose baseline condition is already impaired. Thus, the wide-spread application of surgical interventions is limited, although they offer a longer symptom free period and might prolong the survival of the patients, even under palliative circumstances. Even though one must not lose the main objective of the procedure: pain relief and QoL enhancement.

Surgical interventions can improve QoL as there is a higher chance for patients to tolerate solid intake or fluids and there is less need for total parenteral nutrition, like in the case of PEGs (67). Chi et al. found that the return of symptoms or death is less likely to occur in patients who went through a surgical intervention than those who received an endoscopic solution for their symptoms (96). Despite all the negative effects, the reason to support surgery in palliative cases is the fact all the studies which we have found in the literature proved a longer survival in this group.

It is still controversial who are the patients that can benefit from surgeries and what are the indicators of worse outcomes. Lots of studies examined this aspect and found correlations between the survival and prognostic factors as low albumin, elevated blood urea- nitrogen and alkaline phosphatase or clinical factors like age, radiotherapy, ascites, carcinomatosis, multiple sites of obstruction, or palpable mass (81). Nevertheless, there are studies not supporting this (67).

Although, in some very selected cases disseminated tumour spread results in a very complex surgery. Foutopoulou et al. found it feasible to perform these operations even if it results short-bowel syndrome and consecutive total parenteral nutrition. Despite, they rather advised to treat these patients conservatively as these operations may cause severe morbidity and reduction in QoL (98). A later conducted study, in the same centres, by Armbrust et al. suggested that even these kinds of surgeries can extend therapeutic opportunities for patients, highly selected (114).

It is essential to determine who are the ones who can benefit from surgeries, whose operation is feasible to avoid surgical failure and inappropriate interventions. Lodoli et al. suggest some features for prediction. According to them a proximal occlusion tends to result in lower success rates, due to the shortening of the already, anatomically short jejunal mesentery. Interestingly, they found that bowel dilatation, without a real obstruction is associated with higher failure rates as well. Their explanation was the decreased motility of the bowels because of the widespread peritoneal infiltration, that prevented surgeons to create ostomies (109).

Previous studies suggest that age, disease extent and nutritional status to be important factors as well, of which they have created a risk stratification tool (83). According to these and their own data Perri et al suggest a scoring system in which they take albumin level, presence of ascites more than 2 litres, age, and non-ovarian tumour origin into account (101). Another group of investigators found factors like ECOG status, platinum sensitivity, ascites < 500 ml, the type of stoma and the number of anastomoses to be the ones influencing results, emphasizing the importance of pre-operative frailty assessment (114). Nevertheless, according to Daniele et al. cachexia, low performance status, and poor nutritional status emerged as significant predictors of worse survival irrespective of the chosen treatment modality (103).

During the treatment of MBO it is crucial to have a reliable triage system to shorten the length of hospitalization and to avoid unnecessary surgical interventions to provide the best QoL possible. As MBO occurs subacutely, it is possible to start its treatment in an outpatient setting. Lee at al. developed an MBO programme which proved to achieve all the goals, as the rate of surgical interventions, frequency of recurrent episodes of MBO and the length of hospital stay was lower in the intervention group, and the possible chance of continuation of oncologic care was higher (108).

Table 7 summarizes the advantages and disadvantages of all the interventions used in the management of MBO.

Table 7. Treatment Strategies of MBO: Benefits and Drawbacks (55)

Treatment Method	Advantages	Disadvantages
Somatostatin Analogues	- Effective in symptom relief within 24 hours to 4 days - Can be used long-term with minimal toxicity - Reduces bowel and pancreatic secretion	- Requires continuous infusion or regular administration - May not be effective in all patients
Dexamethasone	- Effective in symptom relief within 5 to 7 days - High success rates (around 89%) - Useful in cases of small bowel obstruction	- Limited use in small bowel obstruction cases - Adverse events such as unpleasant perianal sensations in some patients
Diatrizoate Meglumine	-Effective in restoring bowel function (84% success rate)	- If contrast material does not appear in the large bowel within 24 hours, surgery is inevitable in 99% of cases
Percutaneous Gastrostomy	- Feasible in very vulnerable patients - Good symptom control	- Leads to short bowel syndrome, requiring total parenteral nutrition - Not suitable for patients with multiple obstructions
Stent Placement	- High success rate for implantation - Relatively low chance of requiring further surgical intervention - Prolonged survival in certain cases	- Recommended mainly for large bowel or duodenal obstructions - Less effective if multiple obstructions are present
Surgical interventions	- Provides definitive relief from obstruction - Prolonged symptom-free periods	- High morbidity and mortality rates - Not suitable for all patients, especially those with poor overall health

The studies included in the review were graded to monitor their quality according to the criteria set out by the NHS Executive in their Reviews on Commissioning Cancer Services. This grading ensured that only the strongest evidence was considered (Table 8).

Table 8. Grading of Literature (55)

Grading was performed according to the criteria set out by the NHS Executive in their Reviews on Commissioning Cancer Services.

Author, year	Methods	Grade
Castaldo et al. (81); 1981	retrospective observational	IIIA
Malone et al (82);, 1986	retrospective observational	IIIA
Larson et al. (83); 1989	retrospective observational	IIIA
Lee et al. (84); 1991	retrospective observational	IIIA
Cunningham et al. (85); 1995	retrospective observational	IIIA
Cannizzaro et al. (86), 1995	prospective single arm interventional study	IIA
Mangili et al. (87); 1996	retrospective observational	IIB
Campagnutta et al. (88); 1996	prospective single arm interventional study	IIB
Hardy et al. (89); 1998	prospective placebo controlled cross over study	IIIA
Gadducci et al. (90); 1998	retrospective observational	IIIA
Philip et al. (91); 1999	prospective cohort	IIA
Mercadante et al (92); 2000	randomised controlled trial	IC
Brooksbank et al. (93); 2002	retrospective observational	IIIA
Mangili et al. (67); 2005	retrospective observational	IIIA
Matulonis et al. (95); 2005	prospective single arm interventional study	IIC
Pothuri et al. (94); 2005	retrospective observational	IIIA
Chi et al. (96); 2009	prospective study	IIA
Watari et al. (97); 2012	prospective single arm interventional study	IIA
Rath et al. (99); 2013	retrospective observational	IIIA
Fotopoulou et al. (98); 2013	retrospective observational	IIIA
Jutzi et al. (100); 2014	retrospective observational	IIIA
Perri et al. (101); 2014	retrospective observational	IIIA
Peng et al. (113); 2015	randomised controlled trial	IB
Daniele et al. (103); 2015	retrospective observational	IIIA
Zucchi et al. (104); 2016	prospective single arm interventional study	IIA
Dittrich et al. (105); 2017	retrospective observational	IIIB
Miłek et al. (106); 2017	prospective single arm interventional study	IIB
Heng et al. (107); 2018	retrospective observational	IIIA
Lodoli et al. (109); 2021	retrospective observational	IIIA
Jones et al. (110); 2022	retrospective observational	IIIA
Armbrust et al. (114); 2022	retrospective observational	IIIA
Cole et al. (111); 2023	retrospective observational	IIIA
Walter et al. (112); 2024	prospective single arm interventional study	IIA

5. DISCUSSION

Examining different aspects of QoL shows us the complexity of the field. In some cases, it can be clearly seen that individual factors, social context, religious beliefs, education or relationships can influence the decision of the patients. It is an important message for healthcare providers, as these factors must be considered.

Regarding ECP, we managed to demonstrate that reproductive health awareness is significantly influenced by factors such as previous pregnancies and age. As key findings we found that(1) patients who were more health-conscious sought medical advice more promptly; (2) women with a history of previous pregnancies exhibited higher levels of health consciousness; (3) reproductive health awareness increased with age.

We have found that general health awareness had an impact on reproductive health. It is in accordance with our findings. Our literature search revealed the significance maintaining fertility as a key determinant of the QoL. We detected a nearly 20% gap in the therapeutic effectiveness of the standard treatment(115), which we would like to reduce with the possible introduction of novel targets and therapies. In order to prove it we constructed a novel study to examine the combined effect of the LND-IUD and combined weight reduction therapy, consisting of metformin and liraglutide, on patients with BMI > 30, having EHA or low-grade FIGO stage 1A EEC and a wish of further childbearing. In this investigation we would like to assess the possible increase in pCR rates with the new treatment combination comparing to the standard of care, focusing on the obesity and insulin resistance related hormonal and metabolic changes leading to EEC.

Talking about the QoL in the context of fertility sparing management of endometrial cancer or the effect of conscious behaviour on reproductive health one must admit that there are evident therapeutic interventions aiming the enhancement of QoL. On the contrary our review pointed on the fact that in the case of MBO it is different, as therapeutic decisions are not straightforward. MBO is a potentially lethal condition with poor survival outcomes (116, 117). Therapeutic interventions may cause long-term hospitalisation or severe adverse effects (118, 119). In the palliative setting the main aims are symptom and pain management in order to ameliorate QoL, which should be presented in the patient-physician communication as well (118, 119). Despite, healthcare providers should seek for long-lasting therapeutic options, often an invasive method, to

provide the best QoL achievable. Decisions about invasive measures must be made with the active involvement of the patients and relatives, considering that personal factors, spiritual beliefs, psychological and psycho-social factors play an important role in decision-making (120). The active involvement of the patients and their families is crucial, due to the frequency and severity of complications of potential surgical interventions.

5.1. Retrospective Observational Study- Sociodemographic and Medical Characteristics of Women Applied for Emergency Contraception

Our findings highlight that individuals with a high level of health consciousness are more likely to seek medical advice promptly. This behaviour demonstrates a proactive and informed approach to healthcare, emphasizing the importance they place on their overall well-being.

Our study shows a connection between reproductive health awareness and women who have previously been pregnant. The results indicate that these women have higher levels of health consciousness. This suggests that experiences related to reproductive health may enhance their overall healthcare awareness and needs. Furthermore, our study revealed a significant positive correlation between health consciousness and age. As people age, their awareness and mindfulness about health-related matters tend to increase. This finding illustrates how health consciousness evolves over a person's life, with age potentially influencing health attitudes and behaviours.

The scoring system we used provided a detailed evaluation of these aspects among study participants. Existing literature has established a link between certain lifestyle behaviours, such as smoking, regular alcohol consumption, and engaging in unsafe sexual practices (like unprotected sex and frequent partner changes), and a higher risk of developing various diseases, including mouth cancer, lung cancer, sexually transmitted infections, and HPV-associated cancers (121-123) . While moderate drinking may lower the risk of some diseases (such as diabetes, cardiovascular, and chronic kidney disease), it is linked to a two to fourfold increased risk of oral and oesophageal cancer (122).

Human papillomavirus (HPV) is the most prevalent viral infection in the reproductive tract and one of the most widespread causes of sexually transmitted infections worldwide (124). Persistent high-risk genital HPV infection is responsible for approximately 99.7%

of all cervical cancer cases, which is among the most common cancers affecting women, with an estimated 528,000 new cases reported in 2012 (125). HPV testing is clinically valuable in secondary prevention, particularly for triaging low-grade cytological abnormalities, and it proves higher sensitivity than cytology as a primary screening method. This is why it is increasingly becoming the primary screening method in many countries. WHO recommends HPV vaccination as the most cost-effective public health measure in the fight against cervical cancer (126, 127).

In Europe, ECPs containing levonorgestrel require a prescription after consulting a practitioner in Hungary and Poland(128). January 2015, the European Commission issued a decision allowing the sale of ECPs containing ulipristal acetate without a prescription throughout the EU. Several countries have implemented this recommendation, although over-the-counter dispensing is still age-restricted (129). In Hungary, all hormonal contraceptives, including ECPs, are prescription-only and require a medical consultation.

Our previous study identified condom rupture and a history of previous pregnancies as the primary motivators for using emergency pills (10). In the current study, health-conscious individuals sought medical help significantly faster than those with lower health consciousness scores. Literature indicates that people with healthy habits get more frequent health checkups (130). This study is the first to describe that health-conscious individuals seek medical help sooner.

Participants in the study showed increased health consciousness with age. Research indicates that general practice visits increase with age (131-133). Compared to people under 50 (2%), those over 51 (27%) had screening health exams more frequently (131, 132). It was concerning that 40% of women under 30 did not routinely get pap smears. Data from the Australian Cervical Cytology Registry shows that over one-third of women under 30 do not get pap smears, and this number has been declining since 1996. (131) US data from 1976 to 2000 also shows an increase in cervical adenocarcinoma among young women (134). Delaying cervical screening increases the risk of cervical cancer spread (131, 135).

Interestingly, previous pregnancies also affect reproductive health awareness. In our study, more health-conscious patients had been pregnant before. Parenthood plays a significant beneficial role in physical and mental health and self-esteem. (136-138) Studies show that parents of young children smoke and drink less frequently (139-143).

Older parents have more positive health habits than childless individuals, although this difference may only apply while children live with their parents. (139, 144). However, Becker's work shows that, at older ages, there is no difference in lifestyle factors between childless adults and adults who have had children. It is possible that this only applies to the time that children live with their parents (139).

Our findings highlight the crucial role of health consciousness in shaping health-related behaviours and decisions. Understanding the connections between unintended pregnancy and health can provide valuable insights for clinical practice and health policy (145). Health-conscious individuals exhibit healthier habits, better adherence to medical recommendations, and enhanced quality of life (146). Trust in the patient-physician relationship mediates 28% of the impact of health consciousness, highlighting its influence on healthcare outcomes (147). Given the positive correlation between health consciousness and patient-physician trust, telehealth is vital for addressing the immediate healthcare needs of health-conscious individuals. Telehealth's fast and accessible nature aligns with proactive approach, facilitating timely consultations and interventions (148).

Early health education is crucial, fostering awareness of well-being. This comprehensive approach aims to raise health awareness among older demographics and cultivate health consciousness, particularly regarding sexual health, among the younger population. By instilling this awareness early, the goal is to empower the younger generation to take advantage of modern opportunities for improved health outcomes.

This analysis, which includes sociodemographic details, lifestyle elements, health-related information, and an awareness score system, enhances understanding of the relationship between lifestyle factors and reproductive health decisions. The development of an awareness score system provides a quantifiable measure, contributing to a structured assessment of health consciousness.

The study's reliance on a telemedicine platform introduces potential selection bias, as individuals opting for telehealth services may differ from those seeking in-person consultations. Additionally, self-reported data during telehealth consultations may be susceptible to recall and social desirability biases, potentially affecting the accuracy of reported lifestyle factors. The cross-sectional design limits the establishment of causation, necessitating longitudinal studies for a comprehensive understanding of temporal relationships. The study mainly focuses on the correlation between lifestyle factors and

awareness scores with ECP utilization, leaving room for further exploration of additional outcome measures in future research.

The observed correlation between reproductive health awareness and prompt medical consultation in ECP use has direct implications for clinical practice. Healthcare providers should integrate discussions about lifestyle factors, such as smoking, alcohol consumption, and contraceptive practices, into routine reproductive health consultations, offering personalized interventions.

Comprehensive health education in routine care, focusing on reproductive health awareness, menstrual cycles, and contraceptive options, can empower patients to make informed decisions.

The correlation between health awareness and prompt medical consultation underscores the value of integrating telehealth in clinical practice. Telehealth enhances accessibility, offering a convenient platform for health-conscious individuals to seek timely reproductive health consultations.

This approach aligns with personalized education and counselling opportunities provided by telehealth, ensuring that individuals, regardless of location, can access quality reproductive healthcare. Embracing telehealth contributes to preventing unintended pregnancies by providing timely, tailored, and comprehensive reproductive health interventions.

The correlation between reproductive health awareness and prompt medical consultation in ECP use highlights critical avenues for future research. Investigating telehealth utilization in reproductive healthcare is essential. Understanding factors influencing patients' preferences for telehealth, barriers to adoption, and the impact of virtual interventions on reproductive health outcomes would enhance understanding of this evolving healthcare model. Longitudinal studies can provide insights into the sustained impact of health consciousness on reproductive health decision-making. Examining how reproductive health awareness evolves over time and its influence on healthcare-seeking behaviours can deepen understanding of long-term reproductive health patterns. Comparative effectiveness studies are needed to assess outcomes of different contraceptive counselling methods. Comparing traditional in-person consultations with telehealth interventions can help determine the most efficient and patient-centred methods for delivering reproductive health information and interventions.

Integrating principles of behavioural economics into research design could offer insights into decision-making processes related to ECP use. Understanding behavioural factors influencing choices and adherence to reproductive health practices can inform the development of effective interventions. Addressing these research areas will deepen understanding of the interplay between health consciousness, telehealth utilization, and reproductive health outcomes, refining strategies aimed at preventing unintended pregnancies and improving reproductive healthcare.

5.2. Protocol for a Prospective Randomized Interventional Trial- Comprehensive Evaluation of a Levonorgestrel Intrauterine Device, Metformin, and Liraglutide for Fertility Preservation in Endometrial Cancer

A study focused on innovative methods to diagnose and treat endometrial carcinoma must address various complexities (149), including public health implications, ethical and legal considerations, and equitable access to care. These issues are vital for effectively implementing oncofertility counselling, which supports female cancer patients facing fertility threats from cancer treatments (34). Evidence-based oncofertility counselling requires a multidisciplinary approach, involving medical oncologists, gynaecologists, pathologists, radiologists, reproductive endocrinologists, mental health counsellors, social workers, and clinical researchers, to ensure comprehensive and informed decision-making (149). Integrating such services must adhere to international guidelines (35, 150) to avoid medicolegal repercussions and uphold ethical standards, enabling patients to make informed choices about fertility preservation options (151). This multidisciplinary framework emphasizes the moral obligation to support individual autonomy in medical decision-making while ensuring the welfare of potential offspring and others (152).

The LNG-IUD is established as the most effective form of progesterone for treating endometrial hyperplasia, with minimal systemic side effects (153, 154). To complement the progesterone effect of the LNG-IUD, metformin, an oral anti-diabetic drug, has been used for its potential anti-cancer properties. Metformin activates adenosine monophosphate (AMP)-activated protein kinase (AMPK), affecting cellular metabolism and intracellular signalling by promoting oxidative metabolism and inhibiting the mTOR pathway(69, 155). This inhibition of mTOR, often activated in endometrial carcinoma (EC) cells, helps overcome resistance to progestins, induces cell cycle arrest and

apoptosis, suggesting metformin's role as a promising therapeutic agent in EC treatment (156).

A meta-analysis comparing metformin plus LNG-IUD versus LNG-IUD monotherapy for treating EHA found no clear difference in regression rates of hyperplasia between the two treatments, with very low-certainty evidence. It remains unclear whether the combination therapy impacts rates of abnormal uterine bleeding, hysterectomy, or adverse effects. Therefore, the authors conclude that there is insufficient evidence to support or refute the use of metformin with standard therapy and emphasize the need for more robust and long-term RCTs to address this clinical question (157).

A retrospective analysis of 75 patients found that fertility-sparing treatment of early-stage endometrial cancer with LNG-IUD and metformin resulted in higher, though not statistically significant, complete response rates and effective fertility preservation. The authors suggest that the combination of megestrol acetate (MA), LNG-IUD, and metformin might be the most effective option for women desiring future pregnancies with low-risk early-stage endometrial cancer (158).

Additionally, the glucagon-like peptide-1 (GLP-1) receptor agonist, liraglutide, has shown promising results in managing diabetes and cancer treatment. Although the literature on this topic is limited, liraglutide has been shown to reduce human prostate cancer incidence. Similarly, GLP-1 receptor agonists have been found to reduce the in vitro proliferation and in vivo growth of prostate cancer cell lines (159). A cohort study indicated that people with Type 2 diabetes who took GLP-1receptor agonists had a lower risk of developing colorectal cancer than those taking other medications(160). However, initial studies have not yet extended to gynaecological malignancies, particularly regarding fertility preservation.

5.3. Systematic Review on The Management of Malignant Bowel Obstruction in Gynaecological Cancer Patients

To reduce complications, various attempts have been made to identify factors influencing surgical outcomes, though the results are often inconclusive. Reliable factors for assessing potential risks include blood albumin levels, presence of ascites, surgery complexity (e.g., stoma placement, residual bowel length, number of bowel resections),

general performance status, and frailty (83, 101, 161). Additionally, some authors suggest considering patients' life expectancy (63).

However, surgical solutions should be prioritized as they offer lower recurrence rates of obstructive episodes, longer symptom-free survival, and extended overall survival compared to less demanding procedures (90, 96, 103, 162, 163). This is supported by a review of 868 patients by Furnes et al., which found surgery effectively relieved obstructive symptoms, allowed diet reintroduction, and enabled earlier discharge (164). Some suggest longer survival rates might be due to the potential reintroduction of chemotherapy (165), although chemotherapy alone is not effective in restoring bowel function in heavily pretreated patients (166).

When deciding on surgery, interventions must be conducted carefully (167), considering the procedure's purpose. The type of surgery depends on the location and multiplicity of the obstruction, tailored to each situation. In such cases, cytoreduction is no longer the goal; instead, symptom management procedures (e.g., bowel resections, bypasses, ostomies) should be performed.

If surgery is not feasible, less invasive measures like stent placement or percutaneous gastrostomy are preferred. Stents are mainly recommended for solitary large bowel or duodenal obstructions (100), promising high success rates and low chances of further surgical intervention with prolonged survival (168, 169). For multiple obstructions, gastrostomy is a better management solution, feasible in vulnerable patients and effective for symptom control whether performed radiologically or endoscopically (82, 84-86, 88, 93, 94, 99, 104, 105, 111). Both gastrostomies and jejunostomies lead to short bowel syndrome, necessitating total parenteral nutrition and involving nutritional specialists in patient management (170).

Until decision on surgery is made, several drugs are needed to relieve symptoms. Some authors suggest starting with conservative management of MBO as spontaneous or treatment-induced resolution can occur in many patients. Conservative treatment might also optimize patients for surgery. Initial symptomatic care should focus on pain management, control of vomiting, and restoration of basic homeostatic parameters.

Supportive care must address electrolyte imbalances caused by increased intestinal fluid secretion, inflammatory responses, and emesis (171). Opioid use is often necessary for pain management, with bowel movement inhibition reducing cramping. After

resolving a malignant bowel obstruction (MBO) episode, minimizing long-term opioid use is essential to avoid side effects and dependency. Pain management should follow the WHO analgesic ladder, starting with NSAIDs and adjuvants, progressing to minor opioids, and considering major opioids only if necessary (172).

Bowel function can often be restored using diatrizoate meglumine, routinely used in MBO diagnostics, showing 84% effectiveness. A meta-analysis by Branco et al. concluded that if contrast material doesn't appear in the large bowel within 24 hours, surgery is inevitable in 99% of cases (173). Galardi et al. found that patients who underwent a small bowel diatrizoate meglumine follow-through test were operated on earlier than those who did not (174).

In our systematic review, somatostatin analogues showed promising results in MBO management by reducing bowel content accumulation, decreasing motility, and secretion (62). Octreotide, at a dosage of 0.3 mg/day, was the preferred drug, achieving over 82% symptom control within four days without major complications.

Corticosteroids, particularly dexamethasone, were widely investigated for their anti-inflammatory and anti-secretory properties, significantly responding to MBO in at least half of the patients (63). The combination of dexamethasone, lanreotide, and metoclopramide might be most effective in conservative MBO treatment, offering combined anti-inflammatory, secretion-reducing, and motility-restoring actions (175).

Substantial evidence demonstrates that palliative care programs significantly improve the QoL for patients. Integrating palliative care into general oncologic treatment should begin as early as possible to maximize benefits (176, 177). Oncologic patients with intra-abdominal disseminated cancer are at elevated risk of developing bowel obstruction. Providing dietary interventions and laxatives to prevent constipation is crucial for these patients (102), as early detection of MBO improves outcomes and established local management protocols can reduce hospital stays and improve QoL (108).

Radiologic methods, especially CT scans, are crucial in diagnosing MBO, determining the obstruction's location and multiplicity. Contrast enhancement is widely used to assess obstructions, and Gastrografin can resolve symptoms, though its predictive value is most important (107).

Alongside diagnostics, clinicians must engage with patients' symptoms and start supportive care, including pain management and electrolyte restoration. Nasogastric

tubes (NGTs) can relieve nausea and vomiting quickly, although their routine use is not well-supported by data. In 2014 Paradis et al. (178) conducted a systematic search on data related to this topic, from 1966 to 2014. They have found only one paper with relevant data, but this was not strong enough to make it into evidence (179). According to this retrospective study conducted by Fonseca et al. (92) prolonged NGT use can be uncomfortable and lead to complications such as epistaxis, necrosis, laryngeal disorders, regurgitation, and aspiration pneumonia, thus extending hospital stays and decreasing the quality of life in palliative care settings. Selective use of NGTs, considering individual risks and benefits, is necessary.

Combining dexamethasone, octreotide, and metoclopramide appears most promising in conservative MBO treatment. Based on synthesized data, we propose a treatment algorithm for managing malignant bowel obstruction in gynaecologic oncologic patients (Figure 8.)

Current society guidelines suggest that treatment algorithms must be managed individually as there is lacking evidence on treatment modalities, thus encouraging further investigations on this topic (61, 120). The review of the literature reveals that decision-making in the management of MBO is complex and not straightforward. Treatment plans must be personalised and involve a multidisciplinary team, considering all aspects of the patient's condition. It is crucial to acknowledge that patients' perspectives on their treatment may differ significantly from those of healthcare providers, necessitating a holistic approach in care (180).

To facilitate easier decision making, the development of risk stratifying algorithms is necessary to determine patients who would benefit from surgery (181), on the other hand, robust prospective trials are needed in this field to collect data on specific treatment modalities to be capable of creating universal guidance for the management of this patient population.

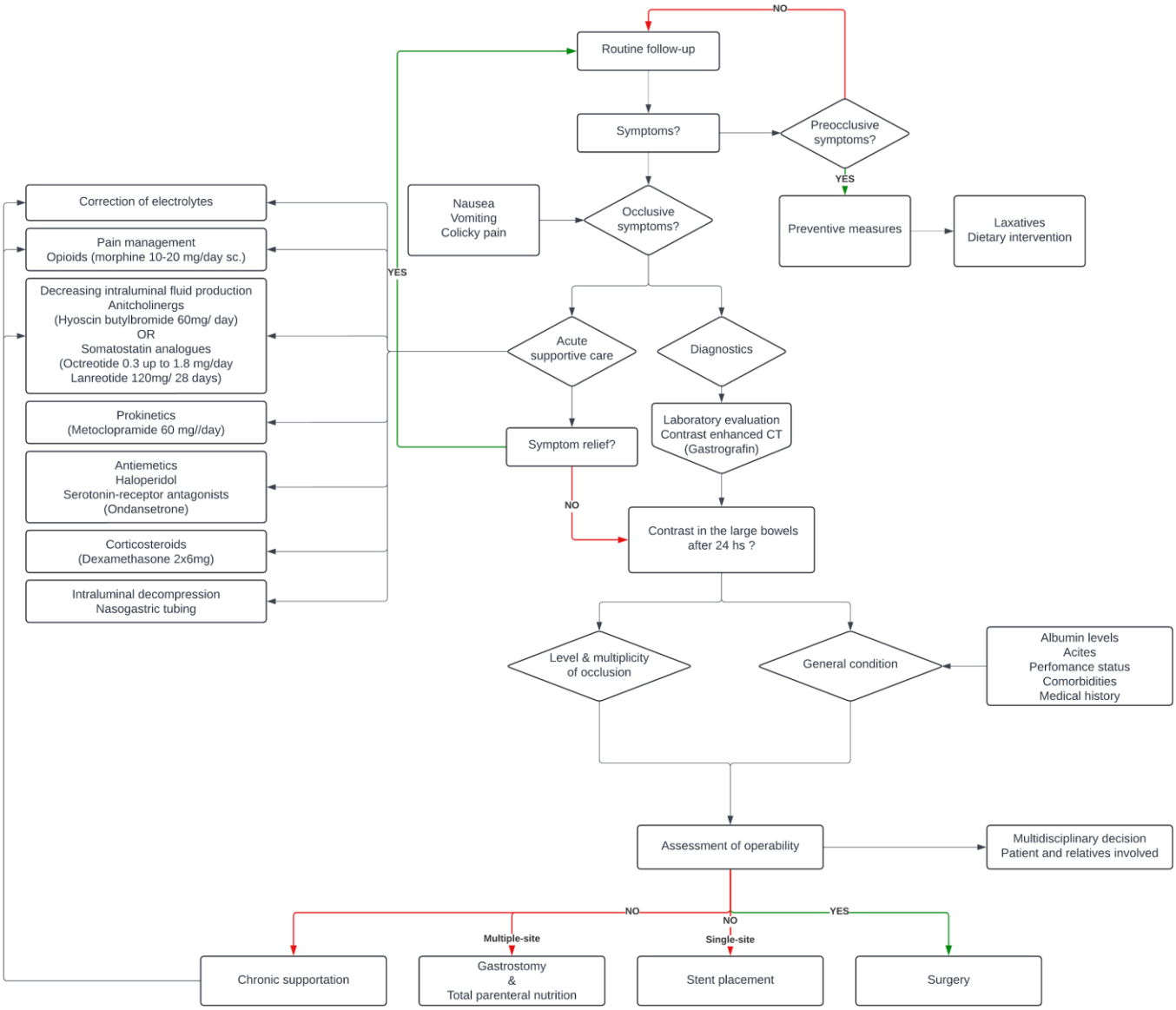

Figure 8. Therapeutic Algorithm of MBO (55)

6. CONCLUSIONS

This thesis focused on the following questions:

1) In our investigation we studied the relationship between health awareness and the use of emergency contraceptive pills. We managed to prove the aforementioned correlation, as we found that patients more involved in their health, practicing healthier habits do seek medical consultation earlier, which at the same time contributes to better health promotion and a reduced risk of health problems.

2) In our work we identified factors influencing reproductive health awareness among emergency contraceptive pill users. We found significant correlation between age and previous pregnancies on reproductive health awareness. Both establishments emphasize the significance of lifestyle factors influencing reproductive health decisions.

3) We aimed to assess the feasibility of performing a study on enhancing the efficacy of fertility-sparing interventions in endometrial hyperplasia and early-stage endometrial cancer. Combining LNG-IUD with metformin and liraglutide significantly enhances the regression of endometrial hyperplasia and early-stage endometrial cancer in patients with obesity while maintaining a favourable safety profile. The integrated approach of using metabolic therapy alongside localized hormonal treatment addresses the underlying risk factors associated with obesity and endometrial cancer, offering a promising fertility-preserving alternative to conventional surgical methods.

4) In our systematic review we tried to identify the best therapeutic alternatives, that may contribute to the optimal QoL improving management of gynaecologic cancer patients suffering from MBO. We found that the optimal management of MBO is still controversial. Given the limited availability of strong evidence, it is challenging to establish a single therapeutic approach for patients with malignant bowel obstruction. Our recommendation highlights the need for individualised treatment strategies. Due to the absence of definitive guidelines, healthcare providers must tailor treatment plans to each patient's specific circumstances, acknowledging that the objectives of treatment may differ between patients. Development of holistic, patient-

centred management pathways are crucial. Our systematic review underscores the lack of high-quality evidence, with most studies being retrospective and the few prospective studies involving small patient cohorts. Data heterogeneity, originating from differences in patient populations, data collection methods, local management practices, and treatment intentions, further complicates comparability. Future investigations should prioritise prospective data collection through multicentric international collaborations to generate robust evidence and address the outstanding questions in the management of malignant bowel obstruction.

7. SUMMARY

Introduction:

In gynaecological care quality of life might be affected by numerous factors. The integrity of reproductive health and different aspect of oncologic care are cornerstones of maintaining female QoL. We investigated the effect of lifestyle factors on reproductive health awareness, possible enhancement of fertility sparing treatment in endometrial cancer and the protection of QoL under palliative circumstances.

Methods:

We conducted a retrospective observational study on the cohort of a Hungarian data bank containing follow-up data of 447 women. We collected data on medical history, lifestyle factors, health awareness and specifications of this consultation to create a score.

We made a robust literature search to investigate the potential for a combined metabolic and hormonal therapy in early-stage EEC.

Comprehensive literature searches were conducted on MBO across various databases without restrictions. 4866 articles were screened, 34 meeting the inclusion criteria.

Results:

Earlier pregnancies and older age were associated with greater reproductive health awareness with faster report for a post-event pill.

The investigation of combination therapy proved to be feasible in EEC.

Our literature search found that surgical intervention remains the definitive treatment for MBO, however conservative methods offer varying degrees of symptom relief and are often considered when surgery is not feasible.

Conclusions:

More health-conscious women consult a doctor earlier, which can reduce the chance of various health damage and enhance QoL. Our study emphasizes the significance of lifestyle factor influence on reproductive health decisions and QoL.

Maintaining fertility is a key determinant of QoL. We found that the integrated approach of combined treatment offers a promising fertility-preserving alternative to conventional surgical methods.

There is an urgent need for high-quality research to develop clear guidelines for MBO management in gynaecologic cancer patients to improve patient outcomes by aiding clinicians in treatment decisions.

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9. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

Publications related to the thesis:

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10. ACKNOWLEDGEMENTS

On this page I would like to express my gratitude to all the friends and colleagues who encouraged and helped me on my way to accomplish this work and without whom this could not have been realized.

I owe my gratitude to my supervisor, to Balázs Lintner, for his friendship, help, guidance and constant support on this way.

I would like to thank Márton Keszthelyi his tremendous help in these research projects, without whom it could have been hardly possible to achieve these results.

I am especially grateful to Professor Szabolcs Várbíró for taking our project into his research program, for believing in me and for his support.

I would like to thank Professor Nándor Ács for his help.

Special thanks to the Science Management Working Group, the Doctoral School, for supporting the writing and completion of my dissertation as soon as possible. I am grateful to my consultant, dr. Marianna Török, who helped in writing the thesis.

I would like to express my gratitude to all the colleagues who participated in the process of our research: Gergő Leipold, Péter Hársfalvi, Attila Keszthelyi, Lotti Keszthelyi and Zsófia Tóth.

And finally, I would like to thank my family their constant support.