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SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

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CSIRZÓ ÁDÁM

Patobiokémia

című program

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Témavezető: Dr. Valent Sándor, egyetemi docens

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MEDICAL AND SURGIGAL TREATMENT OF ENDOMETRIOSIS

Ph.D. Thesis

ÁDÁM CSIRZÓ M.D.

Translational Medicine Program

Doctoral School of Molecular Medicine Sciences

SEMMELWEIS UNIVERSITY

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“QUID PRO QUO”

LATIN PHRASE

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TABLE OF CONTENT

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1 LIST OF ABBREVATIONS

BMI	Body Mass Index
CHC	Combined Hormonal Contraceptive
CI	Confidence Interval
CINeMA	Confidence in Network Meta-Analysis
CL	Conventional Laparoscopy
CNGOF	French College of Gynaecologists and Obstetricians
ESHRE	European Society of Human Reproduction and Embryology
GnRH	Gonadotropin-Releasing Hormone
GRADE	Grades of Recommendation, Assessment, Development, and Evaluation
HAS	French National Authority for Health
MD	Mean Difference
NSAID	Nonsteroidal Anti-Inflammatory Drug
OR	Odds Ratio
PICO	Population, Intervention, Comparison, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RAL	Robot-Assisted Laparoscopy
ASRM	American Society for Reproductive Medicine
RCT	Randomized Control Trial
ROBINS-I	Risk Of Bias In Non-randomized Studies—of Interventions
SD	Standard Deviation
SERM	Selective Estrogen Receptor Modulator
SUCRA	Surface Under the Cumulative Ranking
VAS	Visual Analog Scale

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2 STUDENT PROFILE

2.1 Vision and mission statement, specific goals

My vision is to make endometriosis related pain a concept of past, with one pill a day. My mission is to find the most effective pain relief therapy for endometriosis.

My specific goals are to compare conventional laparoscopy and robot assisted laparoscopy in endometriosis surgeries and to compare different medications in the treatment of dysmenorrhea, dyspareunia, and overall pelvic pain.

2.2 Scientometrics

Number of all publications:	3
Cumulative IF:	9.9
Av IF/publication:	3.3
Ranking (SCImago): Q3:0, Q4:0	D1:2, Q1:1, Q2:0,
Number of publications related to the subject of the thesis:	2
Cumulative IF:	6.4
Av IF/publication:	3.2
Ranking (Sci Mago): Q3:0, Q4:0	D1:1, Q1:1, Q2:0,
Number of citations on Google Scholar:	12
Number of citations on MTMT (independent):	11
H-index:	2

The detailed bibliography of the student can be found on page 62.

2.3 Future plans

My future goals include gaining more experience in both conservative and surgical therapy of endometriosis, to possibly ease the pain of as many patients as I can in the future.

Even though I find clinical practice and patient care very important I would like to carry on my scientifical work as well: my future goals include carrying out more valuable studies contributing the field of endometriosis, and obstetrics and gynecology in general.

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As I regard teamwork as a basis of success, I am a member of the Endometriosis Team of my clinic, through this work group, and by the help of my mentor, István Szabó MD, I have chance to perform and assist CL endometriosis surgeries and to assist in RAL endometriosis and gynecological surgeries as well.

As I also regard highly teaching and sharing knowledge with the next generations I would also like to teach in the future for residents, medical students, and Ph.D. students as well.

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3 SUMMARY OF THE THESIS

During my Ph.D. work my main focus was on endometriosis and its treatment: in order to gather more pieces of information, I compared CL and RAL in endometriosis surgeries, and I evaluated the available medications in the treatment of dysmenorrhea, dyspareunia, and overall pelvic pain. I carried out two meta-analyses on these two topics.

We found 13 eligible articles for CL and RAL comparison, and after the synthesis of the date available.

In these articles we found that there is no significant difference between RAL and CL in the intraoperative and postoperative complications, conversions to open surgery. There was no demonstrable difference in length of hospital stay, rehospitalization rate. CL and RAL have no statistically, nor clinically significant difference in terms of intraoperative blood loss. During RAL the operating time and operating room time is significantly longer than during a CL procedure.

Summing up the results of CL and RAL comparison meta-analysis RAL have no demonstrable advantage compared with CL.

We conducted a systematic search in the field of medical management of endometriosis related pain: 45 studies were available for data extractions, enrolling approximately 10,000 patients in these studies: during our network meta-analysis we created 8 networks and a total of 16 treatments were analyzed.

According to our results for dysmenorrhea, GnRH agonists combined with CHCs provided the greatest pain relief after three months of treatment. Regarding dyspareunia, CHCs were the most effective option, while for overall pelvic pain, CHCs or progestins paired with aromatase inhibitors delivered the most favorable outcomes.

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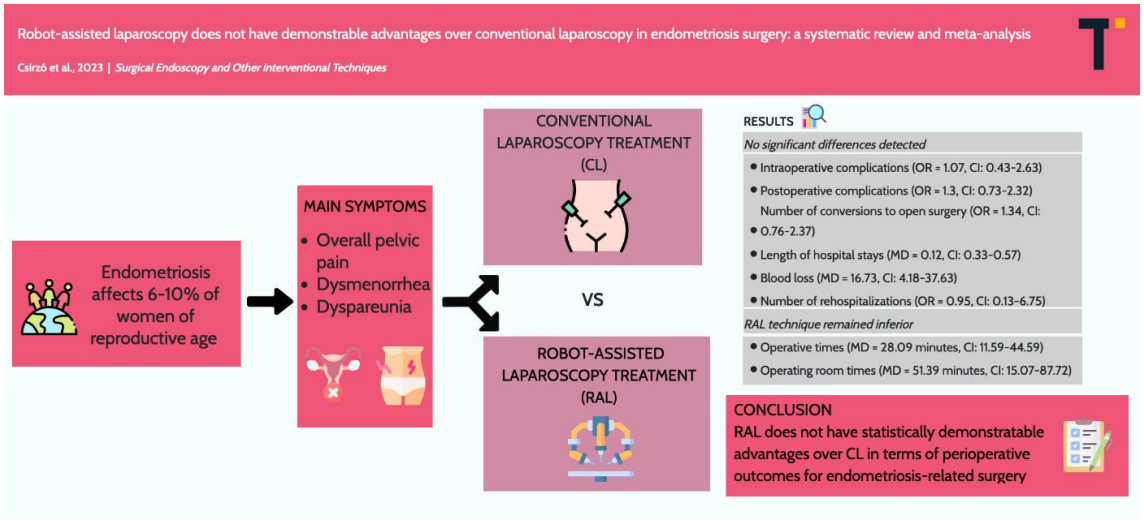
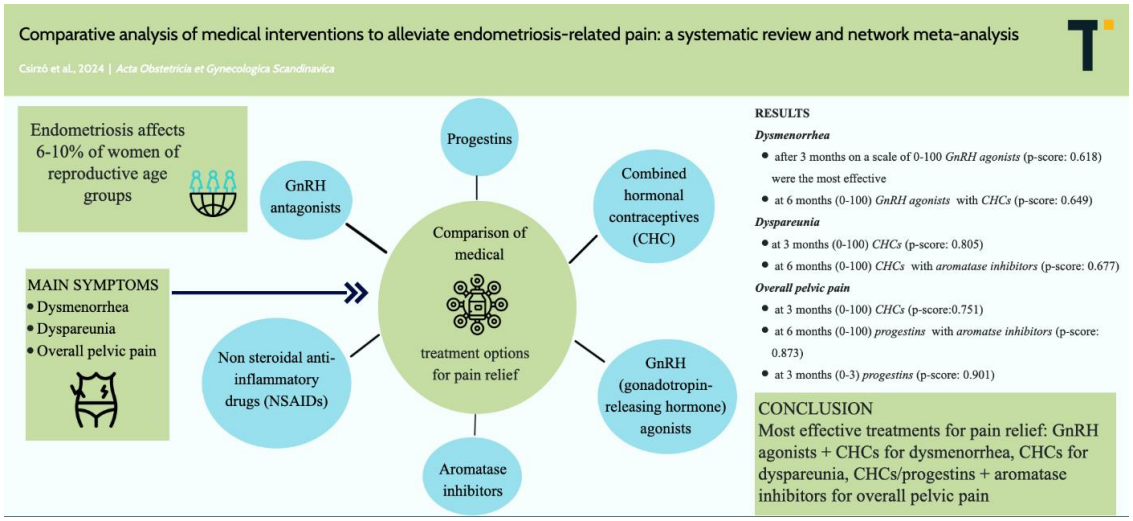
4 GRAPHICAL ABSTRACT





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5 INTRODUCTION

5.1 Overview of the topic

5.1.1 What is the topic?

The topic is endometriosis which is a common estrogen-dependent gynecological condition characterized by chronic pelvic pain and infertility.

5.1.2 What is the problem to solve?

Globally, approximately 70 million women of reproductive age suffer from it. The disease manifests in various forms and degrees of severity (1,2). While many women are affected by the disease, it remains an enigmatic field of gynecology: while approximately 10-15% of women of reproductive age groups are affected, the exact origin and pathomechanism of the disease is still unknown (3).

5.1.3 What is the importance of the topic?

Endometriosis is marked by the presence of functioning endometrial-like tissue outside the uterine cavity, triggering an inflammatory response (2) and the primary symptoms include dysmenorrhea, dyspareunia, dysuria, dyschezia, and infertility (4). Various treatment options are available, including medications, surgical procedures, and non-medical management strategies, with the goal of the reduction of pain and the improvement of fertility. It does not need to be explained that it is highly important to find the best of each modality of the treatments, and the one that is most fitting for the characteristic of the disease and for the exact patient’s needs.

5.1.4 What would be the impact of our research results?

I personally hope that as a result of our study we can compare the benefits and drawbacks of RAL and CL in endometriosis surgeries and that we can find the best medication for dysmenorrhea, dyspareunia, and overall pelvic pain.

5.2 Surgical treatment of endometriosis

Surgical techniques for endometriosis treatment primarily involve minimally invasive procedures, offering benefits, such as shorter numbers of hospital stay days, reduced trauma, reduced postoperative pain, minimal scarring, lower risk of adhaesion formation and a lower risk of infection compared to open surgeries (5). Conventional laparoscopy (CL) is considered the standard of care in today's endometriosis surgeries due to these advantages.

However, CL has some limitations, including 2-dimensional (2D) visualization, ergonomic difficulties for the surgeon, restricted instrument movement, and high dependence of tremors of surgeons (6). Also, CL requires extensive training to develop proficiency in hand-eye coordination and depth perception. Another drawback of CL which roots in the restricted instrument movement is the difficulty of handling large tissue masses (6). With the increasing adoption of advanced techniques like robot-assisted laparoscopy (RAL), many of these challenges are being addressed.

RAL retains the benefits of minimally invasive surgery while providing additional advantages. Using 3D technology, robot-assisted surgery enhances visualization, offers instruments with seven degrees of freedom, allows for tremor-free manipulation, and reduces surgeon fatigue. Additionally, it features a much shorter learning curve compared to traditional laparoscopy (5).

Studies over the years have demonstrated clinically significant advantages of RAL in many surgical fields, such as rectal cancer resection and distal pancreatectomy (6,7). Compared to CL, RAL has been associated with reduced postoperative pain and blood loss (8). However, its main drawbacks remain the lack of tactile feedback and the high cost of setups and maintenances, also high costs of sterilization.

5.3 Medical treatment of endometriosis

Currently, the most effective non-invasive treatment for endometriosis, considering both potential side effects and benefits, is hormonal therapy (9,10). Hormonal treatments can be classified into long-term and short-term options. Long-term treatments include combined hormonal contraceptives (CHCs), progestins, aromatase inhibitors, selective estrogen receptor modulators (SERMs), nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. Among these, CHCs and progestins are the first-line treatments due to their

mild, well-tolerated side effects, safety for long-term use, and affordability (11). Short-term treatments consist of gonadotropin-releasing hormone (GnRH) antagonists and analogs, though their menopause-like side effects—such as total estrogen suppression leading to significant bone loss and vasomotor symptoms—restrict their use to a maximum of six months (9,12).

However, efforts are being made to extend the duration of short-term hormonal therapies by exploring the potential effectiveness of combining them with CHCs and progestins (12,13).

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6 OBJECTIVES

6.1 Study I. - Comparing CL and RAL in terms of endometriosis surgeries

I wanted to compare the effectiveness and safety of conventional laparoscopy and robot-assisted surgery. To compare CL and RAL I wanted to compare the differences between the perioperative complications, the blood loss with the 2 types of procedures, the length that the surgeries take, and the length of hospital stays.

6.2 Study II. – Comparing the available medical treatment methods of endometriosis

I also wanted to compare the available medical treatments for endometriosis-related pain: I compared the available medications for dysmenorrhea, dyspareunia, and for overall pelvic pain.

7 METHODS

In methods section, I would like to summarize the methods, I used in order to compare the effectiveness and safety of CL and RAL in endometriosis and the methods I used to compare the available medications for endometriosis-related pain.

7.1 Study I.

In this section I try to summarize the methods that my colleagues and I used during the comparison of conventional laparoscopy and robot-assisted surgery. Our systematic review and meta-analysis were reported to comprehend the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 Statement (14). The review followed the recommendations of the Version 6.3 of Cochrane Handbook for Systematic Reviews of Interventions (15). The presented review was registered on PROSPERO (York, UK) with the registration number of CRD42023397045.

7.1.1 Literature search and eligibility criteria

A systematic literature search was performed using three medical databases, MEDLINE (via PubMed), Cochrane Library (CENTRAL), and Embase on the February 15th of 2023. The primary domains of the search key were the words „endometriosis”, „robot-assisted surgery”, and „laparoscopy”. Case reports, case series, conference abstracts, trial protocols, letters, and reviews got excluded. Language, or any kind of other restrictions were not used.

Papers were selected as eligible if they met our PICO (Population, Intervention, Comparison, Outcome) framework. Articles included if they were published on premenopausal women who underwent endometriosis surgery (P). The diagnosis of endometriosis was based on either of the following criteria: clinical symptoms, imaging techniques, surgery findings, or histologic results. The studies that got included required robot-assisted surgery as an intervention (I) compared to the conventional laparoscopic approach (C). The outcomes were different perioperative outcomes. These outcomes were all types of intra-, and postoperative complications, operative time, operating room time, anesthesia time, number of recurrences, blood loss (estimated), and the length of hospital stay following surgery (O). Another important criterion was that the included studies had to define the outcomes mentioned above in the same way for the two surgical approaches.

7.1.2 Study selection and data extraction

During the selection and data collection period EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) was used for duplicate removal, rayyan.ai for title-abstract selection, and EndNote X9 for full-text selection. On all levels of the selection stage, two independent authors screened the publications, the disagreements were resolved by the involvement of a third, independent author.

Two authors extracted the data independently into predefined Excel spreadsheets (Office 365, Microsoft, Redmond, WA, USA). All the following data were extracted from each papers that were selected as eligible: name of the first author, the year of publication, study type, study location, number of centers involved in the study, study design, demographic data (sample size, age, body mass index (BMI), infertility presence, previous surgeries, details of procedures, and number of surgeons performing the operations) and data for the outcomes for statistical analysis. Discrepancies were solved by the involvement of a third reviewer. Cohen's kappa coefficient (κ) was calculated after each phase in order to measure interrater reliability (16).

7.1.3 Quality assessment

The quality of the outcomes was assessed separately by two reviewers using the risk of bias tool Risk Of Bias In Non-randomized Studies—of Interventions (ROBINS-I) for non-randomized- and RoB 2 for randomized trials. Any occurring discrepancies were resolved by a third author. The VISualization (Robvis) tool was used to visualize the results (17).

The recommendations that were set up by the workgroup "Grades of Recommendation, Assessment, Development, and Evaluation (GRADE)" were strictly followed to closely evaluate the quality of evidence (18).

7.1.4 Data synthesis and analysis

The odds ratio (OR) with a 95% confidence interval (CI) was employed to assess the impact of intra- and postoperative complications, while mean differences (MDs) were utilized for outcomes related to operation durations. To determine the OR, the total number of patients in each group and the number of those experiencing the event of interest were extracted from each study. For continuous outcomes, between-group mean

differences and standard deviations (SDs) were used to calculate the effect size. Data from the selected studies were combined using a random-effects model, applying the Mantel–Haenszel method with the Hartung–Knapp adjustment (19,20). In order to estimate $\tau 2$, the Paule-Mandel method was used and the Q profile method was used to calculate the CI of $\tau 2$. A funnel plot of the logarithm of effect size versus the standard error for each trial was used to assess publication bias.

Statistical heterogeneity between trials was evaluated using the Cochrane Q test and I^2 statistic. Outlier and influence analyses were conducted based on the guidelines of Harrer et al. and Viechtbauer and Cheung (19,21). Forest plots were used to visually summarize the results. When relevant, prediction intervals (i.e., the anticipated range of effects for future studies) were reported, following the recommendations of IntHout et al. 2016 (22). All analyses were performed using R version 4.1.3, using the 'meta' and 'dmetar' packages (23–25).

7.2 Study II.

In this section my goal is to summarize the methods that we used in order to compare the available medical treatments for endometriosis-related pain. First, we reported our systematic review and network meta-analysis based on the recommendation of the PRISMA 2020 Statement (14).

The review followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions, Version 6.3.8 (26). The presented review was registered on PROSPERO (York, UK) with the registration number of CRD42022374466.

7.2.1 Literature search and eligibility criteria

A comprehensive search was conducted on May 14, 2023, with the usage of the three presented databases: MEDLINE (via PubMed), Cochrane Library (CENTRAL) and Embase. We also looked for potentially unpublished trials on the clinical trials' registry (http://clinicaltrial.gov) webpage, to widen the range of our study and to find every possible data that were currently available back at the time of the comprehensive search. The main components of the search key were endometriosis, pain-relief substances, pain and "random" to find randomized control trials (RCTs). Language criteria or other possible filters were not used.

Papers on premenopausal women who were previously diagnosed with endometriosis (P-Population) were included. The diagnosis of endometriosis was based on either of the following criteria in all articles: clinical symptoms and/or imaging methods and/or laparoscopic findings, and/or histological findings. The studies included evaluated different pain medications for endometriosis (I-Intervention), comparing them to placebo or other treatments for the condition (C-Comparison). The outcomes measured were the reduction in various pain symptoms (overall pelvic pain, dysmenorrhea, dyspareunia) at three and six months after starting treatment (O-Outcome). Pain was assessed using either a visual analog scale (VAS) ranging from 0–10 or a numerical rating scale (NRS) from 0–100. Data from the endometriosis-specific Biberoglu and Behrman scale, which ranges from 0–3, were also included.

Those RCTs were selected as eligible that included premenopausal adult female patients presenting with clinically suspected (based on either symptoms and/or imaging-methods) and/or diagnosed with laparoscopic techniques and/or endometriosis as confirmed by histological methods.

The investigations aimed to assess the effectiveness of various medical treatments for managing endometriosis-related pain, including but not limited to: GnRH agonists, GnRH agonists with add-back therapies, GnRH antagonists, GnRH antagonists with add-back therapies, combined hormonal contraceptives (CHCs), progestins, danazol, gestrinone, mifepristone, aromatase inhibitors, selective estrogen receptor modulators (SERMs), cyproterone, NSAIDs, and opioids. We also looked for studies reporting outcomes such as changes in total endometriosis-related pelvic pain scores, dysmenorrhea scores, dyspareunia scores, dyschezia scores, and dysuria scores. We excluded cross-over trials, expectant management, articles lacking outcome data at three or six months, single-arm studies, and those assessing surgical interventions or combining medications with surgical interventions. Studies without network connections were also excluded after data extraction.

7.2.2 Study selection and data extraction

For duplicate removal EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) was used, rayyan.ai was used for title-abstract selection, and EndNote X9 was used for full-text selection. On every level of the selection process, two independent reviewers

screened the publications, and any occurring disagreements were resolved by the involvement of a third reviewer.

Two authors extracted the data independently into predefined Excel spreadsheets (Office 365, Microsoft, Redmond, WA, USA). From the articles that were selected as eligible the following data were extracted: the names of the first authors, publication year, type of the study, study location, number of centers involved, design of the study, demographic data (sample size, age) and data for the outcomes for statistical analyses. Any occurring discrepancies were solved through the involvement of a third reviewer. Cohen's kappa coefficient (κ) was computed after each step in order to assess the interrater reliability (16).

7.2.3 Quality assessment

The quality of the articles was assessed separately by two reviewers using the risk of bias tool RoB 2. Any disagreements were resolved by the involvement of a third reviewer.

CINeMA (Confidence in Network Meta-Analysis) was used to evaluate the confidence in the findings of the network meta-analysis (27).

7.2.4 Data synthesis and analysis

Before conducting network meta-analyses, network geometries for each outcome were visualized using network plots to evaluate whether the treatments in the included studies were interconnected (28) In case an article presented several doses of a given drug, we selected the dose that was deemed most effective by the authors.

All examined outcomes were continuous; therefore MD was calculated as the effect size measure. A common estimate for heterogeneity was assessed across the different comparisons. As it was anticipated prior, considerable between-study heterogeneity was present, so a random-effects model was used to pool effect sizes. The calculation was made in a frequentist framework following the description of Harrer et al. (19). Multi-arm study correlation was also taken into consideration.

To assess inconsistency, the loop-specific approach was used. This method evaluates the consistency assumption by comparing direct and indirect estimates for a specific comparison within each closed loop of treatments. Inconsistency was considered

acceptable if the indirect estimate, along with its 95% confidence interval, fell within the 95% confidence interval of the direct estimate for the same treatment comparison.

Additionally, ranking probabilities for all treatments were calculated to establish a treatment hierarchy for each outcome. Primarily, p-scores were used, which provided the probability that a given treatment ranks first among the included treatments. Moreover, surface under the cumulative ranking (SUCRA) plots were also analyzed (29).

A comparison-adjusted funnel plot was created to assess network-wide publication bias and small study effect for outcomes with works with at least 10 studies in the network (30).

The results were displayed using various plots to facilitate comparison between treatments. Forest plots were used to compare treatments more easily, while p-scores and SUCRA plots illustrated the treatment rankings. Netsplit plots were employed to highlight any potential inconsistencies, and funnel plots were utilized to assess publication bias. Additionally, direct evidence plots were included to evaluate the reliability of effect size estimates within the network meta-analysis model.

All calculations were done with the help of the R-statistical software (version 4.2.3; R Core Team, 2023) (31) Netmeta and BUGSnet packages were used for anaylses visualisation (32,33).

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8 RESULTS

8.1 Study I - Comparison the effectiveness and safety of CL and RAL

8.1.1 Screening and selection

A total of 2,014 studies were identified during the search. After removal of 1,382 duplicates, remained 632 eligible studies by title abstract, of which 38 were eligible for full-text selection.

At the end, 13 articles were selected tot he meta-analyses and the data was extracted from these 13 articles (**Figure 1**).

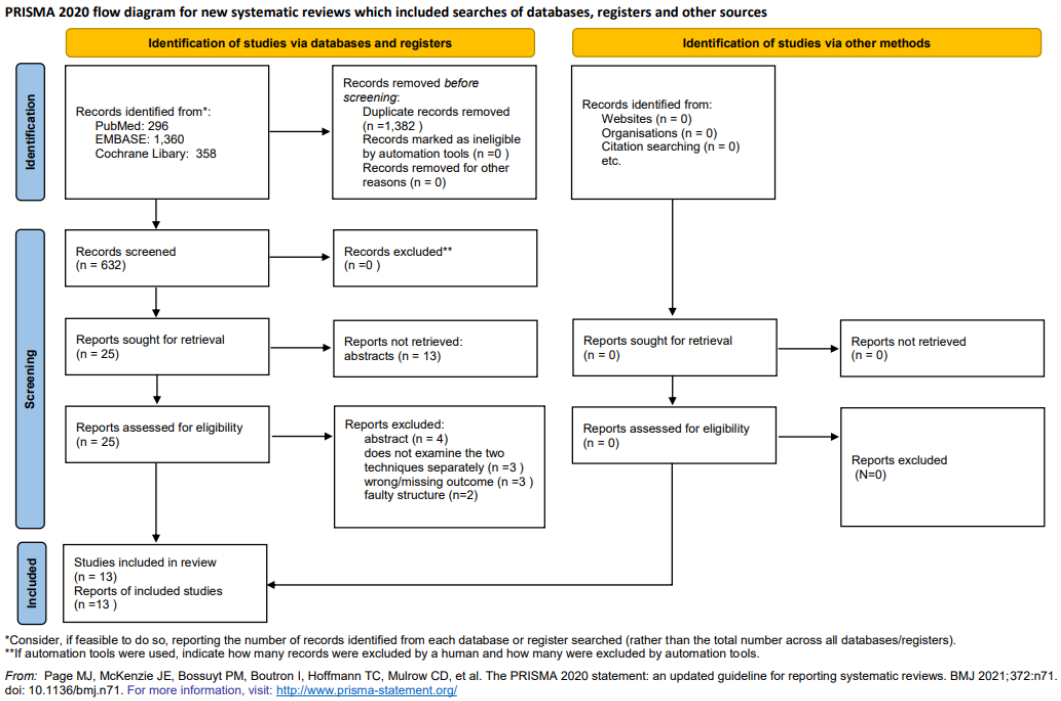

Figure 1 *– The PRISMA flowchart of the selection process (Figure 1 was published in Csirzó Á, Kovács DP, Szabó A, et al. Robot-assisted laparoscopy does not have demonstrable advantages over conventional laparoscopy in endometriosis surgery: a systematic review and meta-analysis. Surg Endosc. 2024;38(2):529-539. doi:10.1007/s00464-023-10587-9)*

8.1.2 Characteristics of the selected studies

Of the 13 included articles, one was an RCT, four were prospective, and eight were retrospective cohort studies, all studies were published between the years of 2010 and 2022. Eleven of the selected articles implemented multiport laparoscopic surgery, only two of them applied the single port technique (34,35). Ten studies reported the type of

robot that was used during their respective studies, in all cases this robot was the da Vinci robot. Ten studies reported the number of surgeons performing the surgeries, this number was ranging from one to five. Ten articles evaluated the experience of the surgeons: the expertise of the surgeons based on subjective reports and/or metric scales, in all cases according to their subjective scales, the surgeons performing endometriosis surgeries were experts.

In the CL group 1,009, in the RAL group 1,012 patients got selected. Baseline data are summarized on **Table 1**.

Table 1 – *Basic characteristics of the selected studies (Table 1 was published in Csirzó Á, Kovács DP, Szabó A, et al. Robot-assisted laparoscopy does not have demonstrable advantages over conventional laparoscopy in endometriosis surgery: a systematic review and meta-analysis. Surg Endosc. 2024;38(2):529-539. doi:10.1007/s00464-023-10587-9)*

Author	**Year**	**Study type**	**rASRM stage**	**No. of. surgeons**	**Group**	**Sample size**	**Age**	**BMI**
Ferrier (36)	2022	p	II./III./IV.	3	RAL	61	36±7	25±5
					CL	61	35±7	26±8
Raimondo (37)	2021	p	III./IV.	1	RAL	22	38±7	24.5 (21;27)
					CL	22	36±5	22.5 (21;24)

Hiltunen (38)	2021	r	I./II./III./IV.	N.A.	RAL	18	N.A.	24 [18;38]
					CL	76	N.A.	26 [19;39]
Lee (35)	2020	p	N.A. (just ovarian)	N.A.	SP-RAL	40	28.6±5.8	21.28 ±3.78
					SP-CL	54	30.69±5.82	20.37 ±2.36
Le Gac (39)	2020	p	III./IV.	2	RAL	23	25±3	25±3
					CL	25	37±8	25±4
Moon (34)	2018	r	I./II./III./IV.	3	SP-RAL	68	32.4±6.8	23.1± 3.4
					SP-CL	52	33.1±7.9	21.1± 3
Soto (40)	2017	RCT	I./II./III./IV.	5	RAL	35	34.3±7.2	26.1± 5.2
					CL	38	34.5±8.5	24.8± 5.9

Le Carpentier (41)	2016	r	N.A. (just bladder)	1	RAL	15	28.5 [N.A.;N.A.]	23.8 (N.A.; N.A.)
					CL	22	29 [N.A.;N.A.]	21.9 (N.A.; N.A.)
Nezhat (42)	2015	r	III./IV.	1	RAL	147	30 [21;38]	23 [19;32]
					CL	273	31 [19;42]	23 [19;29]
Magrina (43)	2015	r	III./IV.	3	RAL	331	40±10.1	26.1± 5.9
					CL	162	38.3±10.7	25.5± 5.7
Nezhat (44)	2014	r	III./IV.	1	RAL	147	39 [34;44]	27.36 [23.9; 34.09]
					CL	86	38 [31;44]	24.53 [22.27

								;26.96]
Dulemba (45)	2013	r	I./II./III./IV.	1	RAL	180	32.6±9.7	27.9±7.7
					CL	100	29.2±9.2	26.8±11.9
Nezhat (46)	2010	r	I./II./III./IV.	N.A.	RAL	40	35	24 [19;37]
					CL	38	33	23 [18;31]

The mean ages and BMIs among the groups were rather similar, along with the severity of the endometriosis that was surgically treated. However, the latter varied between studies; five studies included only severe cases of endometriosis (37,39,42–44), but this was not used as a selection criterion. In terms of study designs, the study by Soto et al. (40), the only RCT which got included to the meta-analysis, was considered the highest quality. However, its main limitation was the inclusion of not only the diagnosed but the suspected cases with endometriosis as well. Another limitation was that data on anesthesia time and postoperative recurrence were not thoroughly presented, making them unsuitable for analysis.

8.1.3 Results of the intraoperative complications

Firstly, we examined the intraoperative complications, which for data was presented in 11 selected articles. It is important to highlight that only the number of the detected complications were presented, their type was not specified. Our result was that there was no between-group differences regarding the number of complications (OR = 1.07, CI

0.43–2.63). The relative frequency of complications in the RAL group was 1.21% and 1.32% in the CL group. Data are presented on **Figure 2**.

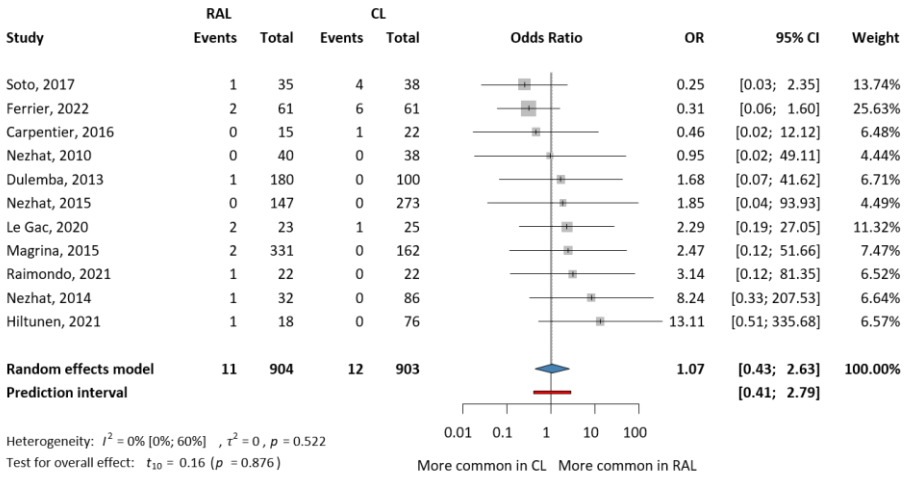

Figure 2 – *Comparison of RAL and CL regarding the odds ratio of intraoperative complications (measured in event numbers) (Figure 2 was published in Csirzó Á, Kovács DP, Szabó A, et al. Robot-assisted laparoscopy does not have demonstrable advantages over conventional laparoscopy in endometriosis surgery: a systematic review and meta-analysis. Surg Endosc. 2024;38(2):529-539. doi:10.1007/s00464-023-10587-9)*

The number of postoperative complications were also presented in 11 articles, with the exact timing of the complication was not presented. Our result was that there was no between-group differences regarding the number of postoperative complications (OR = 1.3, CI 0.73–2.32). Data are presented on **Figure 3**. The relative frequency of postoperative complications in the RAL group was 7.96%, and 10.07% in the CL group. Additionally, four articles classified these complications using the Clavien-Dindo system, yielding results consistent with those of previous studies.

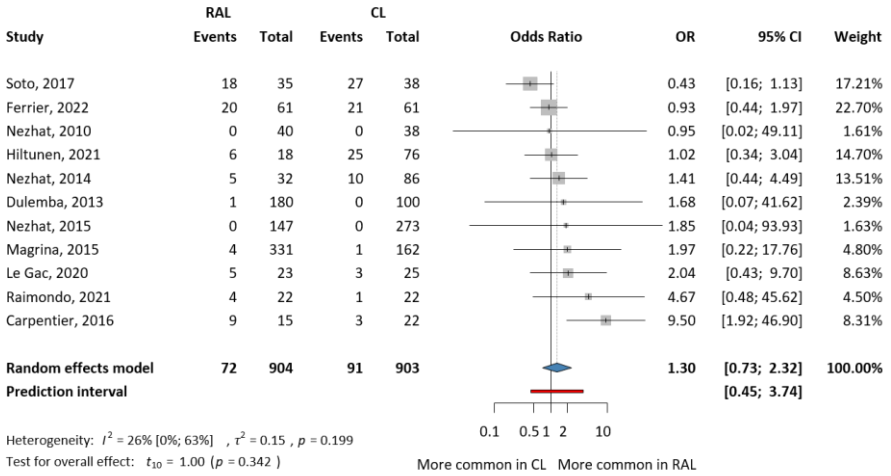

Figure 3 - *Comparison of RAL and CL regarding the odds ratio of postoperative complications (measured in event numbers)(Figure 3 was published in Csirzó Á, Kovács DP, Szabó A, et al. Robot-assisted laparoscopy does not have demonstrable advantages over conventional laparoscopy in endometriosis surgery: a systematic review and meta-analysis. Surg Endosc. 2024;38(2):529-539. doi:10.1007/s00464-023-10587-9)*

The number of laparotomy conversions to open surgery was investigated in 10 articles with the result that neither CL nor RAL had clinically relevant, higher conversion rates (OR = 1.34, CI 0.76–2.37). Data are presented on **Figure 4**. The relative frequencies of conversions in the RAL group were 0.74% and were 0.49% in the CL group. The number of rehospitalizations was evaluated in 3 articles. No significant difference was observed between the two procedures (OR = 0.95, CI 0.13–6.75).

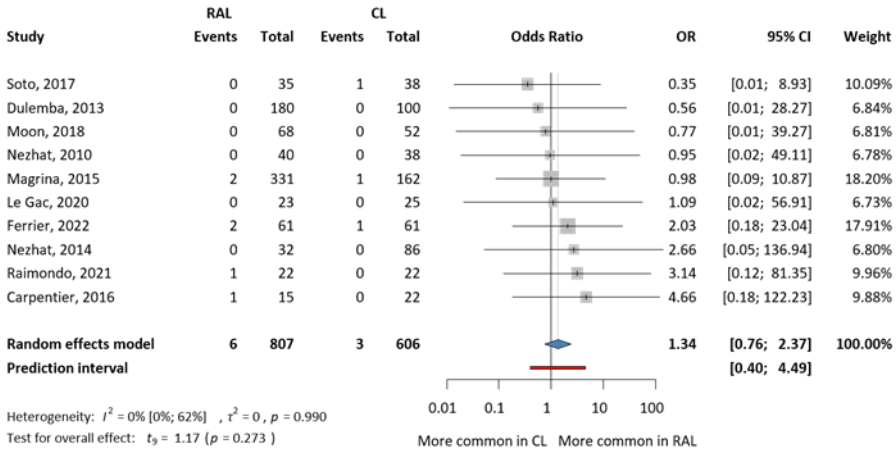

Figure 4 - *Comparison of RAL and CL regarding the ratio of conversions to open surgery (measured in event numbers) (Figure 4 was published in the Supplementary Materials of Csirzó Á, Kovács DP, Szabó A, et al. Robot-assisted laparoscopy does not have demonstrable advantages over conventional laparoscopy in endometriosis surgery: a systematic review and meta-analysis. Surg Endosc. 2024;38(2):529-539. doi:10.1007/s00464-023-10587-9)*

8.1.4 Comparison of estimated blood loss

During-surgery blood loss measured in milliliters was examined in 11 articles, 1 article (Lee 2020) reported blood loss in grams of hemoglobin per deciliter, so these data were excluded from the analysis. Approximately during RAL surgeries the blood loss was 16 ml higher, but this data not clinicaly nor statisticaly significant (MD = 16.73, CI 4.18–37.63) Data are presented on **Figure 5**.

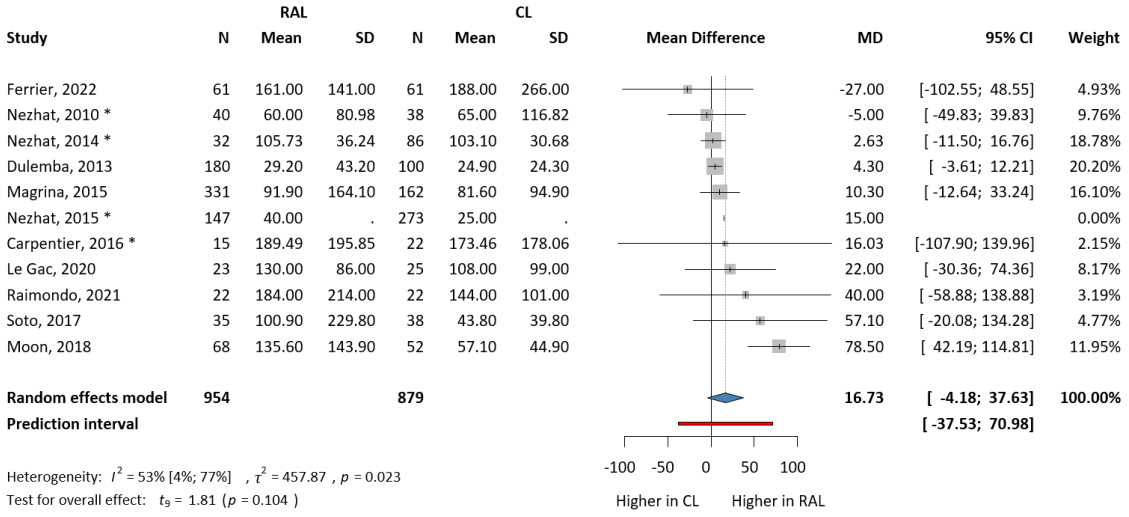

Figure 5 – *Comparison of RAL and CL regarding the mean differences of the estimated blood loss during the procedures (measured in millilitres) (Figure 5 was published in the Supplementary Materials of Csirzó Á, Kovács DP, Szabó A, et al. Robot-assisted laparoscopy does not have demonstrable advantages over conventional laparoscopy in endometriosis surgery: a systematic review and meta-analysis. Surg Endosc. 2024;38(2):529-539. doi:10.1007/s00464-023-10587-9)*

8.1.5 Comparison of the lengths of the procedures

The operative time, measured in minutes from skin incision to wound closure was evaluated in 12 articles: For robot-assisted technique, time included the time that docking and undocking takes. The results shown that operative time took almost half an hour longer with RAL. This result can be considered relevant both clinicaly and statisticaly (MD = 28.09, CI 11.59–44.59). Data are presented on **Figure 6**.

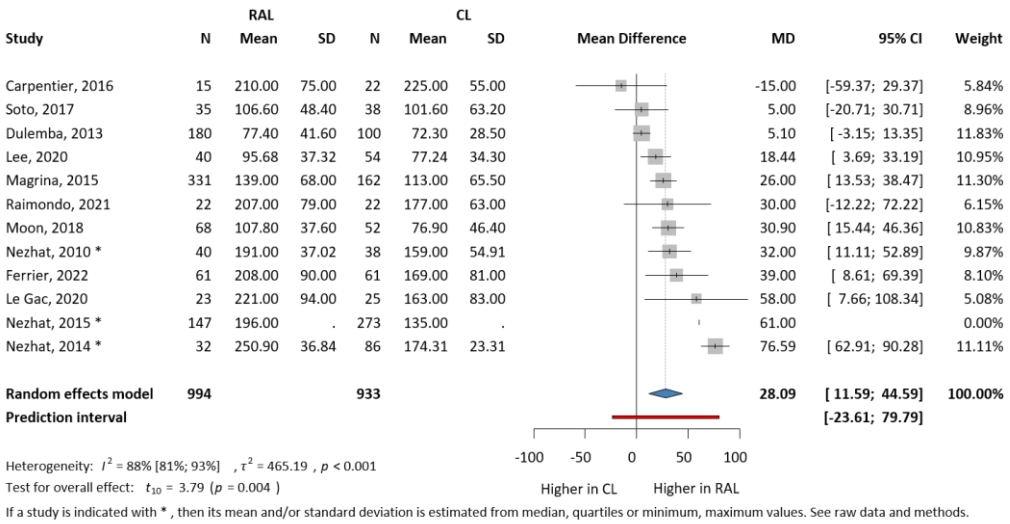

Figure 6 – *Comparing RAL and CL regarding mean difference of operating times (measured in minutes) (Figure 6 was published in Csirzó Á, Kovács DP, Szabó A, et al. Robot-assisted laparoscopy does not have demonstrable advantages over conventional laparoscopy in endometriosis surgery: a systematic review and meta-analysis. Surg Endosc. 2024;38(2):529-539. doi:10.1007/s00464-023-10587-9)*

Three studies evaluated the time spent in the operating room, measured in minutes from patient arrival to departure, including docking and undocking times for RAL. The results similarly favored CL (MD = 51.39, CI 15.07–87.72), showing clinical relevance and statistical significance. Data are presented on **Figure 7**.

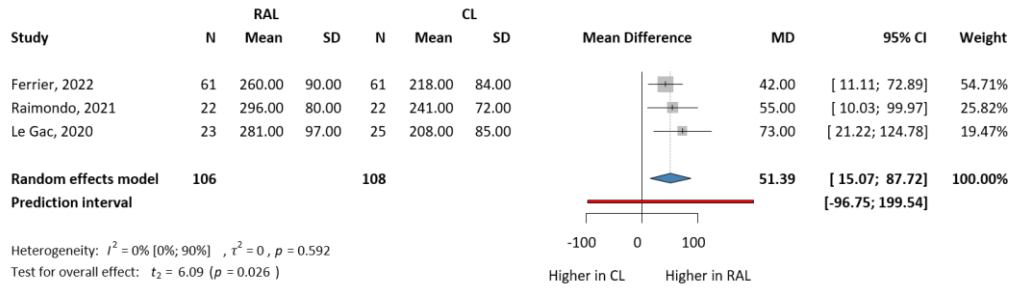

Figure 7 – *Comparing RAL and CL regarding time spent in the operating room (measured in minutes) (Figure 7 was published in Csirzó Á, Kovács DP, Szabó A, et al. Robot-assisted laparoscopy does not have demonstrable advantages over conventional laparoscopy in endometriosis surgery: a systematic review and meta-analysis. Surg Endosc. 2024;38(2):529-539. doi:10.1007/s00464-023-10587-9)*

8.1.6 The length of hospital stay

The number of days spent in hospital following the surgery was compared in 8 studies: showing no relevant clinical or statistical (MD = 0.12, CI 0.33–0.57) differences **Figure 8**.

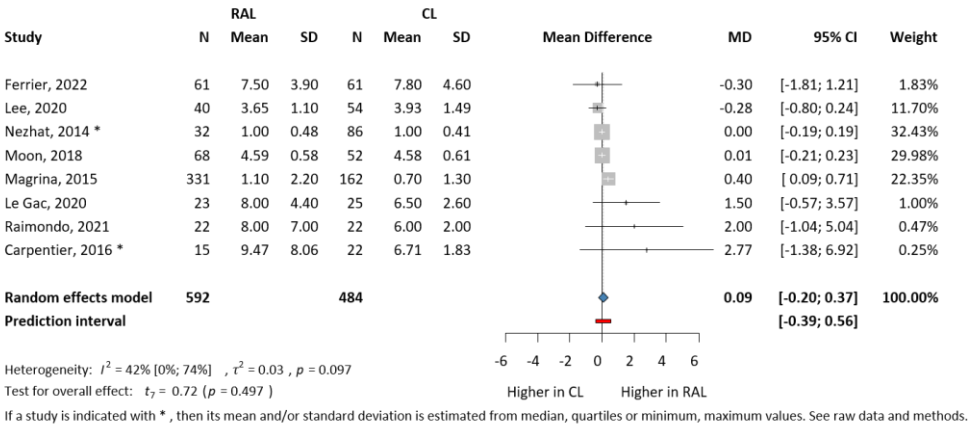

Figure 8 - *Comparing RAL and CL regarding the mean difference of length of hospital stay (measured in days) (Figure 8 was published in the Supplementary Material of Csirzó Á, Kovács DP, Szabó A, et al. Robot-assisted laparoscopy does not have demonstrable*

advantages over conventional laparoscopy in endometriosis surgery: a systematic review and meta-analysis. Surg Endosc. 2024;38(2):529-539. doi:10.1007/s00464-023-10587-9)

8.2 Study II – Comparative analysis of medical interventions in endometriosis

8.2.1 Screening and selection

In total, our systematic search identified 1,314 studies. After removing duplicates and screening the remaining records, we identified 45 studies eligible for qualitative and quantitative synthesis. The selection process is shown in **Figure 9**.

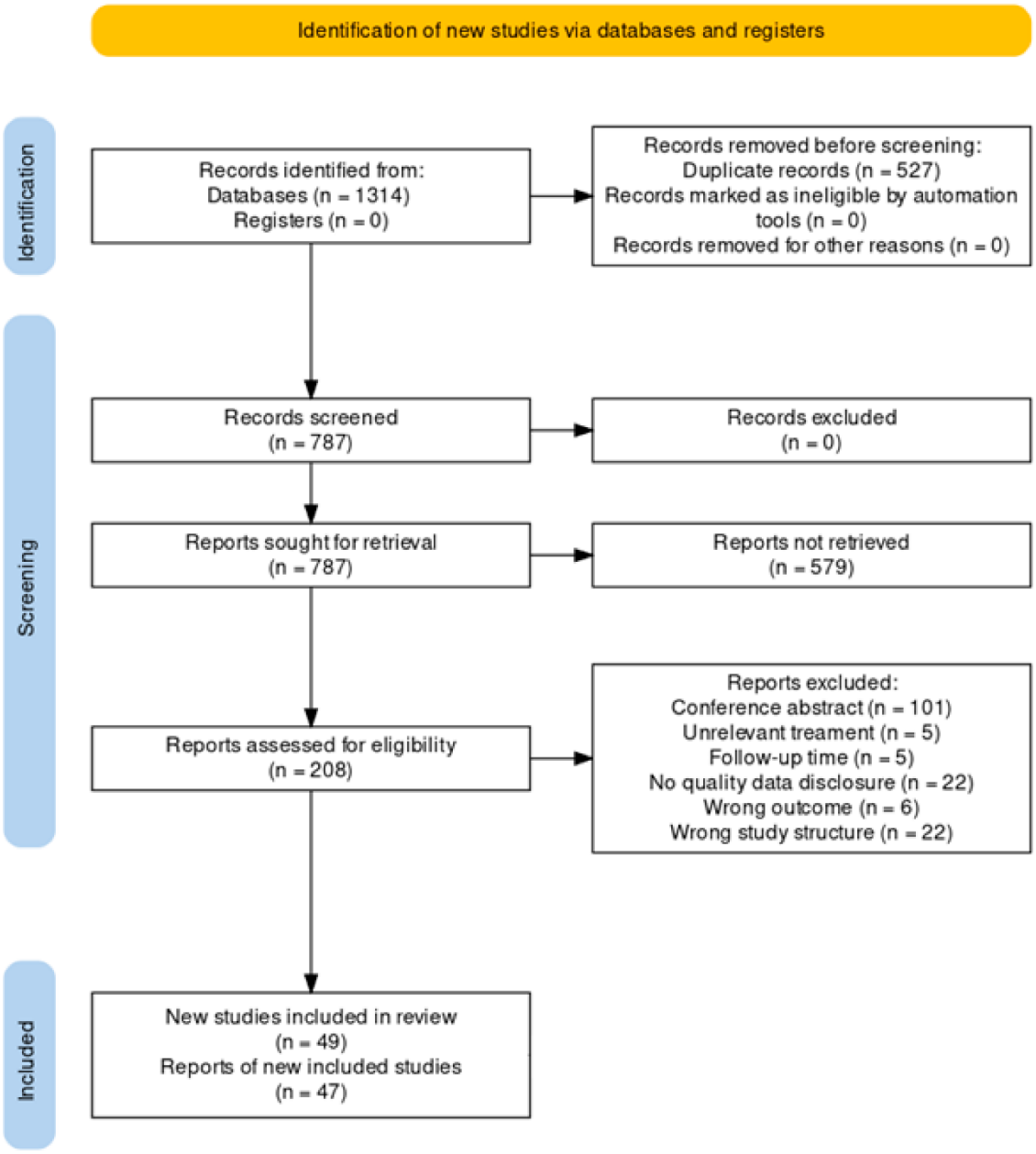

Figure 9 – *PRISMA flow diagram detailing the selection process (Figure 9 was published in Csirzó Á, Kovács DP, Szabó A, et al. Comparative Analysis of Medical Interventions to Alleviate Endometriosis-Related Pain: A Systematic Review and Network Meta-Analysis. J Clin Med. 2024;13(22):6932. Published 2024 Nov 18. doi:10.3390/jcm13226932)*

8.2.2 Basic characteristics of the selected studies

In total, 10,529 patients were involved from 16 different countries between 1987 and 2022.

8.2.3 Outcomes

Including the placebo group, a total of 15 treatments and treatment combinations were evaluated. Due to limited data, we were not able to compare all drugs directly with each other. The active substances and their combinations were categorized into 16 broader groups based on their mechanisms of action, as detailed in **Table 2**.

Table 2 - *Final active ingredient groups following merging of substances (Table 2 was published in the Supplementary Material of Csirzó Á, Kovács DP, Szabó A, et al. Comparative Analysis of Medical Interventions to Alleviate Endometriosis-Related Pain: A Systematic Review and Network Meta-Analysis. J Clin Med. 2024;13(22):6932. Published 2024 Nov 18. doi:10.3390/jcm13226932)*

1.	GnRH antagonists
2.	GnRH agonists
3.	CHCs
4.	progestins
5.	GnRH agonists + progestins
6.	aromatase inhibitors + progestins
7.	GnRH agonists + CHCs
8.	LNG-IUDs
9.	aromatase inhibitors + CHCs
10.	danazol
11.	CHCs + danazol
12.	GnRH agonists + aromatase inhibitors
13.	gestrinone
14.	mifepristone + gestrinone
15.	GnRH antagonists combination
16.	SERM

Outcomes were measured using two scales: 0–100 and 0–3, with higher scores indicating greater pain intensity. The study focused on three types of pain: overall pelvic pain, dysmenorrhea, and dyspareunia. Follow-up data were collected at three and six months, resulting in 12 combinations of follow-up time, pain scale, and type of pain. However,

certain data points—dysmenorrhea (0–3 scale) at six months, dyspareunia (0–3 scale) at three and six months, and overall pelvic pain (0–3 scale) at six months—were excluded due to an insufficient number of studies. Consequently, eight networks were analyzed. Data on additional pain aspects, such as pelvic tenderness, pelvic induration, dyschezia, and dysuria, were unavailable for inclusion in the network analysis.

8.2.4 Dysmenorrhea, on a scale 0-100, after 3 months

Five articles evaluated a total of six types of treatments on dysmenorrhea, scaling from 0 to 100, following three months of treatment (47–50). GnRH agonists recorded the highest p-score (0.618) deeming it to be the best option, and the lowest p-score was achieved by placebo (0.268). Although it is important to note that none of the drugs showed significant difference compared to placebo groups. Data are presented on **Figure 10**.

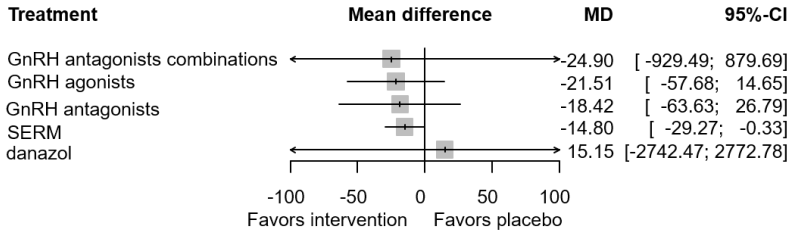

Figure 10 - *Forest plot of dysmenorrhea on a scale of 0-100 after 3 months (Figure 10 was published in the Supplementary Material of Csirzó Á, Kovács DP, Szabó A, et al. Comparative Analysis of Medical Interventions to Alleviate Endometriosis-Related Pain: A Systematic Review and Network Meta-Analysis. J Clin Med. 2024;13(22):6932. Published 2024 Nov 18. doi:10.3390/jcm13226932)*

8.2.5 Dysmenorrhea, on a scale 0-3, after 3 months

Three articles evaluated a total of four types of treatments regarding dysmenorrhea, scaling from 0 to 3, following three months of treatment (12,51,52). GnRH agonists recorded the highest p-score again (0.828) and the lowest p-score was achieved by placebo, again(0.145). Although it is important to note that again, none of the drugs showed significant difference compared to placebo groups. Forest plot is presented on **Figure 11**.

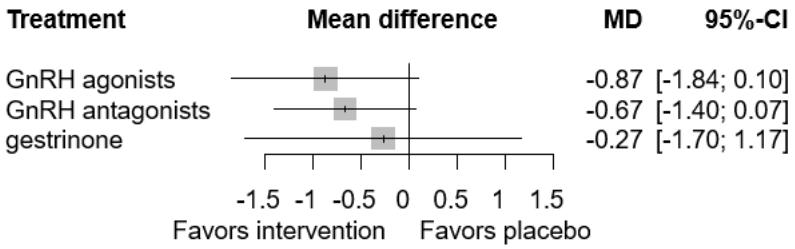

Figure 11 - *Forest plot of dysmenorrhea on a scale of 0-3 after 3 months (Figure 11 was published in the Supplementary Material of Csirzó Á, Kovács DP, Szabó A, et al. Comparative Analysis of Medical Interventions to Alleviate Endometriosis-Related Pain: A Systematic Review and Network Meta-Analysis. J Clin Med. 2024;13(22):6932. Published 2024 Nov 18. doi:10.3390/jcm13226932)*

8.2.6 Dysmenorrhea, on a scale 0-100, after 6 months

Ten articles evaluated a total of seven types of treatments regarding dysmenorrhea, scaling from 0 up to 100, following six months of the treatment (13,48,53–60). GnRH agonists combined with CHCs achieved the highest p-score (0.649) and CHCs the lowest (0.339). Data is presented on **Figure 12**. No articles were available that examined placebo, as a result of this fact, CHCs were chosen as reference. None of the examined drug (groups) showed a statistically significant difference compared to CHCs.

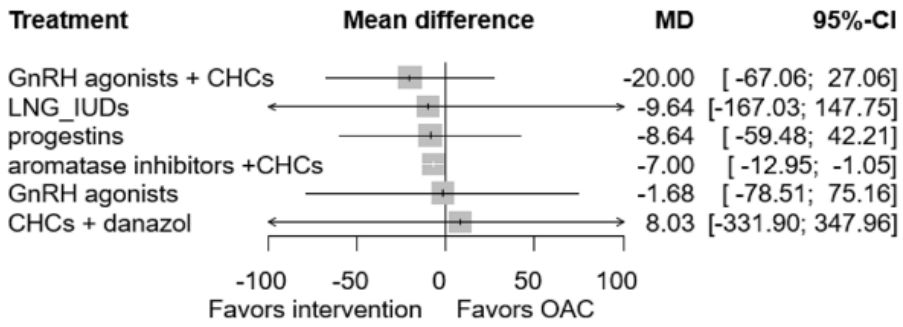

Figure 12 – *Forest plot of dysmenorrhea, on a scale 0-100, after 6 months (Figure 12 was published in Csirzó Á, Kovács DP, Szabó A, et al. Comparative Analysis of Medical Interventions to Alleviate Endometriosis-Related Pain: A Systematic Review and Network Meta-Analysis. J Clin Med. 2024;13(22):6932. Published 2024 Nov 18. doi:10.3390/jcm13226932)*

8.2.7 Dyspareunia, on a scale of 0-100, after 3 months

Seven articles evaluated a total of seven types of treatments regarding dyspareunia, scaling from 0 to 100, following three months of treatment (47–49,57,58,61,62). CHCs achieved the highest p-score (0.805), and placebo the lowest one (0.381). None of the examined drugs showed a statistically significant difference compared to placebo. Forest plot of the result is presented on **Figure 13**.

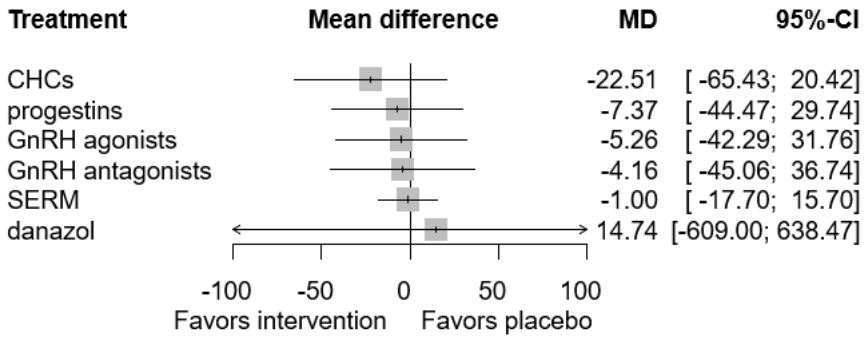

Figure 13 – *Forest plot of dyspareunia, on a scale of 0–100, after 3 months (Figure 13 was published in the Supplementary Material of Csirzó Á, Kovács DP, Szabó A, et al.*

Comparative Analysis of Medical Interventions to Alleviate Endometriosis-Related Pain: A Systematic Review and Network Meta-Analysis. J Clin Med. 2024;13(22):6932. Published 2024 Nov 18. doi:10.3390/jcm13226932)

8.2.8 Dyspareunia, on a scale of 0-100, after 6 months

Eleven articles evaluated a total of eight types of treatments regarding dyspareunia, scaling from 0 to 100, following six months of treatment (13,48,54,56–60,63,64). CHCs combined with aromatase inhibitors got the highest p-score (0.677) and SERMs the lowest p-score (0.315). Once again, none of the drugs showed a statistically significant difference compared to placebo. Forest plot of the result is presented on **Figure 14**.

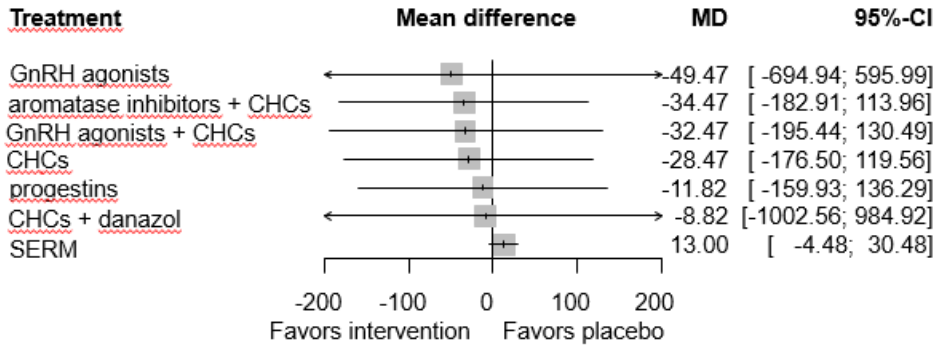

Figure 14 - *Forest plot of dyspareunia on a scale of 0-100 after 6 months (Figure 14 was published in the Supplementary Material of Csirzó Á, Kovács DP, Szabó A, et al. Comparative Analysis of Medical Interventions to Alleviate Endometriosis-Related Pain: A Systematic Review and Network Meta-Analysis. J Clin Med. 2024;13(22):6932. Published 2024 Nov 18. doi:10.3390/jcm13226932)*

8.2.9 Overall pelvic pain, on a scale of 0-100, after 3 months

A total of fifteen articles evaluated seven types of treatments regarding overall pelvic pain, scaling from 0 to 100 following three months of treatment (47,52,62,65–76). Only GnRH agonists and antagonists showed a statistically significant difference compared to

placebo. However, CHCs received the highest p-score (0.751), and placebo the lowest (0.179). Forest plot of the result is presented on **Figure 15**.

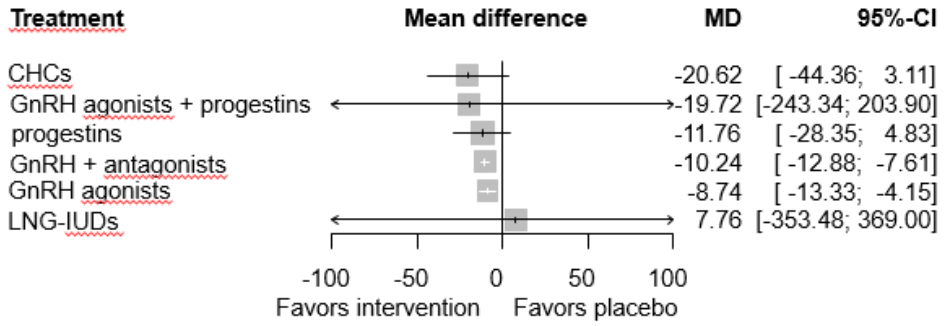

Figure 15 – *Forest plot of overall pelvic pain on a scale of 0-100 after 3 months (Figure 15 was published in the Supplementary Material of Csirzó Á, Kovács DP, Szabó A, et al. Comparative Analysis of Medical Interventions to Alleviate Endometriosis-Related Pain: A Systematic Review and Network Meta-Analysis. J Clin Med. 2024;13(22):6932. Published 2024 Nov 18. doi:10.3390/jcm13226932)*

8.2.10 Overall pelvic pain on a scale of 0-3, after 3 months

A total of 3 articles evaluated 4 types of treatments regarding overall pelvic pain, scaling from 0 to 3, following three months of treatment (12,77,78). Compared to placebo, progestins showed a statistically significant difference, they also achieved the highest p-score (0.901), and GnRH antagonists received the lowest (0.257). Forest plot of the result is presented on **Figure 16**.

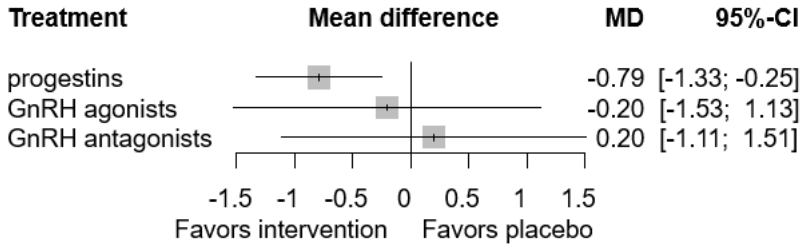

Figure 16 – *Forest plot of overall pelvic pain on a scale of 0-3 after 3 months (Figure 16 was published in the Supplementary Material of Csirzó Á, Kovács DP, Szabó A, et al. Comparative Analysis of Medical Interventions to Alleviate Endometriosis-Related Pain: A Systematic Review and Network Meta-Analysis. J Clin Med. 2024;13(22):6932. Published 2024 Nov 18. doi:10.3390/jcm13226932)*

8.2.11 Overall pelvic pain, on a scale of 0-100, after 6 months

21 articles evaluated a total of 8 types of treatments regarding overall pelvic pain, scaling from 0 to 100, following six months of treatment (54–56,63–65,69,70,73,75,76,79–88). Progestins combined with aromatase inhibitors got the highest p-score (0.873), and placebo the lowest p-score (0.091). Data are presented on **Figure 17**. None of the drugs demonstrated a statistically significant difference when compared to placebo.

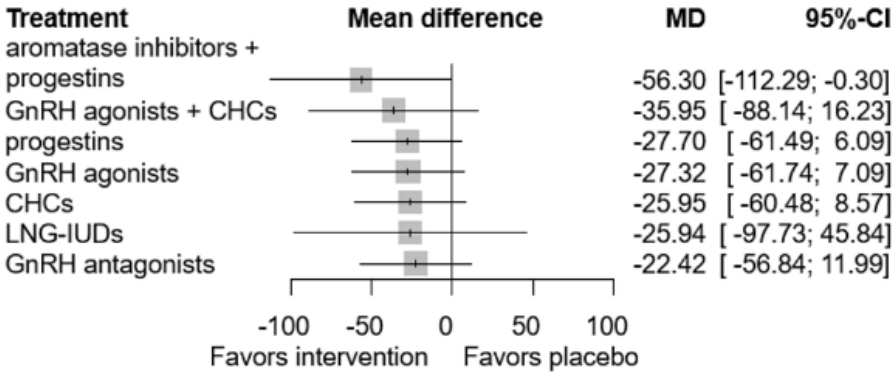

Figure 17 – *Forest plot of overall pelvic pain on a scale of 0-100 after 6 months (Figure 17 was published in Csirzó Á, Kovács DP, Szabó A, et al. Comparative Analysis of Medical Interventions to Alleviate Endometriosis-Related Pain: A Systematic Review and Network Meta-Analysis. J Clin Med. 2024;13(22):6932. Published 2024 Nov 18. doi:10.3390/jcm13226932)*

DOI:10.14753/SE.2025.3200

9 DISCUSSION

9.1 Summary of findings, international comparisons (including all studies)

The systematic review and meta-analysis that we carried out included 13 studies that compared RAL with CL in terms of perioperative outcomes of endometriosis surgeries. Our quantitative comparison confirmed that RAL had no numerical advantages over CL in the aspects we examined. Moreover, we found CL to be superior in terms of operative rooms and the length of the surgery. No subgroup analyses were feasible based on the data we extracted.

In addition to previously existing studies, we examined operating room time as a new outcome (89–91). However, similar results were observed for all other perioperative outcomes. Our findings did not demonstrate the anticipated advantages of RAL over CL regarding intra- and postoperative complications, estimated blood loss, rehospitalization rates, or length of hospital stay, and operative times were approximately 30 minutes longer with RAL. Longer surgeries can be attributed to the average docking time of a RAL surgery that lasts approximately 18.2 minutes (92).

Operating time emerged as the most significant factor linked to postoperative complications and the length of the postoperative hospital stay. According to Magrina et al. every additional 60 minute of operating time increases the odds of postoperative complications and prolonged hospital stay by 57%, and 103%, respectively (43). This can partly attributed to the disproportionate patient distribution. In some of the included articles, the more radical procedures (e.g. endometriosis surgery performed alongside a hysterectomy) were performed and patients with more advanced endometriosis were operated on with RAL according to the revised American Society for Reproductive Medicine (rASRM) staging. This may suggest that the surgeon's preference for a robotic approach introduced bias into the results, potentially influencing the differences in operating times (38,43). Although, during our work we did not find significant differences in rASM classification between CL and RAL. However, Nezhat et al. suggest that procedures for the treatment of severe endometriosis require an increased number in exchanges of camera and instrument, enabling CL to be easier to perform (42).

It is also important to note that the only included RCT found the mean operative time and blood loss within the range of time and volumes previously reported by other

nonrandomized studies. This data suggests that their findings are not likely to be related to bias that are related to the experience of the surgeon, who performs the surgery, or bias related to patient selection (41). As it was expected prior, studies that were focusing on more severe cases, such as bowel involvement in deep infiltrating endometriosis (DIE) or advanced stages (rASRM stage III/IV), reported even longer operative times compared to the mean difference we observed. Similarly, for operating room time, our results indicate a significant difference of approximately 50 minutes. This extended duration may be attributed to the additional preparation required for the robotic system, along with other factors influencing surgical time.

Intraoperative complications played an important role in determining both intraoperative and postoperative outcomes, including operative time (consequently operating room time), estimated blood loss, likelihood of conversion to open surgery, length of hospital stay, and postoperative complications. Most studies reported on relatively low rates of intraoperative and postoperative complications, suggesting that both methods are safe and comparable in terms of complication rates. It is worth noting that Carpentier et al. exclusively operated on bladder DIE, reporting postoperative complication rates of 60% in the RAL group compared to 36% in the CL group (41). Conversion to open surgery was obviously influenced by various factors, such as the patients' history of abdominal surgeries and unexpected technical challenges. The surgeon's experience was a key determinant.

Although other meta-analyses on this topic were carried out previously, their small sample sizes and methodological limitations prompted us to conduct a brand-new meta-analysis. For example, in the meta-analysis by Chen (2016), RAL was compared to CL for endometriosis surgery, and no significant differences were observed across most outcomes except for operating time (89). Similarly, Restaino et al. (2020) and Balla et al. (2018) conducted meta-analyses and found no differences in operating time or complication rates between RAL and CL. However, in the study by Balla et al., which focused exclusively on patients undergoing colorectal resection for endometriosis, only a small percentage (1.7%) of procedures were performed using RAL, and complications were not analyzed separately for RAL and CL (90,91).

Our study found that RAL did not provide a measurable advantage in the routine surgical management of endometriosis. However, it is of course a more complex situation in reality; it is a key observation that longer operative times are strongly associated with increased overall costs, largely attributed to the robotic platform (44). Regarding costs, specific data on endometriosis surgeries are not available as of today, but relevant insights are from related fields: for instance, a database study of 36,188 patients reported that robotic hysterectomy was more expensive than laparoscopic hysterectomy ($9,640 vs. $6,973, $P < 0.01$). Similarly, in gynecological oncology, the additional cost of using RAL for endometrial or cervical cancer was estimated at €1,456 per procedure (93).

Le Gac et al. previously noted that learning curve for robotic surgery could influence docking times, durations of operations, and complication rates (39). Furthermore, studies by Lee et al. and Terzi et al. highlighted significant differences in the learning curves of RAL and CL. For RAL hysterectomies, operative times decreased notably after 23 similar procedures, while CL required approximately 75 surgeries to achieve a comparable efficiency (94,95).

Despite this fact RAL and CL experts have reported of the convenience of RAL, highlighting its overall comfort and the increase in precision of the operating technique. As RAL uses 3D technology and 15 times magnification it offers a better visualization for the operating surgeon. RAL has also ergonomical advantages: it uses techniques that mimic the movement of human joints (hands, wrists, fingers) thus enabling an extensive range of motion that is more precise than the human hand, wrist, and finger movements.

As RAL uses robotic arms the sustained maintenance of positions demanding substantial forces do not cause as much fatigue in the operating surgeon.

However, we should also highlight the undisputed advantages of CL: haptic tissue feedback which enables the operating surgeon to more precisely differentiate healthy-pathological border when operating a DIE nodule.

It is also important to highlight an aesthetic point of view: patients prefer that at CL surgeries the locations of the ports are on the trunk and the smaller diameters of wounds.

However, to report on surgeons point of view it seems that RAL have less negative impacts on the surgeon cognitively and on the musculoskeletal system (96).

Sers et al. reported that performing laparoscopic surgery, particularly on patients with high BMIs, increased the occurrence of non-neutral postures, potentially heightening the risk of musculoskeletal disorders in surgeons (97). As of today, there are no studies that examined the more serious and irreversible effects of CL on surgeons, for instance the potential development of hip and knee joint impairments because of the long lasting unnatural posture during surgeries.

Recommendations for the use of RAL in the surgical treatment of endometriosis remain variable, influenced by factors such as the patient's individual circumstances, the surgeon's expertise, and the availability of resources and equipment. In 2013, the American Association of Gynecologic Laparoscopists (AAGL) advised that RAL should not replace CL or vaginal procedures in cases where women are suitable candidates for CL or vaginal surgery for benign gynecologic conditions (AAGL). According tot he guideline of the Danish Health Authority RAL hysterectomies should not be performed over CL hysterectomies, only after careful consideration of the procedure because it positive effect is uncertain as it offers a longer operating time (98). For advanced-stage endometriosis, RAL is considered a viable first-line option for the surgical treatment of bowel DIE (44,99). Additionally, according to Lee et al. robot-assisted cystectomy for bilateral ovarian endometriomas offers better preservation of ovarian function comparing it to the laparoscopic approach (35). We maintain that the choice to use RAL for endometriosis treatment should be tailored to each patient, factoring in their unique needs, circumstances, and the surgeon's expertise. We encourage patients to consult with their healthcare providers to determine the most suitable treatment plan for their specific situation. It is also important to note that this represents only a snapshot in time. As experienced laparoscopic surgeons increasingly adopt robotic-assisted techniques, future outcomes may differ significantly as expertise with these methods evolves.

Our systematic review and meta-analysis on medical treatments of endometriosis detected 45 different studies that evaluated the medications that were used to relief pain that was associated with endometriosis. Our findings' quantitative synthesis indicated that GnRH antagonists are the most effective to treat dysmenorrhea, CHCs are the best option to treat dyspareunia, and for overall pelvic pain the best care is to choose CHCs or progestins combined with aromatase inhibitors.

The first network meta-analysis evaluating treatment options for endometriosis was published in the year, 2019. It demonstrated that expectant management, progestins, and GnRH agonists were effective in reducing pain compared to placebo. However, despite a comprehensive analysis, no definitive conclusion was reached regarding whether pharmaceutical or surgical interventions were superior (100). A year later, Samy et al. carried out a meta-analysis that deemed dienogest, CHCs and elagolix to be the highest efficacy in the reduction of pelvic pain after three months. After six months, GnRH agonists, LNG-IUDs, and dienogest received the highest rankings. Overall, GnRH agonists and CHCs were identified as the most effective treatments for reducing pain associated with dysmenorrhea (101). It is also important to note that according to the latest guidelines of the French National Authority for Health (HAS) and the French College of Gynaecologists and Obstetricians' (CNGOF) CHCs and LNG-IUDs are the first choice for the management of endometriosis-related pain (102).

Over a 3-month follow-up period, GnRH agonists were identified as the most effective treatment for dysmenorrhea. This described effectiveness is attributed to the induction of secondary amenorrhea, that reduces discomfort by eliminating menstrual bleeding. After 6 months of follow-up, our findings suggest that GnRH agonists combined with CHCs should be prioritized. Based on our results, it should be recommended in routine clinical practice to initiate GnRH agonist therapy and complement it with CHCs after the first 3 months.

Regarding dyspareunia, it is important to note that CHCs were preferred therapeutic option during all 3-month follow-up periods. At the 6-month follow-up, the combination of CHCs with aromatase inhibitors demonstrated the highest effectiveness. However, the difference was not statistically significant compared to the most effective 3-month therapy, which also consisted of CHCs. Therefore, CHCs remain the first choice for treatment across the 6-month observation period in clinical practice, according to our findings.

Regarding overall pelvic pain, after 3 months of follow-up period, CHCs were the drugs that received the highest p-score on a scale of 0-100. It should be noted, albeit, that GnRH agonists and antagonists were the only drugs that demonstrated a significant difference comparing them with placebo. Despite this fact, when interpreting the collective results,

CHCs should be the first therapeutic choice. Conversely, on a scale of 0-3, progestins proved to be the most effective, displaying the sole significant difference. On a separate 0-3 scale, progestins were the most effective treatment, demonstrating the only significant difference. It should be noted that only three studies used the 0-3 scale, while 16 studies relied on the 0-100 scale. As such, CHCs are recommended in clinical practice based on the findings from the more widely used 0-100 scale. At the 6-month follow-up, progestins combined with aromatase inhibitors emerged as the most effective treatment for overall pelvic pain. However, since no 3-month follow-up data is available for this combination, direct comparison with CHCs is limited. Thus, both CHCs and progestins combined with aromatase inhibitors can be considered effective options for alleviating overall pelvic pain.

Commonly used medications in clinical practice, such as NSAIDs, were not investigated in the eligible articles. NSAIDs have a long history of easing pain, particularly in the management of dysmenorrhea. Even though its long history available studies suggest that its usage is mostly based on clinical practice rather than evidence (103). Rofecoxib, cyclooxygenase-2 inhibitor got tested in 2004 for easing pain in endometriosis, but it had been withdrawn from the market (104).

Opioids have also a long history in pain management. However, their effectiveness in reducing endometriosis-associated pain has not been evaluated in clinical trials, nor were they included as a potential option in the 2022 guideline from the European Society of Human Reproduction and Embryology (ESHRE) (105).

9.2 Strengths (including all studies)

Firstly, it is important to highlight that we followed a rigorous protocol, when we compared RAL and CL, which had been registered in advance. Another important advantage of our study the large number of cases and the long study period it covers. Although previously there were meta-analyses carried out on this topic our study included more articles than the previous one which was published in 2020. We examined operating room time as a new outcome which is an advantage comparing with other meta-analyses on the topic.

In our meta-analysis on medical treatments of endometriosis approximately 10,000 patients were enrolled with a good study design strengthened by the overall high quality

of the selected articles. The Cochrane handbook and PRISMA-NMA statements were followed through the process.

9.3 Limitations (including all studies)

One of the largest limitation of our meta-analysis on the comparison of RAL and CL is that most of the studies were retrospective ones and only one RCT got included. Most of the selected studies patient selection was based on availability to the robotic surgery room. Another important limitation is that some of the articles performed only certain, very organ-specific interventions and operated only on a specific severity of endometriosis, is way not representing the full range of the disease. Furthermore, it is important to highlight that the same author has contributed to some of the selected articles

To speaking of limitations on the meta-analysis focusing on medications of endometriosis, variability in the diagnostic criteria for endometriosis among the included studies contributed to increased heterogeneity. In some treatment arms, the limited number of available studies prevented robust conclusions. Additionally, grouping individual drugs or drug combinations into broad categories may have obscured differences between specific medications. Moreover, there was a notable risk of bias in specific domains of the RCTs included.

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10 CONCLUSIONS

Our experiments focused on the following questions:

10.1 Study I

According to our results there was no notable difference regarding the intraoperative and postoperative complications between CL and RAL group. There was no demonstrable difference between CL and RAL in terms of conversion rate to open surgery by laparotomy.

During RAL surgeries the blood loss was marginally higher, but this data was not deemed relevant statistically nor clinically. We also found that RAL endometriosis surgeries are approximately half an hour longer – this result is both clinically and statistically significant.

10.2 Study II

According to our results there was no notable difference regarding the hospital days spent after surgeries between CL and RAL group.

The quantitative synthesis of our findings' indicate that GnRH antagonists are the most effective to treat dysmenorrhea. According to our results CHCs are the best option in the treatment of dyspareunia. Our results indicate that for overall pelvic pain the best therapy is to choose CHCs or progestins combined with aromatase inhibitors.

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11 IMPLEMENTATIONS FOR PRACTICE

During my Ph.D. work my colleagues and I demonstrated that RAL have no specific advantage compared to CL in endometriosis related surgeries. However, it should be strongly noted that the fact that RAL will possibly improve and the collective knowledge of the whole worlds' surgeons will highly grow it is possible that even in the near future RAL surgeries can have a demonstrable advantage even in endometriosis surgeries. To summarize, I would like to emphasize that the results of my work do not mean at any means that RAL surgeries should not be practiced while easing endometriosis related pain.

According to my results, to medically treat endometriosis related pain for dysmenorrhea GnRH antagonists should be used as a first line therapy, CHCs are the most effective for dyspareunia, and CHCs or progestins combined with aromatase inhibitors are the most effective drugs to ease overall pelvic pain.

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12 IMPLEMENTATION FOR RESEARCH

12.1 Methodology issues

As RAL is a technology that probably will improve a lot in the future, new companies will step into the market of robotic surgery, I encourage every surgeon who uses RAL and CL both in endometriosis related surgeries to publish new RCTs and new meta-analyses as the results because of the aspects mentioned above could be different from the current studies and even my research, even in the near future.

And it is unnecessary to mention that medical therapies of endometriosis should also be closely, and regularly monitored by future studies.

12.2 Study design

I personally advise other researchers to focus on the new aspects of robotic surgery and to measure and compare the possibly new techniques with CL which is the current gold standard in endometriosis surgeries.

I also advise focusing on new medications to find the best non-surgical treatment methods for endometriosis related pain.

12.3 New aspects

As my results were novel in endometriosis related pain’s treatment no meta-analyses can stay valid for a long period as new and new studies will come out. I personally hope that my research will encourage other fellow researchers to carry out their new studies on surgical and non-surgical treatments of endometriosis, studying aspects that I or no one did study before thus enriching our knowledge on endometriosis and to provide better and better means to fight against the disease.

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13 IMPLEMENTATION FOR POLICYMAKERS

It is very important to note that even though RAL has no demonstrable advantages compared with CL in endometriosis surgeries we would not like to encourage policy makers to only advise the usage of CL in endometriosis surgeries as RAL technology before improvement and a world-wide knowledge gain. However, it would be beneficial if endometriosis related RAL surgeries were closely monitored and more information, databases would be there for future research purposes.

We also encourage policy makers to possibly reduce the price of GnRH antagonists, CHCs and aromatase inhibitors combined with progestins for women who have endometriosis related pains.

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14 FUTURE PERSPECTIVES

First of all, I would like my work to be the basis of the therapy of patients: my work clearly highlights which medications are the most effective in endometriosis related-pain and that right now there is no demonstrable advantage of CL compared to RAL in endometriosis surgeries.

However, it should also be noted that these results are only for the present and for the near future: it is highly possible that RAL will be developing fast in the future decades: technologies will be more advanced and surgeons all over the world will gather a lot more experiences in robot-assisted surgeries.

As a result, I encourage other professionals to carry out as many RCTs and other researchers to carry out new meta-analyses at least every few years on this topic to have the latest pieces of information always.

Not only surgical techniques, but medications should also be evaluated frequently, if new drugs will appear on the global market they should be compared with the already existing medications.

To summarize, I hope that the meta-analyses I carried-out can be the basis of new guidelines and an encouragement for future generations to examine the best possible surgical and medical therapies in the relief of endometriosis related pain.

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16.1 Publications related to the thesis

Csirzó Á, Kovács DP, Szabó A, Fehérvári P, Jankó Á, Hegyi P, Nyirády P, Sipos Z, Sára L, Ács N, Szabó I, Valent S. Robot-assisted laparoscopy does not have demonstrable advantages over conventional laparoscopy in endometriosis surgery: a systematic review and meta-analysis. Surg Endosc. 2024 Feb.

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Csirzó Á, Kovács DP, Szabó A, Szabó B, Jankó Á, Hegyi P, Nyirády P, Ács N, Valent S. Comparative Analysis of Medical Interventions to Alleviate Endometriosis-Related Pain: A Systematic Review and Network Meta-Analysis. J Clin Med. 2024 Nov.

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16.2 Publications not related to the thesis

Kovács D, Szabó A, Hegyi P, Ács N, Keszthelyi M, Sára L, **Csirzó Á**, Mátrai P, Munnoch K, Nagy R, Bánhidy F. Association between human papillomavirus and preterm delivery: A systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2024 Oct.

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