MEDICAL AND SURGIGAL TREATMENT OF ENDOMETRIOSIS

Ph.D. Thesis Booklet

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1. INTRODUCTION

Endometriosis is a prevalent, estrogen-dependent condition characterized by the presence of endometrial-like tissue outside the uterus, thus leading to chronic pelvic pain, infertility, and symptoms like dysmenorrhea and dyspareunia. Endometriosis affects globally 10 to 15% of women of reproductive age while the exact cause and pathomechanisms remain unclear.

Surgical treatment often involves minimally invasive methods such as conventional laparoscopy (CL) or robot-assisted laparoscopy (RAL).

CL, the standard approach, offers benefits like reduced recovery time but is limited by 2D visualization and ergonomic constraints. RAL addresses these issues with 3D imaging, improved precision, and reduced surgeon fatigue, even though its high price and lack of tactile feedback are significant drawbacks.

Medical management typically involves hormonal therapy, with combined hormonal contraceptives (CHCs) and progestins serving as first-line, long-term treatments due to their safety and affordability. Short-term options, like GnRH analogs, are limited by menopause-like side effects, prompting research into combining these therapies for extended use.

Surgical and medical approaches aim to alleviate pain and enhance fertility outcomes. Advanced technologies in surgery and evolving drug therapies are improving treatment strategies. However, endometriosis remains a complex and enigmatic field of gynecology requiring further research.

2. OBJECTIVES

2.1. Study I. - Investigating the effectiveness and safety of CL and RAL

In order to compare conventional laparoscopy and the novel robot assisted laparoscopy in my meta-analysis we compared the two methods by the occurrence of perioperative complications, the blood loss during the two procedures, length of the surgeries with the two types of procedures, the length of hospital stays with the two types of procedures.

2.2. Study II. - Investigating the available medical treatments for endometriosis-related pain

In my second meta-analysis that I carried out during my Ph.D. studies I tried to compare different medications in the treatment of dysmenorrhea, dyspareunia, and overall pelvic pain.

3. METHODS

The systematic reviews and meta-analyses involved in my Ph.D. work were reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 Statement. The reviews followed the recommendations of the Version 6.3 of Cochrane Handbook for Systematic Reviews of Interventions and the review protocols were registered on PROSPERO (Study I. under registration number CRD42023397045; and Study II. under registration number CRD42022374466).

3.1. Literature search and eligibility criteria

We performed a systematic literature search in three databases using MEDLINE (via PubMed), Cochrane Library (CENTRAL), Embase for both Study I and II.

Original articles were included if they were published on premenopausal women who underwent endometriosis surgery and the basic requirement was to compare CL and RAL for Study I. For Study II 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. We also looked for studies reporting outcomes such as changes in total endometriosis-related pelvic pain scores, dysmenorrhea scores, dyspareunia scores.

3.2. Study selection and data collection

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 independently extracted data into a predefined Excel spreadsheet (Office 365, Microsoft, Redmond, WA, USA), and the occurring discrepancies were resolved by the involvement of a third reviewer.

3.3. Quality assessment

For Study I. 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. 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

For Study II. 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.

3.4. Data synthesis and analysis

At Study I., 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. 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. 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.

At Study II., 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. 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. Multi-arm study correlation was also taken into consideration.

To assess inconsistency, the loop-specific approach was used. 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.

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) ((2023), R.C.T) Netmeta and BUGSnet packages were used for analysis visualization.

4. RESULTS

4.1. Study I.

11 articles presented data on intraoperative complications: we found that there were 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.

The number of postoperative complications were presented in 11 articles, with the exact timing of the complication not presented. Our result was that there were no between-group differences regarding the number of postoperative complications (OR = 1.3, CI 0.73–2.32). The relative frequency of postoperative complications in the RAL group was 7.96%, and 10.07% in the CL group.

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). The relative frequencies of conversions in the RAL group were 0.74% and 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).

Blood loss was reported in 12 articles, during RAL surgeries the blood loss was 16 ml higher, but this data was not clinically nor statistically significant (MD = 16.73, CI 4.18–37.63).

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 clinically and statistically (MD = 28.09, CI 11.59–44.59).

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.

4.2 Study II.

4.2.1. Dysmenorrhea, on a scale 0-100, after 3 months

5 articles evaluated a total of 6 types of treatments 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).

4.2.2. Dysmenorrhea, on a scale 0-3, after 3 months

3 articles evaluated a total of 4 types of treatments: GnRH agonists recorded the highest p-score again (0.828) and the lowest p-score was achieved by placebo, again(0.145).

4.2.3. Dysmenorrhea, on a scale 0-100, after 6 months

10 articles evaluated a total of 7 types of treatments: GnRH agonists combined with CHCs achieved the highest p-score (0.649) and CHCs the lowest (0.339).

4.2.4. Dyspareunia, on a scale of 0–100, after 3 months

7 articles evaluated a total of 7 types of treatments: CHCs achieved the highest p-score (0.805), and placebo the lowest one (0.381).

4.2.5. Dyspareunia, on a scale of 0–100, after 6 months

11 articles evaluated a total of 8 types of treatments: CHCs combined with aromatase inhibitors got the highest p-score (0.677) and SERMs the lowest p-score (0.315).

4.2.6. Overall pelvic pain on a scale of 0–100 after 3 months

15 articles evaluated a total of 7 types of treatments: 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).

4.2.7. Overall pelvic pain on scale of 0-3 after 3 months

3 articles evaluated a total of 4 types of treatments: 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).

4.2.8. Overall pelvic, pain on scale, of 0-100 after 6 months

21 articles evaluated a total of 8 types of treatments: progestins combined with aromatase inhibitors got the highest p-score (0.873), and placebo the lowest p-score (0.091).

5. CONCLUSION

5.1. 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. Our results also indicate that during RAL surgeries the blood loss is marginally higher compared to CL but this difference is not statistically nor clinically relevant. However, it is a both clinically and statistically higher difference that RAL surgeries are around half an hour longer than CL surgeries when operating on endometriosis. Our results also indicate that there is no notable difference in terms of the hospital stays after RAL and CL endometriosis surgeries.

5.2. Study II.

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

6. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

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