

Investigation of Determinants in Quality of Life of Gynaecologic Patients

PhD thesis

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1. Introduction

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". Health-related quality of life (further: quality of life (QoL)) 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. 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.

These domains are often affected by gynaecological conditions. Surgical procedures for gynaecological conditions 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. Additionally, long-term outcomes, including changes in body image, sexual dysfunction, and infertility, underscore the lasting impact of these treatments. For this thesis we aimed three conditions in different fields of gynaecology which do have a great impact on QoL.

2. Objectives

In our research, we aimed to address 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.

We hypothesized a connection between sociocultural, environmental, and contraceptive responsibility, and emergency contraception use.

In this study we aimed to:

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

Lifestyle factors play a crucial role in the pathogenesis of endometrial cancer. 14% of these occur in the perimenopause, 5% younger under 40 years of age presenting a great demand for fertility-preserving therapies. We investigated whether there would be a more potent treatment than the standard one.

- 3) We set a study-plan on fertility-preserving cancer treatment options with higher fertility success rates.

In the case of end-stage gynaecologic cancer patients, a potential life-threatening and QoL deteriorating syndrome is the malignant bowel occlusion (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. Sociodemographic and Medical Characteristics of Women Applied for Emergency Contraception

3.1.1 Patients and Characteristics

447 individuals were enrolled from July 2021 to September 2021, on the telemedicine consultation platform, <https://esemenyutan.hu>. This service was available to patients, looking for emergency contraceptive prescriptions following consultations with gynaecologists. Patients were asked to fill a standardized set of questions investigating their lifestyle.

Our investigation involved a comprehensive analysis of patient records, sociodemographic details, lifestyle elements and health-related information. The study was approved by the Institutional Review Board of Semmelweis University (SE RKEB: 125/2022).

3.1.2. Reproductive Health Awareness Score (RHAS)

The collected data underwent rigorous quality control procedures. 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, the participants' engagement with preventive health measures, and ovulation status. The study investigated contraceptive practices and preferences for future contraceptive methods. We created a scoring system in which higher numbers suggest higher health awareness.

3.1.3. Statistical Analysis

Shapiro–Wilk test was used to test the normality of continuous variables and 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 $p < 0.05$.

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

This protocol was developed in harmony with the guidelines outlined in the Standard Protocol Recommendations for Interventional Trials (SPIRIT) reporting template. Our multi-centred randomized 1:1:1 open-label interventional phase III clinical trial consists of three treatment arms: levonorgestrel intrauterine device (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, if wish of further childbearing and obesity (BMI>30) are present.

Early-stage endometrial cancer (EEC) is meant to be FIGO stage I, grade 1 disease without lymphovascular space or myometrial invasion, according to MRI or transvaginal ultrasound (TVUS) findings.

3.2.2. Objectives

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.

The secondary outcomes include, the assessment of histological changes compared to baseline after 3, 6, 9, 12 months; monitoring changes in glucose and insulin levels and weight for 12 months.

3.2.3. 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 between 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 for arms B and C (LNG-IUD plus metformin and LNG-IUD plus metformin plus liraglutide) is expected to be 86.7%. To reach at least 80% power with equal group size, the sample size needed is 33/group. 24% of the participants are expected to be drop out, resulting in a target sample size of 44 participants/group (total sample size = 264).

3.2.4. 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 as 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.

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

3.3.1. Search Strategy

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

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

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.

3.3.2. Selection Process and Selection Protocol

Following a systematic search of databases and subsequent duplication removal, selection was conducted according to the PICO criteria. 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.

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 were excluded.

Two authors independently 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. A third reviewer resolved the discrepancies.

3.3.3. 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.

4. Results

4.1. Sociodemographic and Medical Characteristics of Women Applied for Emergency Contraception

4.1.1. Reproductive Health Awareness Score and Elapsed Time

Linear regression analysis showed that time elapsed till requesting a medical consultation was inversely correlated with the reproductive health awareness score. The more health-conscious the women were, the faster they made a phone call. (Figure 1.)

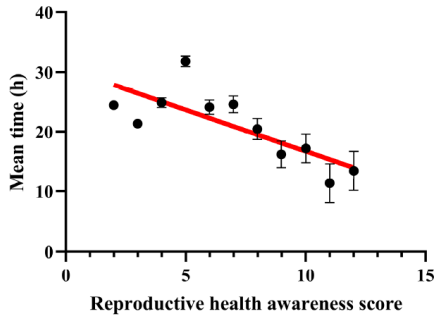


Figure 1. Mean Time and RHAS Correlation

Data are presented as mean + SEM. Pearson correlation: $r = -0.7755$; $R^2 = 0.6014$; p value = 0.005

4.1.2. RHAS 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 2), besides, the

reproductive health awareness score increased significantly with age (Figure 3).

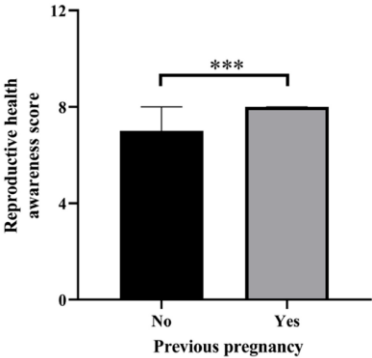


Figure 2. Previous Pregnancy and RHAS

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

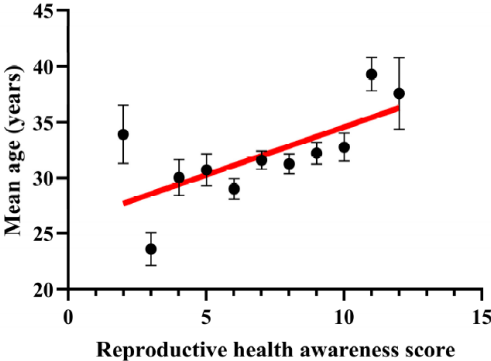


Figure 3. Age and RHAS

RHAS showed a positive correlation with age. Data are presented as mean + SEM. Pearson correlation: $r = 0.6823$; $R^2 = 0.4655$; p value = 0.0207.

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

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

LNG-IUD is approved as a standard therapy in case of fertility-sparing procedures. 3000 mg (or maximum tolerated dose) of metformin will be administered to the study participants. Liraglutide, a long-acting GLP-1 agonist, administered via subcutaneous injection once daily. To enhance gastrointestinal tolerability, an initial dose of 0.6 mg which will be escalated to 1.2 mg, for certain patients, to 1.8 mg daily.

Inositol (2×2g), a diet plan, and minimal exercise of 40–60 min of walking will be introduced. Exercise levels are measured using the Active Australia Survey.

4.2.2. Randomisation

Patients will be randomly allocated in a 1:1:1 ratio to arm A (LNG-IUD), arm B (LNG-IUD plus metformin), or arm C (LNG-IUD plus metformin and liraglutide). This will be conducted in a blind manner to eliminate selection bias.

4.2.3. Treatment of Adverse Events and Study Discontinuation

Local investigators will handle any adverse events (AE) in accordance with current good clinical practice guidelines. AEs will be documented, detailing its nature, onset, resolution times, severity, treatment and outcome. Follow-up examinations may be conducted as needed to ensure patient safety.

The study will be terminated early if the Institutional Review Board (IRB) identifies any of the following: serious

adverse drug effects; diagnosis of a new malignancy, participants encountering unexpected, significant, or unacceptable risks, or the treatment proves to be ineffective.

4.2.4. Baseline Assessments and Follow-Up

Baseline assessments adhere to the trial's standard operating procedure. During the first visit, in case of a negative a urine pregnancy test, LNG-IUD will be inserted 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 habits. Medical consultation and the initiation of diabetic medications will also commence during this phase.

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 to rule out disease progression. If complete pathologic remission 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.

At the 3, 6, 9-month follow-up visits, patients with progressive disease (PD) or recurrence will be withdrawn from the trial. Those showing complete response (CR), partial response (PR), or stable disease (SD) will continue therapy and will be reassessed after 3 months. At 12th month visit, if CR will not be achieved, hysterectomy will be advised.

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.

2068 Patients were included from 34 studies. Studies identified were mainly observational studies but there were no restrictions in the type. All studies, reporting management of MBO associated with gynaecological malignancy were included without any limitations.

4.3.2. Medical Management

4.3.2.1. *Diatrizoate Meglumine*

Limited number of studies are available and comparable on the use of Gastrografin in patients with MBO. Its true value lies in the ability of determining the optimal time of surgery. This is crucial because conservative treatment success rates are low in complete bowel obstruction, urging timely surgical intervention.

4.3.2.2. *Somatostatin Analogues*

Ocreotide (OCT) emerges as the predominant medication investigated for managing MBO. Symptom resolution varied across studies, occurring within 24 hours to 4 days, doses ranging from 100 $\mu\text{g}/\text{day}$ to 0.9 mg/day . OCT exhibits a high rate of vomiting control, with an overall response rate of 81.8%- 93.1%. The absence of major AEs underscores its safety and potential to enhance the QoL by obviating the need for nasogastric tube placement in these patients. Tailored medical protocols involving antisecretory drugs like OCT, remain standard of care for patients with contraindications to surgery, as complications are noted in a minority of cases.

4.3.2.3. *Dexamethasone (DEX)*

The use of DEX in managing MBO is promising. Our analysis of three studies involving 163 patients exclusively diagnosed with OC, highlights its efficacy. The dosage ranged from 4- 16mg/day. The use of DEX is limited specifically in cases of small bowel obstruction, whether administered intravenously or subcutaneously. DEX 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 DEX's role as a valuable therapeutic option, offering relief and improving quality of life.

4.3.3. Invasive Interventions

4.3.3.1. *Percutaneous Gastrostomy (PEG)*

PEG tube enables feeding or gastric decompression of patients unable to take adequate nutrition orally or needing relief from vomiting and nausea due to impaired gastric motility.

Patients treated with this option are usually not eligible for operations because of their general condition, or abdominal status. Studies consistently report high technical success rates, often close to 100%. The reduction in symptoms, particularly nausea and vomiting, is substantial, with many studies reporting symptom relief in nearly all patients. The implantation of gastrostomy has positive effects on QoL.

4.3.3.2. *Stent Placement*

Gynaecological malignancies, especially OC can cause obstruction on the large bowels. The results are contradictory. Although the intervention is feasible and offers a good option for treatment, there is a meaningful need for intervention because of the complications. There is also a limitation by nature of the disease as 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.

Surgical interventions can be demanding for the patient and sometimes a longer period is needed for recovery, mainly for those whose baseline condition is already impaired.

Surgical interventions can improve QoL as there is a higher chance for patients to tolerate solid intake or fluids. Despite all the negative effects, the reason to support surgery is that all the studies found, proved a longer survival in this group.

It is still controversial who are the patients that benefit from surgeries and what are the indicators of worse outcomes. Correlations found between survival and prognostic factors are low albumin, elevated blood urea- nitrogen and alkaline phosphatase or clinical factors like age, radiotherapy, ascites, carcinomatosis, multiple sites of obstruction, or palpable mass.

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 feasible to start treatment in an outpatient setting. In this manner the rate of surgical interventions, frequency of recurrent episodes of MBO and the length of hospital can be lowered with the maintenance of the possible chance of continuation of oncologic care.

5. Conclusions

This thesis focused on the following questions:

1) In our investigation we studied the relationship between health awareness and the use of ECPs. We managed to prove that patients more involved in their health, practicing healthier habits do seek medical consultation earlier, which contributes to better health promotion and a reduced risk of health problems.

2) In our work we identified factors influencing reproductive health awareness among ECP users. We found significant correlation between age and previous pregnancies on reproductive health awareness. Both establishments emphasise

the significance of lifestyle factors influencing reproductive health decisions.

3) We aimed to assess the feasibility of performing a study on improving 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. Our recommendation highlights the need for individualised treatment strategies. 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 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 MBO.

6. Bibliography of the candidate's publications

Publications related to the thesis:

Tóth R, Lóczi L, Török M, Keszthelyi A, Leipold G, Ács N, Várbíró S, Keszthelyi M, Lintner B. Sociodemographic and

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Leipold G, **Tóth R**, Hársfalvi P, Lóczi L, Török M, Keszthelyi A, Ács N, Lintner B, Várbió S, Keszthelyi M. Comprehensive Evaluation of a Levonorgestrel Intrauterine Device (LNG-IUD), Metformin, and Liraglutide for Fertility Preservation in Endometrial Cancer: Protocol for a Randomized Clinical Trial. *Life.* 2024; 14(7):835. **IF: 3.2**

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Publications not related to the thesis:

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ΣIF: 17.4