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EFFECTS OF ENDOMETRIOSIS ON QUALITY OF LIFE

(Benefits of combined hystero-laparoscopic surgery for quality of life and
fertility performance in endometriosis)

Doctoral (PhD) thesis booklet



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INTRODUCTION

Endometriosis is a common, progressive, chronic disease that affects women. It is a largely benign but potentially debilitating gynecological disorder with a rare malignant transformation. Endometriosis generally affects 10-15% of the female population in reproductive age. Additionally, it is estimated to affect 20-50% of women with fertility problems (sub-fertility or infertility) and 40-60% of women with menstrual disorders. This disorder is differentiated by the growth of endometrial-like tissue outside the uterine cavity and is dependent on estrogen. Organs remote from the pelvis, such as the lungs and skin, can also be affected. Endometriosis was first described as an "adenomyoma" in 1860 by Austrian pathologist Karl Freiherr von Rokitansky.

The first formal description of the disease was made by Dr. John Sampson in his article describing 13 cases where endometrial tissue was observed during abdominal surgery. Initially, women who developed symptoms similar to those of endometriosis were considered demon-possessed, witches, or madmen, and were rejected and sometimes even murdered with contempt by society. Nearly 2500 years ago, Hippocratic physicians documented a similar medical condition called "chronic pain."

Thomas Sydenham and others called women who had this symptom "hysteria." The attitude of male health professionals in the early days, insufficient technology at that time and the complexity of endometriosis led to a delayed discovery of the disease. Therefore, the affected women were in an agonizing state for most of their lives, which may have facilitated the development of some of the behaviors called "obsession." Due to the complexity of its pathogenesis, endometriosis is quite difficult to identify using universally standard biomarkers. Several attempts had little or no success... The biggest challenge with the disease is the delay in diagnosis by around 4 to 8 years, which often requires invasive interventions such as laparoscopy and, less frequently, diagnostic laparotomy. Previous studies have shown that rates vary between countries; 6-10% in the US, 7% in Canada, 10% in the UK, 10% in Hungary, 3.7% in Australia and 18.6% in Italy.

The quality of life (QoL) of women with symptomatic endometriosis is significantly reduced by subfertility or infertility, chronic pelvic pain, dysmenorrhea (painful periods) and dyspareunia (pain during intercourse). Currently, the only successful treatment of severe endometriosis is surgical removal of visible lesions with or without adjuvant medical therapy. Depending on surgical expertise, recurrence is relatively common and is estimated to be 4.2–75% within 2 years; Therefore, the need for repeated surgery is common.

The purpose of this study is to examine the effectiveness of laparoscopic surgery in improving quality of life, overall well-being, and fertility performance in patients with endometriosis.

Aim of the study

1. It is assumed that there may be a relationship between the medical history of the patient who has undergone a cesarean section and the increased likelihood of developing endometriosis.
2. It is assumed that combined hysteroscopic and laparoscopic endometriosis surgery significantly improves fertility outcomes in patients with endometriosis.
3. It is assumed that combined hysterolaparoscopy can significantly improve the quality of life of patients with endometriosis. We believe that the validated EHP-36 instrument, VAS and NRS-11 are useful tools for assessing the quality of life of endometriosis patients.

Material and method

The study consists of two parts: the first is a retrospective, the second prospective, which was made at the Department of Endoscopic Surgery of the Départementi of Obstetrics and Gynecology of the Róbert Private Hospital. The retrospective studies based on data collection using the Hospital Database consisted of three parts.

Prospective section

I/1. In the first, 34 patients with post-caesarean scar defects (isthmocoele) were analyzed and its possible association with endometriosis and secondary infertility. Following initial screening, 28 patients agreed to surgical treatment, and all underwent combined hysteroscopic and laparoscopic repair, except for one patient who only opted for hysteroscopic correction, a follow-up that lasted from January 2013 to June 2016.

I/2. The second part evaluated the postoperative fertility performance of 533 endometriosis patients. The study sample consisted of 533 infertile women who had received at least one previous infertility treatment, either artificial insemination (AI) or in vitro fertilization et embryo transfer (IVF. -ET) Between January 2010 and december 2016, all patients underwent combined hysterolaparoscopic surgery. The stage of endometriosis was assessed according to the revised scoring system of the American Fertility Society (rAFS). 455 patients were eligible for final completion of the study. Immediately after surgery, patients who had no obvious postoperative anatomical abnormalities were recommended to become pregnant naturally, while those with proven complete tubal obliteration or who did not become pregnant 12 months after surgery were offered IVF. Patients were followed for up to 24 months, during which time relevant clinical data were collected through personal and electronic communication forms.

I/3. The third part analyzed 777 endometriosis patients about their preoperative quality of life, fertility performance, and the relationship between previous obstetric and gynecological surgeries and endometriosis. In addition, patients' well-being and improvement in quality of life were assessed with verbal questions on the absence of painful symptoms, fertility performance and overall mood during follow-up monitoring or through electronic media.

Prospective section

I/3b. The second branch includes a prospective study to determine quality of life, fertility performance, including genetic predisposition on the onset of endometriosis, and based on a prospective cohort investigation between January 2017 and December 2018 using the modified

Endometriosis Health Profile 36 (EHP–36) questionnaire, visual analog scale (VAS), and Numeric Rating Scale (NRS–11) instruments. The questionnaires were completed before and after surgical procedures. Postoperative follow-up took place in the first 6 months, 12 months and 24 months after surgery via postal questionnaire, email and direct phone conversation. The questionnaire was pretested with the help of volunteer hospital staff and the average time taken to complete the questionnaire was recorded.

Result

Group 1:

The mean age of patients was 36.9 ± 4.5 years, ranging from 23 to 42 years. Of the 28 patients, 20 (71.4%) had a single caesarean section, while 8 patients (28.6%) had ≥ 2 caesarean sections; 17 patients (60.7%) were diagnosed with secondary infertility. Endometriosis of various sites was recorded in 16 patients (57.1%), and stages of endometriosis are between stages I and III, according to ASRM. 1 to 24 months after isthmocele, a significant ($p < 0.001$) reduction in symptoms was observed and the patient's overall health improved.

| Symptoms and Characteristics (n=28) | Number | Percent |
|---|--------|---------|
| Age 36 ± 4.1 (range 29-42) years | - | - |
| All symptoms associated with isthmocele | 5 | 64.3% |
| Dysmenorrhea | 18 | 67.3% |
| Supra-pubic pain (LAP-lower abdominal pain) | 19 | 60.7% |
| Duration of infertility in years (between ± 2 years - ± 8 years) | 17 | 89.3% |
| PMBD (post menstruation bleeding disorder) Length of bleeding in days (between ± 9 - ± 17 days) | 25 | 46.4% |
| CVD (Chronic Vaginal discharge) | 13 | 60.7% |
| History of 1 caesarean section delivery | 17 | 39.3% |
| History of > 2 caesarean section delivery | 11 | 71.4% |
| Cesarean section incision closure (single layer) | 20 | 57.1% |
| Size of isthmocele ($< 6-15 \times 6 \times 15$ mm) | 16 | 25.0% |
| Size of isthmocele ($< 15-20 \times 15 \times 20$ mm) | 7 | 17.9% |
| Size of isthmocele ($> 20 \times 25$ mm) | 5 | 17.9% |
| Endo-myometrium thickness (< 3 mm) | 16 | 57.1% |
| Endo-myometrium thickness (> 3 mm) | 12 | 42.9% |

General characteristics of patients undergoing surgery for isthmocele.

| Intra-Operative characteristics | Number | Percent |
|---|------------------|----------------|
| Average duration of surgery | | |
| Average blood loss | | |
| Endometriosis | 16 | 57.0% |
| Uterine fibroid | 2 | 7.1% |
| Endometrial polyp | 4 | 14.3% |
| Intra-abdominal adhesion | 15 | 53.6% |
| Preoperative clinical outcome | Frequency | Percent |
| Lost to follow up after 3 months post operation | 7 | 25.0% |
| Pregnancy | 14/17 | 82.4% |
| Fertility related characteristics | Frequency | Percent |
| Pregnant – ART | 7/14 | 50.0% |
| Pregnant^ Spontaneous | 7/14 | 50.0% |
| Total number of pregnancies within 24 months post-surgery | 14/17 | 82.4% |

| | | |
|---|-------|--------|
| Total number of non-pregnant patients after 24 months, including those with lost to follow up with infertility issues | 3/17 | 17.6% |
| Total infertility patients before isthmocele surgery | 17/17 | 100.0% |

Table 2a-b. Postoperative outcomes of patients who underwent surgery for isthmocele.

| Symptoms | Relief of symptoms by months | | | | | Total |
|---|------------------------------|----------------|-----------------|-----------------|----------------|------------------|
| | 1st month | 3rd month | 6th month | 12th month | 24th month | |
| Dysmenorrhea | 16 (88.9%) | 17 (94.4%) | 18 (100%) | - | - | 18 (100%) |
| Post- menstrual bleeding disorder (PMBD) Duration of menstruation reduces to 3.6 days \pm 1.069 days | 23 (92.0%) | 24 (96.0%) | 25 (100%) | - | - | 25 (100%) |
| Supra-pubic lower abdominal pain (LAP) | 16 (84.2%) * | 18 (94.7%) | 18 (94.7%) | 19 (100%) | - | 19 (100%) |
| Chronic Vaginal Discharge (CVD) | 10 (76.9%) ** | 13 (100.0%) | - | - | - | 13 (100.%) |
| Infertility | - | - | 5/17 (29.4%) | 8/17 (47.1%) | 1/17 (5.9%) | 14/17 (82.4%) |

Table 2a-b. Postoperative outcomes of patients who underwent surgery for isthmocele.

Group 2

The study looked at the association between different demographic and clinical characteristics and pregnancy history in a sample of 455 endometriosis women diagnosed with endometriosis. The analyzed characteristics included age, length of menstrual cycle, duration of menstruation and stage of endometriosis. The sample was divided into two groups: those who had already been pregnant (n=370) and those who had not (n=85). Participants ranged in age from 25 to 46 years. The distribution between age groups was as follows: 25-30 years (20.0%), 31-35 years (39.3%), 36-40 years (35.0%) and 41-46 years (5.7%).

The proportion of women who have undergone pregnancy was highest in the 31-35 age group (86.0%) and lowest in the 25-30 age group (81.3%). However, the Chi-squared test showed no statistically significant association between age and pregnancy history ($\chi^2(3) = 0.5799, p=0.99$). The length of the menstrual cycle is ≤ 24 days (20.4%), 25-35 days (74.3%) and ≥ 36 days (5.3%). The highest proportion of pregnant women was in the category over 36 days (91.7%), but the Chi-squared test showed no significant association between menstrual cycle length and pregnancy history ($\chi^2(2) = 1.5188, p = 0.409$).

Length of menstruation:

The duration of menstruation was classified as <4 days (27.5%), 5-6 days (48.1%), and ≥ 7 days (24.4%). The highest proportion of pregnant women was in the under 4-day menstrual category (85.6%). However, the Chi-squared test showed no significant association between menstrual

duration and pregnancy history ($\chi^2 (2) = 0.7655, p=0,318$).

Stage of endometriosis:

1st (13.4%), 2nd (29.0%), 3rd (35.6%) and 4th (22.0%).

The highest proportion of pregnant women was in stage 3 (86.4%). However, the Chi-squared test showed no significant association between the endometriosis stage and pregnancy history ($\chi^2 (3) = 0.7474, p = 0.138$).

The analysis showed no statistically significant association between pregnancy history and the demographics and clinical characteristics studied, including age, menstrual cycle length, menstrual duration, and stage of endometriosis. The study also looked at the relationship between the stage of endometriosis and pregnancy outcomes. Participants divided into four groups based on endometriosis stage: stage 1 (n=61), stage 2 (n=132), stage 3 (n=162), and stage 4 (n=100). In each of them, frequency of occurrence and absence of pregnancy were studied.

- Stage 1 endometriosis: 80% of 61 women became pregnant, while 20% did not.
- Stage 2 endometriosis: 76% of 132 women became pregnant, and 24% did not.
- Stage 3 endometriosis: Higher pregnancy rates were recorded among 162 women: 86% became pregnant and 14% did not.
- Stage 4 endometriosis: In the group of 100 women, 81% became pregnant, and 19% did not.

The analysis shows that pregnancy rates vary at different stages of endometriosis, with the highest rates observed in stage 3 (86%) and the lowest in stage 2 (76%). However, the Chi-squared test showed that the differences between stages were statistically not significant ($\chi^2 = 5.5081, p = 0.1382$). These suggest that although there are differences in pregnancy rates at different stages of endometriosis, the differences observed in the sample are not sufficiently substantiated to establish a definite association. The coexistence of symptoms appeared significant for the following variables: dysmenorrhea and obstipation, dysmenorrhea and dull pain, crushing and dull pain, and sharp and dull pain.

| Characteristics | Category | Total (n=455) | | Number of pregnancies (n=85) | | Pregnancy (n=370) | | Chi2 test p |
|----------------------------------|----------|---------------|----------|------------------------------|-------|-------------------|-------|-------------|
| | | n | (Col. %) | n | (%) | n | (%) | |
| Age (years) | 25-30 | 91 | 20.0% | 17 | 18.7% | 74 | 81.3% | 0.099 |
| | 31-35 | 179 | 39.3% | 25 | 14.0% | 154 | 86.0% | |
| | 36-40 | 159 | 35.0% | 35 | 22.0% | 124 | 78.0% | |
| | 41-46 | 26 | 5.7% | 8 | 30.8% | 18 | 69.2% | |
| Length of menstrual cycle (days) | ≤24 | 93 | 20.4% | 18 | 19.4% | 75 | 80.6% | 0.409 |
| | 25-35 | 338 | 74.3% | 65 | 19.2% | 273 | 80.8% | |
| | ≥36 | 24 | 5.3% | 2 | 8.3% | 22 | 91.7% | |
| Length of menstrual (days) | <4 | 125 | 27.5% | 18 | 14.4% | 107 | 85.6% | 0.318 |
| | 5-6 | 219 | 48.1% | 46 | 21.0% | 173 | 79.0% | |
| | ≥7 | 111 | 24.4% | 21 | 18.9% | 90 | 81.1% | |
| Stages of | 1 | 61 | 13.4% | 12 | 19.7% | 49 | 80.3% | 0.138 |

| | | | | | | | |
|---------------|---|-----|-------|----|-------|-----|-------|
| endometriosis | 2 | 132 | 29.0% | 32 | 24.2% | 100 | 75.8% |
| | 3 | 162 | 35.6% | 22 | 13.6% | 140 | 86.4% |
| | 4 | 100 | 22.0% | 19 | 19.0% | 81 | 81.0% |

Table 3. General characteristics of endometriosis in patients with infertility.

| Post-surgical fertility performance among women 25 – 35-years-old with infertility – related endometriosis | | | | |
|--|-----------------------------|--------------|-------------|-------|
| Preoperative ART | Postoperative ART treatment | No pregnancy | Pregnancy | Total |
| | | n (%) | n (%) | n |
| No | No | 15(16.3%) | 77(83.7%) | 92 |
| | Yes | 6(13.6%) | 38(86.4%) | 44 |
| | Total | 21(15.4%) | 115(84.6%) | 136 |
| Yes | No | 14(25.9%) | 40(74.1%) | 54 |
| | Yes | 7(8.8%) | 73(91.2%) | 80 |
| | Total | 21(15.7%) | 113 (84.3%) | 134 |
| Total | | 42(15.6%) | 228(84.4%) | 270 |
| Post-surgical fertility performance among women 36 – 46-years-old with infertility – related endometriosis | | | | |
| Preoperative ART treatment | Postoperative ART treatment | No pregnancy | Pregnancy | Total |
| | | n (%) | n (%) | n |
| No | No | 11(42.3%) | 15(57.7%) | 26 |
| | Yes | 3(16.7%) | 15(83.3%) | 18 |
| | Total | 14(31.8%) | 30(68.2%) | 44 |
| Yes | No | 14(26.4%) | 39(73.6%) | 53 |
| | Yes | 15(17.0%) | 73(83.0%) | 88 |
| | Total | 29(20.6%) | 112(79.4%) | 141 |
| Total | | 43 (23.2%) | 142 (76.8%) | 185 |

Table 5. Postoperative fertility outcomes in patients with endometriosis-related infertility.

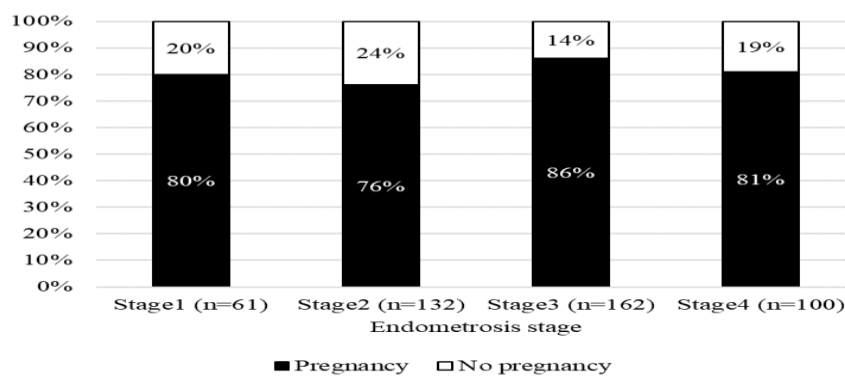


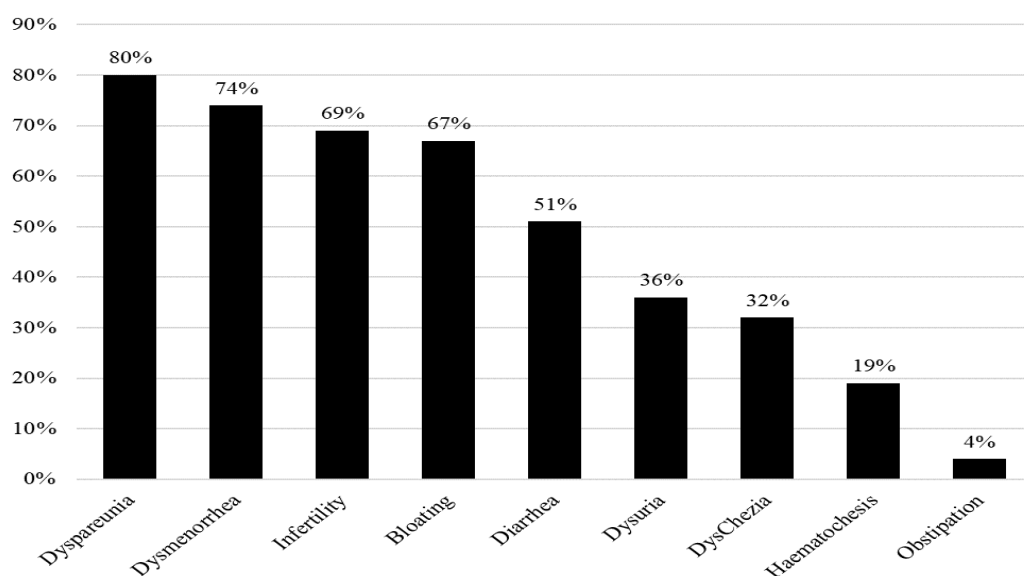
Figure 9. Effect of laparoscopic surgery on fertility performance by stage of endometriosis in Study II.

Group 3:

In the first arm of the study, patients had a mean age of 34.3 ± 5.1 years (18-53 years). The onset of menstruation (menarche) was 13.1 ± 1.4 years, the average duration of monthly bleeding was 5.9 ± 2.1 days, the average age of onset of endometriosis-related symptoms was 29.1 ± 4.3 years, and the time from onset of symptoms to diagnosis of endometriosis was 5.1 ± 2.9 years. The distribution of different stages of endometriosis was as follows: 15% (113/777) of patients at stage I, 31% (243/777) at stage II, and 34% (264/777) at stage III. IV in 20% of patients (157/777). The most common complaints were dyspareunia 80% (621/777) and dysmenorrhea 74% (574/777). Of the 534 patients (69%) who initially complained of infertility, 49 did not want to become pregnant.

| | | Frequency | Percentage | Cumulative (%) |
|--|-----------|-----------|------------|----------------|
| Age of patients | 18-25 | 27 | 3.47% | 3.5% |
| | 26-31 | 155 | 19.9% | 29.5% |
| | 32-37 | 349 | 44.9% | 74.4% |
| | 38-43 | 172 | 22.1% | 96.5% |
| | 44-53 | 27 | 3.4% | 100% |
| Age at menarche | 8-11 | 76 | 9.8% | 9.8% |
| | 12-15 | 664 | 85.5% | 95.3% |
| | 16-20 | 37 | 4.7% | 100% |
| Duration of menstruation | 2-7 | 629 | 81.0% | 81% |
| | 8-15 | 148 | 19.0% | 100% |
| Age at the onset of symptoms | 15-20 | 16 | 2.1% | 2.1% |
| | 21-25 | 136 | 17.0% | 19.1% |
| | 26-30 | 345 | 44.4% | 63.5% |
| | 31-35 | 228 | 29.3% | 92.5% |
| | 36-40 | 47 | 6.1% | 98.5% |
| | 41-43 | 7 | 0.9% | 100% |
| Duration of symptoms before diagnosis | 0-5 | 450 | 57.9% | 57.9% |
| | 6-11 | 286 | 36.8% | 94.7% |
| | 12-18 | 41 | 5.3% | 100% |
| Stages of endometriosis (rASRM) classification | Stadium 1 | 113 | 14.5% | 14.5% |
| | Stadium 2 | 243 | 31.3% | 45.8% |
| | Stadium 3 | 264 | 34.0% | 79.8% |
| | Stadium 4 | 157 | 20.2% | 100.0% |
| Total | | 777 | 100.0% | 100.0% |

Table 6. General characteristics of patients with endometriosis in Study III/a

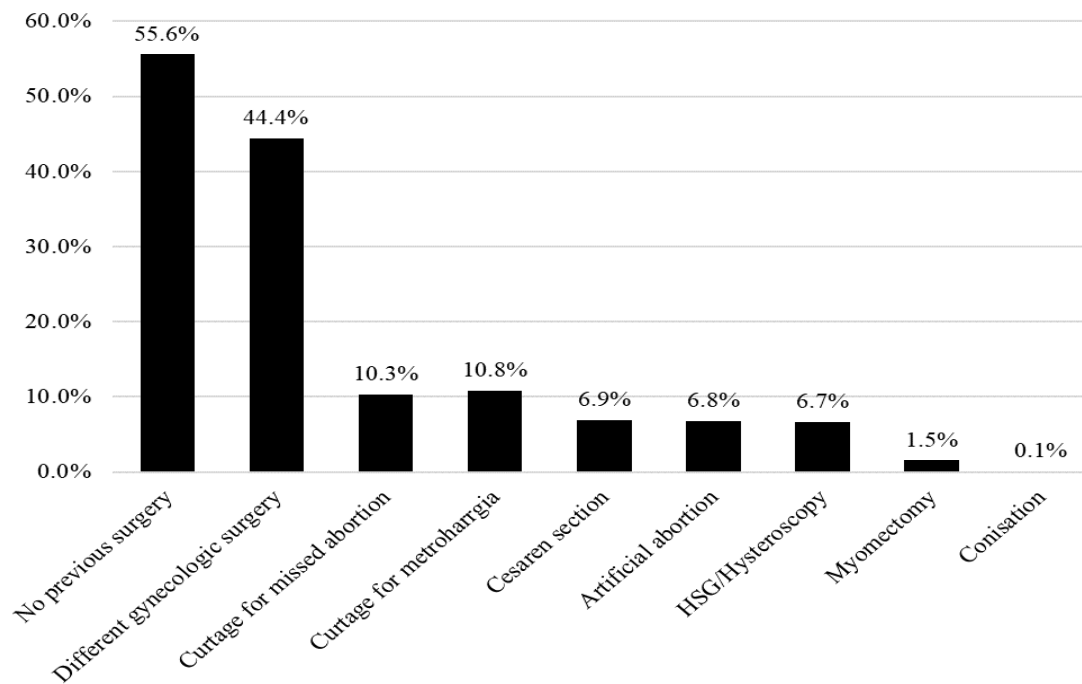


Distribution of endometriosis-related symptoms in study IIIa.

| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|----|--|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| 1 | Dysmenorrh ea | | | | | | | | | | |
| 2 | Dyschezia | 0.223* | | | | | | | | | |
| 3 | Dyspareunia | 0.287* | 0.275* | | | | | | | | |
| 4 | Dysuria | 0.156* | 0.470* | 0.202* | | | | | | | |
| 5 | Bloody defecation | 0.146* | 0.581* | 0.208* | 0.491* | | | | | | |
| 6 | Blooting (abd. swelling) | 0.431* | 0.366* | 0.300* | 0.248* | 0.268* | | | | | |
| 7 | Obstipation (intestinal obstruction) | 0.070 | 0.215* | 0.107* | 0.205* | 0.361* | 0.095* | | | | |
| 8 | Diarrhea | 0.318* | 0.469* | 0.250* | 0.318* | 0.383* | 0.570* | 0.146* | | | |
| 9 | Crushing pain | 0.572* | 0.271* | 0.243* | 0.204* | 0.223* | 0.467* | 0.100* | 0.423* | | |
| 10 | Obtuse pain | 0.040 | 0.226* | 0.119* | 0.260* | 0.246* | 0.124* | 0.064* | 0.194* | -0.039 | |
| 11 | Sharp pain | 0.279* | 0.233* | 0.455* | 0.185* | 0.185* | 0.292* | 0.052 | 0.324* | 0.242* | -0.005 |

Relationship between pain type and symptoms in patients with endometriosis in study IIIa.

*P<0.001. In dysmenorrhea, the most likely type of pain was crushing pain. There was no characteristic pain for dyschezia, since all three type occurred. In dyspareunia, the most likely type of pain was sharp pain. In the case of dysuria, there was no characteristic pain, since all three occurred.



Endometriosis Incidence of other previous gynecological surgeries prior to onset of endometriosis symptoms in women in study IIIa

The success rate of live births was 94.2% (327/347) and pregnancy loss was 5.8%. Overall, women's quality of life gradually improved. In terms of overall improvement in QoL, we recorded significantly 57-59% at the first follow-up, 74-85% at the last (after the first year), and all women reported significant improvement ($p=0.0005$). Participants with right ovarian endometriosis experienced all types of pain. Endometriosis of the left ovary was mainly associated with dysmenorrhea, bloating and dysuria. There was no pronounced pain type for superficial peritoneal involvement. Multiple unilateral or bilateral ovaries cause all forms of pain. Deep peritoneal endometriosis with bladder peritoneum involvement also caused all types of pain. Great physical pain of all types was reported, with participants with deep rectovaginal septum endometriosis and intestinal peritoneal involvement. Dyschexia, dyspareunia, bloating, constipation, diarrhea, dysuria and bloody bowel movements occur in patients who have a deep rectovaginal septum (RVS-BR) without intestinal involvement.

| Localization | Dysmenorrhea | Dys-Chazia | Dyspareunia | Bloating (abdominal swelling) | Obstipation | Diarrhea | Dy-suria | Bloody defecation |
|---|--------------|------------|-------------|-------------------------------|-------------|----------|----------|-------------------|
| Right ovary | X | X | | X | X | X | X | X |
| Left ovary | X | | | X | | X | | |
| Superficial-peritoneal involvement | | | | | | | | |
| Deep involvement of the ovary with multiple unilateral or bilateral endometriosis | X | X | X | X | X | X | X | X |
| Deep peritoneal endometriosis with bladder peritonium involvement | X | X | X | X | X | X | X | X |
| Deep rectovaginal septum endometriosis with intestinal | X | X | X | X | X | X | X | X |
| Deep rectovaginal septum; RVS-BR without bowel involvement | | X | X | X | X | X | X | X |

The relationship between pain type and endometriosis localization in study IIIa.

The results confirm the presence of diverse and often severe symptoms associated with different localizations of endometriosis and underscore the complexity of diagnosis and treatment of endometriosis. It also emphasizes the comprehensive and individualized choice of therapy in each case, taking into account the specific localization and type of symptoms.

| Time (Months) | Moderate | Significant | Complete | Total |
|----------------|----------|-------------|----------|---------|
| 1st 3 months | | | | |
| No | 7 | 52 | 53 | 112 |
| | 46.70% | 74.30% | 88.30% | 77.20% |
| Yes | 8 | 18 | 7 | 33 |
| | 53.30% | 25.70% | 11.70% | 22.80% |
| Total | 15 | 70 | 60 | 145 |
| | 100.00 % | 100.00% | 100.00 % | 100.00% |
| 1st. 6 months | | | | |
| No | 4 | 52 | 55 | 111 |
| | 40.00% | 75.40% | 84.60% | 77.10% |
| Yes | 6 | 17 | 10 | 33 |
| | 60.00% | 24.60% | 15.40% | 22.90% |
| Total | 10 | 69 | 65 | 144 |
| | 100.00 % | 100.00% | 100.00 % | 100.00% |
| 1st. 12 months | | | | |
| No | 5 | 44 | 51 | 100 |
| | 31.30% | 77.20% | 86.40% | 75.80% |
| Yes | 11 | 13 | 8 | 32 |
| | 68.80% | 22.80% | 13.60% | 24.20% |
| Total | 16 | 57 | 59 | 132 |
| | 100.00 % | 100.00% | 100.00 % | 100.00% |

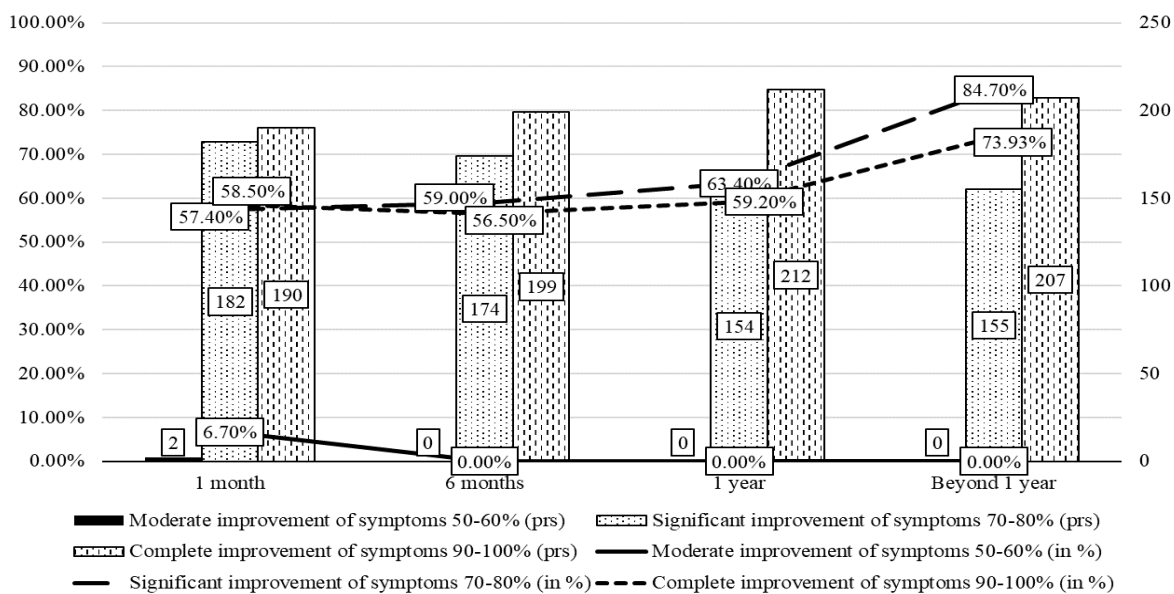
Comparison of improvement in postoperative symptoms at different stages of follow-up in patients with endometriosis in study IIIa.

During the first 3 months of follow-up, the Chi-squared test showed a statistically significant association between symptom improvement and follow-up period $\chi^2 (2) = 12.524, p = 0.002$. After 6 months of follow-up, the Chi-squared test again showed a statistically significant relationship, $\chi^2 (2) = 9.988, p = 0.007$. During the 12-month follow-up, the Chi-squared test result is $\chi^2 (2) = 20.988$, with a p-value of less than 0.001. In all three follow-up periods (3, 6 and 12 months), Chi-squared tests consistently indicate statistically significant differences. These findings suggest that symptom improvement levels vary significantly between patients over time, underscoring the importance of individualized postoperative care and monitoring.

95% confidence intervalum

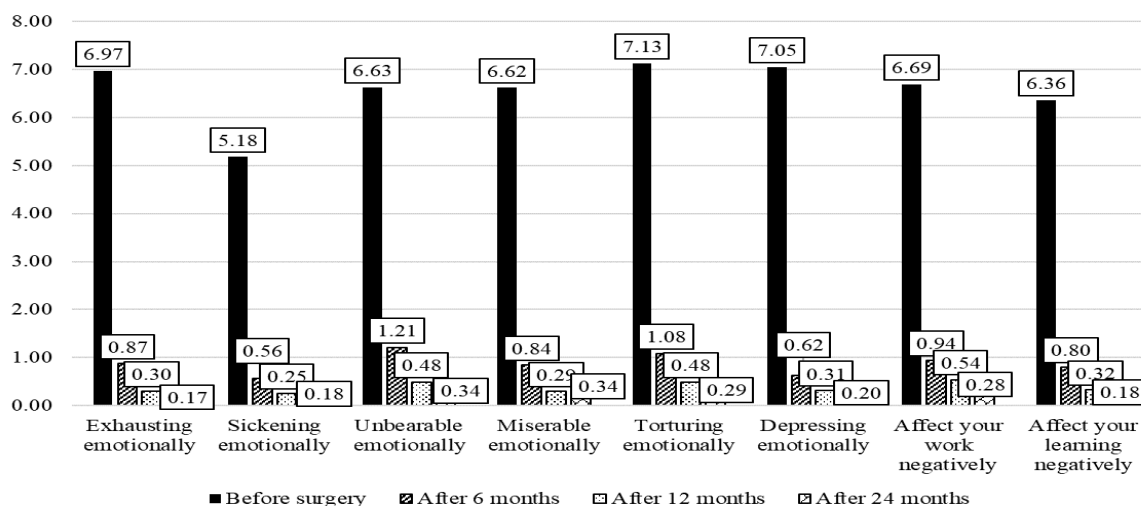
| Vizit | Improvement | Chi-square | df | Sig | Odds ratio | Lower | Upper |
|---------------|--|------------|----|--------|------------|-------|--------|
| 1 month | Little improvement less than 50% | 1.253 | 1 | 0.263 | 0.000 | 0.000 | 0.000 |
| | Moderate improvement in symptoms 50-60% | 30.418 | 1 | <0.001 | 0.052 | 0.012 | 0.220 |
| | Significant improvement in symptoms 70-80% | 0.823 | 1 | 0.364 | 1.152 | 0.012 | 0.220 |
| | Total improvement in symptoms 90-100% | 2.125 | 1 | 0.145 | 1.254 | 0.925 | 1.702 |
| 6 months | Moderate improvement in symptoms 50-60% | 29.912 | 1 | <0.001 | 0.000 | 0.000 | 0.000 |
| | Significant improvement in symptoms 70-80% | 2.3519 | 1 | 0.126 | 1.272 | 0.935 | 1.731 |
| | Complete improvement of symptoms 90-100% | 0.224 | 1 | 0.636 | 1.076 | 0.758 | 1.445 |
| 1 year | Moderate improvement in symptoms 50-60% | 32.478 | 1 | <0.001 | 0.000 | 0.000 | 0.000 |
| | Significant improvement in symptoms 70-80% | 3519 | 1 | 0.061 | 1.371 | 0.986 | 1.908 |
| | Complete improvement of symptoms 90-100% | 0.077 | 1 | 0.782 | 1.047 | 0.758 | 1.445 |
| Beyond 1 year | Moderate improvement of symptoms 50-60% | 13.988 | 1 | <0.001 | 0.000 | 0.000 | 0.000 |
| | Significant improvement of symptoms 70-80% | 86.37 | 1 | <0.001 | 6.850 | 4411 | 10.637 |
| | Complete improvement of symptoms | 65.441 | 1 | <0.001 | 3.837 | 2.749 | 5.356 |

Postoperative wellbeing and quality of life of endometriosis patients in study III/a.

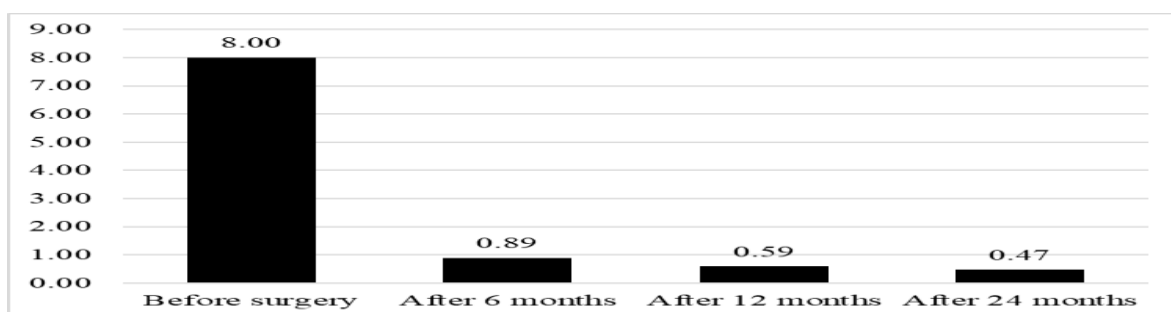


The relationship between well-being and infertility after surgery in study III/a

(There was a significant correlation between rate of improvement and pregnancy one month (Cramer'sV = 0.218; $\chi^2(3) = 31.847$; $p < 0.001$) and six months after surgery (Cramer'sV = 0.213; $\chi^2(2) = 30.302$; $p < 0.001$), one year after intervention (Cramer'sV = 0.232; $\chi^2(2) = 33.510$; $p < 0.001$), at monitoring one year later (Cramer'sV = 0.303; $\chi^2(2) = 43.513$, $p < 0.001$). In the second arm of the study, 81.6% of enrolled patients reported higher education levels and higher income categories. The mean age for diagnosis was 34.2 ± 5.97 years (22 to 48 years). The average duration of infertility was 3.8 ± 2.1 years. The mean time between symptom onset and diagnosis was 9.7 ± 0.35 years. The most commonly reported signs or symptoms were infertility in 70.1%, dysmenorrhea in 82.8%, dyspareunia in 60.9%, bloating in 93.1% and urination discomfort in 49.4%. During surgery, the left ovary was often observed as the only organ affected (42.5%), while involvement of the rectovaginal septum occurred in 55.2% and superficial peritoneal implantation in 66.7%. The third stage of endometriosis is most commonly observed (48.3%). Data analysis on the NRS-11 scale showed 85/87 patients (94.8%) with mean preoperative pain scores between 6 and 10 (moderate to severe pain). Postoperative pain perception improved to an average of 0-2 points (no or mild intermittent discomfort) in 71/87 patients (81.6%). Before surgery, the mean VAS score was 8-10 (moderate to severe pain) in 82 out of 87 patients (94.3%). Postoperative VAS score decreased to 0.47-0.89 (minimal or painless) in 81/87 patients (93.1%). The completion rate was 100%, except for three pregnancy cases. After surgery, all patients reported significant changes and improvements in quality of life indices. All Mauchly variance homogeneity tests showed heteroscedasticity.



Psycho-emotional evaluation of individuals before and after surgery according to different follow-up intervals (April-June 2 and 24 months) in study III/b.



| Multivariate Tests | Value | F | Hypothesis df | Error df | Sig. |
|--------------------|--------|----------|---------------|----------|--------|
| Pillai's Trace | 0.933 | 391.797b | 3 | 84 | <0.001 |
| Wilks' Lambda | 0.067 | 391.797b | 3 | 84 | <0.001 |
| Hotelling's Trace | 13.993 | 391.797b | 3 | 84 | <0.001 |
| Roy's Largest Root | 13.993 | 391.797b | 3 | 84 | <0.001 |

SUMMARY OF RESULTS

Our study consisted of two main parts. In the first part, three retrospective studies involved collecting patient information from the hospital database. The study involved 28 women with post-caesarean isthmocoeles who underwent combined hysteroscopic and laparoscopic correction. Postoperative fertility was 82.4% (n=14/17). Endometriosis was found in 16 patients (57.1%) who had not previously had endometriosis before caesarean section. After surgery, patient satisfaction was 92.9% (26/28) with improved quality of life. In study II, data from 455 patients with endometriosis-related infertility were collected between 2010 and 2018 using combined radical laparoscopic surgery and ART. The pregnancy rate was 81.3% (370/455), 94.2% (327/347) with live birth and 5.8% (20/347) pregnancy loss. Spontaneous pregnancy occurred in 39.5% of patients (146/370), 3.8% of women (14/370) after AIH and 56.8% (210/370) after

IVFET. Patients over 35 years of age had a higher chance of conception after surgery (84% vs. 77% [p=0.039]). By comparison, this effect is 91.3% vs. 74.1% (p=0.007; OR=3.7; 95% CI=1.4–9.8) in the ≤ 35 and >35 age groups. There was no significant difference in reproductive performance at different stages of endometriosis.

Study III was based on data from 777 endometriosis patients who underwent combined hysteroscopy-laparoscopic surgery combined with occasional ART treatment. Postoperative quality of life significantly improved; 46-49% showed moderate-significant improvement and 35-54% achieved complete resolution of symptoms (p<0.0005). These results can be observed in the most common complaints: dyspareunia (80%), dysmenorrhea (74%) and infertility (69%). The fourth study was a prospective study of 87 women with endometriosis who were required to complete a modified EHP-36 questionnaire before and after surgery to assess endometriosis in terms of quality of life, overall well-being, and fertility. The women, based on their condition and disorder, e.g. infertility, underwent combined hysteroscopy-laparoscopic surgery, which in all cases included surgical or diagnostic hysteroscopy. This group experienced significant improvements in quality of life (p<0.001). The VAS score for preoperative pain decreased from 8 ± 2.11 (86.0%) for moderate to severe pain to 0.47 ± 1.24 (93.1%) after surgery, representing the level of negligible or no pain, which is a significant improvement (p <0.001). 58.45% (32/61) of infertile women became pregnant. The analysis showed that 77.4% (24/31) of the cases tracked were live births. Postoperative overall well-being was rated as "very good" or "good" by 94.2% (82/87) of participants. There was a significant improvement in sexual life, with 86.2% of women (75/87) rating it as "good" or "very good" (p<0.001).

ANSWERS TO OUR HYPOTHESES

1. Our results show a correlation between a history of cesarean section and an increased incidence of endometriosis development, supporting our first hypothesis.
2. The data obtained show that combined hysteroscopic and laparoscopic endometriosis surgery significantly improved fertility outcomes in patients with endometriosis, supporting our second hypothesis.
3. Our results showed that combined hysterolaparoscopy significantly improved the quality of life of endometriosis patients, and demonstrated that the validated EHP–36 instrument, as well as VAS and NRS–11, are useful tools in assessing the quality of life of endometriosis patients, supporting our third hypothesis.

CONCLUSION

Based on our studies, only extensive and comprehensive studies can confirm the claim that tissue dissemination can cause the development of endometriosis through a direct or sporadic

process caused by certain surgical interventions. Excessive or improperly performed obstetric and gynecological surgical procedures (i.e. abortion, HSG, etc.) can also cause tissue dissemination. Our study has contributed to the literature by providing new perspectives and solutions for the treatment of obstetric and gynecological cases, including possible etiological aspects of the implantation theory of endometriosis. Studies have also established that combined hysterolaparoscopy treatment is an effective and reliable procedure; It has improved women's well-being and quality of life and significantly improved reproductive performance. The study also demonstrates a link between the location of endometriosis and pain-related and other symptoms.

The inclusion of the modified EHP-36 questionnaire could provide a wider range of providers for women in outpatient clinics with early endometriosis as a background of symptoms, reducing the frequency of delayed diagnosis. In summary, our study revealed that radical combined hysteroscopy-laparoscopy or laparoscopic surgery significantly improved fertility performance and, in addition, improved patients' quality of life and overall well-being. Our study also showed that the procedure was safe in the hands of a specialist endoscopic surgeon. Postoperative outcomes highlighted significant improvements in alleviating socioeconomic burdens on individuals or society in general as a result of endometriosis. Finally, in the investigation of this study, we also arrived at some statistically significant results supporting the two dispositions regarding the implantation theory and genetic correlations. However, there was no statistically significant evidence of dietary effects. More comprehensive studies will be required to significantly unravel this theory.

PUBLICATIONS RELATED TO THE THESIS:

1. **Ekine AA**, István F, & Árpád R, & István T, & Boldizsár N. Endoscopic surgical treatment of isthmocele and its probable link with endometriosis. A 3-years retrospective review of combined laparoscopic and hysteroscopic surgery. *Indian J Obstet Gynecol Res.* 2018; 5:458–464. 10.18231/2394-2754.2018.0105.(IF:1.34)
2. **Ekine AA**, Fülöp I, Tekse I, Rucz Á, Jeges S, Koppán Á, Koppán M. The Surgical Benefit of Hysterolaparoscopy in Endometriosis-Related Infertility: A Single Center Retrospective Study with a Minimum 2-Year Follow-Up. *J Clin Med.* 2020. február 13.; 9(2):507. doi: 10.3390/jcm9020507. PMID: 32069800; PMCID: PMC7073634. (IF: 3.9)
3. **Ekine AA**, Fülöp I, Tekse I, Kovács Z, Siklós P, Koppán Á, Koppán M. Effectiveness of Combined Hysterolaparoscopy on the Quality of Patients with Endometriosis: A Retrospective Review in Hungary. *J Women's Health Dev.* 2020; 3:032–055. (IF: 1.1)
4. **Ekine AA**, Fülöp I, Racz A, Koppán A, Siklós P, Koppán M. The benefits of Radical Laparoscopic Surgery and a Modified Endometriosis Health Profile–36 (EHP–36) on Quality of life. *Journal of Women's Health and Development* 3 (2020):379-397. (IF: 1.1)

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