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MEDICINE

STUDY OF QUALITY OF LIFE IN PATIENTS WITH COLORECTAL ENDOMETRIOSIS

ABSTRACT OF DOCTORAL THESIS

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I. CURRENT STATE OF KNOWLEDGE

Chapter 1. General data on endometriosis

Endometriosis is a chronic, estrogen-dependent gynecological condition characterized by the presence of ectopic endometrial glands and stroma, associated with a persistent inflammatory response and a progressive fibrotic process [1]. According to the data presented in this thesis, endometriosis is currently considered a complex systemic disease, in which chronic inflammation, immune dysfunction, and hormonal imbalances contribute to the initiation and maintenance of lesions [2–4].

The prevalence of endometriosis is estimated at 6–10% among women of reproductive age, with significantly higher rates observed in patients with chronic pelvic pain and infertility. Delayed diagnosis favors disease progression toward severe forms, including deep and colorectal endometriosis [5,6].

The etiopathogenesis of endometriosis is multifactorial, with several complementary theories described, such as retrograde menstruation, coelomic metaplasia, the theory of embryonic remnants, and vascular or lymphatic dissemination [7]. The thesis emphasizes the major role of chronic inflammation and altered immune response in disease development. The endometriotic microenvironment is characterized by increased infiltration of macrophages, neutrophils, NK cells, and dendritic cells, associated with elevated production of proinflammatory cytokines and chemokines [8–10].

Peritoneal macrophages represent the central cellular population in the pathogenesis of endometriosis and the development of associated fibrosis, accounting for approximately 50% of leukocytes in the peritoneal cavity [11]. These include embryologically derived large peritoneal macrophages (LpM) and monocyte-derived small peritoneal macrophages (SpM). In endometriosis, macrophage phagocytic function is altered, favoring the survival and implantation of ectopic endometrial tissue [12].

Predominant polarization toward the M2 phenotype contributes to disease progression by stimulating angiogenesis, fibrogenesis, and extracellular matrix remodeling. M2 macrophages secrete mediators such as IL-6 (interleukin 6), TNF-α (tumor necrosis factor), HGF (hepatocyte growth factor), and VEGF (vascular endothelial growth factor), which promote cellular recruitment, fibroblast proliferation, and the development of endometriotic

lesions, whereas M1 macrophages exert an inhibitory role; this balance is disrupted in endometriosis [13,14].

Activation of the nuclear factor kappa-B (NF-κB) transcription pathway represents a central mechanism in the maintenance of chronic inflammation, being stimulated by oxidative stress induced by excess peritoneal iron [15]. Prostaglandin E2 (PGE2) contributes to suppression of macrophage phagocytic activity by inhibiting the expression of cluster of differentiation 36 (CD36) and matrix metalloproteinase 9 (MMP-9), thereby favoring lesion persistence [16]. Local hormonal imbalance, characterized by increased estrogen production and overexpression of estrogen receptor β (ER-β), amplifies macrophage recruitment through NF-κB signaling and increased production of monocyte chemoattractant protein-1 (MCP-1), while estrogen further modulates macrophage activity via the CD200R receptor [17,18].

Advances in research have led to the redefinition of endometriosis as a predominantly fibrotic pathology, in which ectopic endometrial glands and stroma represent only a minor component of lesions. Fibrosis is driven by activation of myofibroblasts derived from resident fibroblasts, epithelial or endothelial cells undergoing epithelial–mesenchymal transition, and bone marrow–derived fibrocytes, a process mediated by de novo expression of α-smooth muscle actin (α-SMA) under the influence of tissue stiffness and transforming growth factor-β (TGF-β), resulting in excessive extracellular matrix accumulation, altered tissue architecture, and organ dysfunction [19,20].

Chapter 2. Multidimensional assessment of the impact of endometriosis: instruments, staging, and clinical consequences

Endometriosis has a multidimensional impact that cannot be assessed solely by the anatomical extent of lesions. The thesis highlights the need for standardized instruments to evaluate quality of life and associated symptomatology, particularly in forms with colorectal involvement.

Health-related quality of life is assessed using both generic and disease-specific instruments. The thesis describes questionnaires dedicated to evaluating quality of life in patients with endometriosis, such as the 30-item Endometriosis Health Profile (EHP-30), the European Quality of Life – 5 Dimensions questionnaire (EQ-5D), and the Short Form-36 (SF-

36), as well as instruments used to assess sexual quality of life. Digestive symptomatology is quantified using specific questionnaires, and pain intensity is evaluated through validated scales such as the visual analogue scale (VAS) [21,22].

Endometriosis staging allows characterization of the anatomical extent of disease; however, the thesis emphasizes the lack of a consistent correlation between lesion stage and symptom severity or quality-of-life impact. This discrepancy justifies the systematic integration of quality-of-life assessment into the global evaluation of disease burden and therapeutic effectiveness [23].

Excisional surgical treatment of endometriosis is associated with improvement in pain and functional outcomes, with a favorable impact on quality of life. However, the benefit perceived by the patient is not always proportional to complete symptom resolution, underscoring the importance of patient-centered evaluation [24–26].

The thesis also describes the consequences of endometriosis on pregnancy, highlighting its association with an increased risk of obstetric complications, such as first-trimester bleeding, preeclampsia, gestational diabetes, placental abruption, premature rupture of membranes, intrauterine growth restriction, and preterm birth. These data support the systemic nature of endometriosis and its impact beyond the gynecological sphere [27].

In the context of colorectal endometriosis, the association of digestive symptoms, chronic pain, and potential complications leads to severe impairment of quality of life, emphasizing the need for a multidimensional approach to the evaluation and management of these patients.

II. PERSONAL CONTRIBUTIONS

Chapter 3: Working hypothesis and general objectives

Deep colorectal endometriosis represents one of the most severe forms of endometriosis, being defined by infiltration of endometriotic lesions to a depth greater than 5 mm. Its prevalence is estimated at approximately 1% in the general female population, increasing to 4–37% among patients with pelvic endometriosis. Typical localizations include the pouch of Douglas, uterosacral ligaments, posterior vaginal wall, rectum, sigmoid colon, and urinary tract [26, 28, 29].

This form of disease is characterized by severe symptomatology, dominated by chronic pelvic pain, manifested as dysmenorrhea, deep dyspareunia, and intermenstrual pain. Rectosigmoid involvement may be associated with dyschezia, rectal bleeding, or catamenial diarrhea, with a significant impact on bowel function and daily quality of life [30].

Deep colorectal endometriosis cannot be adequately evaluated exclusively through anatomical or imaging parameters, as a true understanding of the disease requires integration of the subjective dimension related to pain perception, functional limitations, and psychosocial impact. In the absence of validated and adapted instruments, quality-of-life assessment has remained fragmented, with predominant emphasis on anatomical and surgical aspects. The concept of Health-Related Quality of Life (HRQoL) provides an appropriate conceptual framework for evaluating this dimension; however, its application in deep colorectal endometriosis has long been limited [31]. The discordance between the anatomical outcome of treatment and the subjective perception of well-being constituted the foundation of the working hypothesis of the present thesis.

Based on this premise, the doctoral project was structured into three complementary research directions. Study 1 aimed to identify the determinants of postoperative quality of life by integrating clinical and psychometric variables into a unified analysis. Secondarily, it sought to characterize the clinical, demographic, and surgical profile of patients with colorectal endometriosis. The central hypothesis was that deep colorectal endometriosis exerts a major and multidimensional impact on women's lives and that this impact can be objectively measured through the use of the SF-36 questionnaire.

In this context, Study 2 aimed to validate the SF-36 questionnaire for patients with colorectal endometriosis by assessing its validity, reliability, and sensitivity to change, in order to support its use as a reference instrument for HRQoL evaluation. Study 3 analyzed the correlation between SF-36 scores, pain intensity assessed by VAS, and digestive symptomatology, with the objective of demonstrating that postoperative improvement in quality of life is possible even in the presence of residual digestive dysfunctions.

The general aim of the thesis was to achieve a comprehensive and objective evaluation of the quality of life in surgically treated patients with deep colorectal endometriosis, demonstrating that therapeutic success is not limited to lesion excision or improvement of

objective symptoms, but is reflected in global functional recovery and restoration of the patient's biopsychosocial balance, assessed through validated and sensitive instruments.

Chapter 4: General research methodology

The research was designed as a retrospective analysis of prospectively collected data, conducted at Rouen University Hospital (Rouen, France) between June 2009 and November 2016. This design, consisting of a prospectively assembled cohort analyzed retrospectively, allowed the collection of clinical data in real time, which were subsequently evaluated systematically, providing a longitudinal perspective on postoperative outcomes in patients with deep colorectal endometriosis.

Patients diagnosed with deep endometriosis involving the rectum or sigmoid colon were included, for whom surgical treatment was indicated to relieve pain and restore digestive function. Surgical procedures were performed laparoscopically by a multidisciplinary team experienced in colorectal endometriosis surgery, within a university setting based on the principles of evidence-based medicine.

Patients were enrolled in the international database *Centre d'Investigations et de Recherche sur l'Endométriose* (CIRENDO), an interregional prospective clinical cohort gathering cases treated in university centers in Rouen, Lille, Amiens, and Caen (G4 Group), after obtaining informed consent for the use of data for research purposes. This database aims to centralize and standardize clinical, surgical, and quality-of-life data, facilitating the development of multicenter research. Data collection and storage were conducted in accordance with national data protection regulations and were authorized by the *Commission Nationale de l'Informatique et des Libertés* (CNIL) and the *Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé* (CCTIRS). The study was conducted according to the approved protocol (NCT02294825) and the principles of the Declaration of Helsinki.

The surgical technique was adapted to the extent of the lesions: rectal shaving for superficial involvement, disc excision for unifocal lesions with partial invasion, and segmental rectosigmoid resection for extensive or stenotic infiltrations.

This methodological framework aimed to achieve an integrated evaluation of the impact of surgery on quality of life, encompassing both the objective dimension of the surgical procedure and the subjective, psychometric dimension of perceived health status.

Patient selection was based on predefined criteria established in the CIRENDO protocol to ensure cohort homogeneity and internal validity of the analysis. Included were patients with histologically confirmed deep colorectal endometriosis, aged between 18 and 50 years, who underwent complete surgical treatment in participating centers and for whom complete clinical data were available.

An essential inclusion criterion was the complete completion of self-administered questionnaires—SF-36, Gastrointestinal Quality of Life Index (GIQLI), Knowles–Eccersley–Scott Symptom Questionnaire (KESS), and VAS—administered preoperatively and at 12 months postoperatively.

We excluded the cases without histological confirmation, those with incomplete data or loss to follow-up, patients with concomitant chronic digestive diseases that could influence GIQLI or KESS scores, surgical procedures performed outside G4 centers, as well as pregnant patients or those in the early postpartum period.

The application of these criteria allowed the constitution of a well-defined cohort representative of patients with deep colorectal endometriosis, reducing selection bias and enabling valid comparisons between preoperative and postoperative assessments. Data were collected prospectively according to the standardized CIRENDO protocol, using structured clinical forms and validated questionnaires.

The instruments used to evaluate quality of life and symptomatology were SF-36, GIQLI, KESS, and VAS, which were self-administered under minimal medical supervision to ensure confidentiality and accuracy of responses. Questionnaires were administered at two distinct time points: preoperatively and at 12 months postoperatively. For the psychometric validation of SF-36, a control group consisting of healthy women without endometriosis or other chronic diseases was included.

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 23.0, applying descriptive, comparative, and correlational methods appropriate to the objectives of each study. Detailed descriptions of the statistical tests used are provided in the chapters dedicated to individual analyses.

The main limitation of the study lies in the absence of a separate analysis of the influence of postoperative complications, recurrences, or functional sequelae on quality-of-life scores. This approach was deliberate, as the central objective of the research was to evaluate the validity, reliability, and sensitivity to change of the SF-36 questionnaire, as well as to compare preoperative and postoperative quality of life using multiple validated instruments.

Chapter 5: Study 1 – Determinants of postoperative quality of life in patients with colorectal endometriosis: a multidimensional clinical and psychometric analysis

This study was based on the premise that the impact of colorectal endometriosis must be evaluated beyond the strictly anatomical dimension, explicitly incorporating the patient's perception of the disease and of postoperative recovery. Postoperative quality of life is influenced not only by lesion excision but also by how patients perceive pain, by the restoration of digestive function, and by the recovery of psychological balance, given that a relevant proportion of patients report emotional disturbances associated with chronic pain and its impact on body image and femininity [32].

The working hypothesis was that patients with colorectal endometriosis present a particular clinical and psychological profile, characterized by complex symptomatology, multifocal pelvic involvement, and self-reported emotional disturbances, and that surgical treatment leads to pain reduction (VAS) and improvement of digestive function (GIQLI and KESS) at 12 months postoperatively. The objectives of this approach included the evaluation of postoperative changes in pain intensity and digestive function through comparative analysis of VAS, GIQLI, and KESS scores before and after surgery, these variations being used as objective indicators of functional recovery. In parallel, a detailed description of the demographic and clinical profile of patients with deep colorectal endometriosis was performed, considering age, body mass index, surgical history, and type of anatomical involvement. Disease severity was assessed using the rAFS score, and the distribution of endometriotic lesions within pelvic organs was systematically analyzed. Additionally, the prevalence of self-reported emotional disorders and their association with digestive symptomatology were evaluated.

The analysis included 488 patients from the CIRENDO database, with histologically confirmed deep colorectal endometriosis and complete 12-month follow-up. Age distribution was approximately Gaussian, with a peak around 32–33 years; 68% of patients were aged between 26.4 and 39.4 years, and 95% between 19.9 and 45.9 years (overall range 18–50 years). In the cohort, 30.7% were smokers, and the majority (70.7%) had a BMI ≤ 24.9 kg/m². Self-reported psychological disorders were present in 29.1% of patients, most commonly anxiety (21.7%), followed by sleep disorders (16.2%), depression (10.0%), and panic attacks (6.8%). More than half of the patients (56.6%) had a history of gynecological surgery, predominantly laparoscopic. Dysmenorrhea was reported by 97.7%, dyspareunia by 76.2%, and infertility by 34.2%. rAFS scores clustered in ranges suggestive of severe disease, with extensive involvement and multi-organ impairment.

From a surgical perspective, 90.2% of cases were managed laparoscopically. Complete obliteration of the pouch of Douglas was observed in 56.4% of patients and partial obliteration in 30.9%. Adhesiolysis was required in 92.4% of patients, most frequently rectovaginal (85.2%). Intestinal lesions were predominantly rectal (87.9%) and sigmoid (49.0%). Associated digestive procedures were performed in 83.6% of patients; the most frequent techniques were rectal shaving (33.4%), segmental colorectal resection (25.0%), and disc excision (11.3%). Temporary stomas were used selectively (colostomy 11.3%, ileostomy 2.9%). Urinary tract procedures were required in 15.0% of cases. Postoperative complications had an overall incidence below 15%, the most frequent being ureteral fistulas (7%) and digestive fistulas (2.2%).

In pre- versus postoperative comparison at 12 months, using paired-sample t-tests, KESS and GIQLI scores improved significantly ($p < 0.001$), and dysmenorrhea decreased significantly regardless of analgesic treatment use ($p < 0.001$). Dyspareunia decreased significantly only in patients without preoperative treatment ($p < 0.001$), while in those receiving treatment values remained stable ($p = 0.657$). VAS dysmenorrhea without treatment decreased from 8.4 to 2.1 ($p < 0.001$), and with treatment from 4.7 to 2.9 ($p < 0.001$). VAS dyspareunia without treatment decreased from 5.6 to 1.9 ($p < 0.001$), whereas with treatment it showed no significant change (4.0 to 3.8; $p = 0.657$). The KESS score decreased from 10.6 to 9.1 ($p < 0.001$), and the GIQLI score increased from 76.6 to 90.5 ($p < 0.001$).

In conclusion, this study shows that one year after surgery for colorectal endometriosis there is a significant improvement in pain and digestive function, reflected by decreases in VAS

and KESS scores and an increase in GIQLI scores, supporting the combined use of these instruments in multidimensional postoperative evaluation. The results suggest that therapeutic success should be assessed not only through anatomical parameters but also through functional and psychometric indicators, although the persistence of residual disturbances in a small number of patients indicates the presence of functional and psychological mechanisms that are not fully correctable by surgery alone, which justifies the continuation of quality-of-life instrument validation in Study 2.

Chapter 6: Study 2 – Validation of the SF-36 questionnaire in colorectal endometriosis and comparative pre- and postoperative analysis of quality of life in this patient population

Study 2 was initiated to validate and evaluate the usefulness of the SF-36 questionnaire as a quality-of-life assessment tool in patients surgically treated for deep colorectal endometriosis, in the French language. This approach was motivated by the need to confirm the reliability and internal consistency of SF-36 in a population affected by a complex pathology with major impact on physical and psychological well-being. At the time of study initiation, the literature did not provide relevant data regarding the applicability of the French version of SF-36 in endometriosis, and the lack of validation and demonstrated reproducibility in colorectal endometriosis represented a methodological limitation for comparative evaluation of therapeutic outcomes, given that subjective assessment of quality of life remained dependent on instruments used in other pathologies.

In this context, the study pursued two main directions: (1) analysis of the internal reliability of SF-36 and (2) comparison of SF-36 scores in patients with colorectal endometriosis (preoperatively and at one year postoperatively) with those of a healthy control group, in order to assess the impact of surgery on the physical and mental components of quality of life. The working hypothesis was that SF-36 is a valid instrument sensitive to postoperative clinical changes, reflecting physical and psychological improvement after colorectal endometriosis surgery. It was also assumed that preoperative scores are significantly lower than those of the control group for both components (physical and mental), and that these differences decrease at one year postoperatively, concomitant with improvement in pain and digestive function. The

overall objective was to evaluate the psychometric validity and clinical sensitivity of the SF-36, as well as to estimate the contribution of laparoscopic surgery to the restoration of physical and mental quality of life through a direct comparison with a control group, thereby differentiating disease-related impact from factors related to subjective perception or postoperative adaptation.

Study 2 was designed as a retrospective analysis of prospectively collected data, with a validation component, using the same cohort of 488 patients as in Study 1, diagnosed with deep colorectal endometriosis and operated at Rouen University Hospital (France) between June 2009 and November 2016, with interventions performed by a multidisciplinary team, predominantly laparoscopically. Patients were drawn from the CIRENDO database, a prospective cohort with standardized data on diagnosis, treatment, and postoperative follow-up. Selection included only cases with complete preoperative and one-year postoperative data, including fully completed quality-of-life questionnaires.

Inclusion criteria were histopathological confirmation of deep rectal/rectosigmoid endometriosis, completion of the SF-36 questionnaire preoperatively and at 12 months postoperatively, and availability of complete clinical data; cases with incomplete data or inconsistent questionnaires were excluded. To provide a reference for normality, a control group of healthy women (25–34 years), without endometriosis, chronic digestive disease, or pelvic surgery, was used exclusively for comparison of SF-36 scores.

SF-36 (a multidimensional HRQoL instrument) was analyzed across its eight domains: physical functioning (PF), role limitations due to physical health (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH), as well as the physical component summary (PCS) and mental component summary (MCS) scores, each domain scaled from 0 to 100 (higher values indicating better quality of life). Reliability and internal consistency were assessed using item–scale correlations (considered satisfactory if >0.40), discriminant validity (scaling success rate), and Cronbach's α coefficient (acceptable ≥0.70), applied to both preoperative and postoperative datasets to evaluate stability and sensitivity to change. Clinical sensitivity of SF-36 was analyzed by comparing preoperative versus 12-month postoperative scores and by comparison with the control group. Statistical analyses included mean ± standard deviation (SD), paired-sample t-test (pre vs. post), and independent-sample t-test (patients vs. control), with a significance threshold of $p<0.05$ and 95% confidence intervals (CI), using IBM SPSS v23.0.

All eight SF-36 domains demonstrated good internal consistency preoperatively and at one year postoperatively, with high Cronbach's α values, many domains showing postoperative increases, particularly RP and RE. Scaling success rates were consistently high across all domains (97.7%–99.8%), supporting stable metric performance of the instrument. Internal consistency of subscales (Cronbach's α) was very good already preoperatively (range 0.750–0.922) and was maintained or improved postoperatively (0.818–0.921), with high values reported for BP, PF, and MH. Item-level analysis showed an overall increase in postoperative homogeneity, with notable improvements for RP, BP, and MH. Scaling success remained very high before and after surgery, with only a slight decrease for VT (98.8% to 97.7%).

At 12 months postoperatively, significant improvements were observed in all eight domains and in both composite scores ($p<0.001$). Increases were recorded for: PF (69.8→82.8), RP (41.5→68.4), BP (44.4→69.8), GH (48.1→60.4), VT (35.6→45.8), SF (51.9→70.4), RE (47.7→68.5), and MH (45.9→57.9). Composite scores showed consistent increases: PCS (50.9→70.4) and MCS (45.3→60.6), both with $p<0.001$. Although postoperative values remained below normative levels of the control group, the overall trend indicated convergence toward these values. Mean differences showed the largest increases for RP (+26.9) and BP (+25.4), followed by RE (+20.8) and SF (+18.5), with more moderate increases for PF (+13.1), GH (+12.3), MH (+12.0), and VT (+10.2); PCS increased by +19.5 and MCS by +15.3 ($p<0.001$).

In the context of the widespread use of SF-36 in quality-of-life assessment, the results of this study support the robustness of the instrument in the colorectal endometriosis population, with Cronbach's α values above the acceptable threshold for all dimensions, both preoperatively and postoperatively. In the present analysis, the significant increases in PCS and MCS (50.9→70.4 and 45.3→60.6, respectively) confirm the perceived improvement in general health status after surgery. At the domain level, the most pronounced changes at 12 months were observed for physical role, emotional role, and pain—domains with particularly low preoperative scores—while the overall score trajectory indicates a multidimensional improvement in HRQoL among surgically treated patients. In addition, concordance in the direction of change between individual domains and composite scores supported the coherence of postoperative changes and the utility of SF-36 for evaluation in this population.

Study 2 demonstrates that SF-36 has a stable psychometric structure and adequate internal consistency in patients with deep colorectal endometriosis, confirming its reliability and usefulness for HRQoL assessment before and after surgical treatment. The use of a healthy control group allowed contextualization relative to the general population and showed that, although postoperative scores do not reach normative values, the 12-month evolution is clearly favorable across all domains. Through formal validation of SF-36 in this population, the study provides a methodological framework for standardizing quality-of-life assessment in colorectal endometriosis and supports the integration of validated instruments in evaluating the real benefits of surgery on physical and mental dimensions.

Chapter 7: Study 3 – Analysis of the correlation between pain intensity and quality of life after colorectal endometriosis surgery and the impact of digestive disorders on postoperative recovery

Study 3 was developed based on the observation that, in deep colorectal endometriosis, pain (dysmenorrhea and dyspareunia) represents the major determinant of quality-of-life impairment. Although postoperative symptom improvement is well documented, the relationship between pain intensity and the HRQoL dimensions assessed by SF-36 has been less extensively explored. Moreover, clinical practice has highlighted situations in which some patients report an overall improvement in quality of life despite persistence or even worsening of postoperative digestive symptoms, suggesting that digestive function alone does not fully explain the recovery pattern. The working hypothesis was that postoperative pain reduction correlates directly with increases in SF-36 scores across all domains (physical and mental components), and that deterioration of digestive function (higher KESS, lower GIQLI) does not negate the overall HRQoL benefit, pain remaining the dominant factor. The objectives included evaluation of correlations between VAS (dysmenorrhea/dyspareunia) and SF-36 domains pre- and postoperatively, identification of domains most sensitive to pain-related changes, and analysis of HRQoL evolution in subgroups with worsened KESS or GIQLI scores, to explain the clinical “paradox” of recovery.

The analysis used the same CIRENDO cohort (488 patients operated on for deep colorectal endometriosis), with adjusted subgroups based on questionnaire completion and

symptom presence, assessed preoperatively and at one year postoperatively. The relationship between pain and HRQoL was evaluated using Pearson correlation coefficients between VAS and the eight SF-36 domains (and composite scores), stratified according to analgesic/hormonal treatment use. The second analytical direction addressed the impact of digestive disorders: patients with worsened postoperative KESS scores (n=149) and those with deteriorated GIQLI scores at one year (n=104) were analyzed separately, comparing pre- versus postoperative SF-36 scores using paired-sample t-tests, with 95% confidence intervals (CI) and a significance threshold of $p<0.05$. Statistical analyses were performed using IBM SPSS v23.0.

Pearson analysis showed negative correlations between dysmenorrhea intensity and all SF-36 domains, both preoperatively and at one year postoperatively, with generally stronger relationships postoperatively. For dysmenorrhea, correlations with physical domains (e.g., PF, RP, BP) and with composite scores (PCS, MCS) were significant, indicating that patients with persistent menstrual pain show a clearer association between pain and global functioning. For dyspareunia, correlations were more modest preoperatively and became more evident postoperatively, particularly for certain domains (e.g., SF, GH) and for composite scores, suggesting that reduction of pain during sexual intercourse translates into improvements in physical and psychosocial dimensions. Overall, all SF-36 domains correlated negatively with dysmenorrhea (with and without treatment) and with dyspareunia (particularly without treatment), while in the subgroup with dyspareunia under treatment, significant correlations were observed selectively with specific domains.

In the analysis of digestive symptomatology, 30.5% (n=149) of patients showed worsened KESS scores; however, within this subgroup, significant improvements were observed in all SF-36 domains at one year postoperatively, $p<0.001$, 95% CI (e.g., PF 57.7→78.5; RP 42.8→61.7; BP 47.3→65.7; GH 49.5→55.9; SF 55.2→68.5; RE 52.8→68.9; MH 48.5→57; PCS 52.7→65.5; MCS 48.7→59.5), with $p=0.002$, 95% CI for VT (38.2→43.4), although with smaller magnitudes compared to the overall cohort. Regarding GIQLI, 21.3% (n=104) of patients showed deterioration; in this subgroup, most SF-36 domains displayed changes without statistical significance, while significant increases were observed only for BP ($p=0.006$) and PCS ($p=0.047$).

The results indicate a general improvement in digestive functional scores across the cohort, alongside a heterogeneous postoperative evolution, with a subgroup experiencing

worsening digestive symptoms. At the same time, the analysis supports the concept that postoperative HRQoL improvement does not depend exclusively on optimization of intestinal function, as even in patients with increased KESS or reduced GIQLI scores postoperatively, SF-36 scores may increase compared to preoperative values. This suggests that reduction of pelvic pain may compensate, in the patient's global perception, for the persistence of transit disorders. Furthermore, these findings emphasize the need for a personalized and multidisciplinary therapeutic approach, given the complexity of interactions between pain, digestive function, and psychosocial dimensions of recovery [33].

Study 3 demonstrates that pain reduction (VAS dysmenorrhea/dyspareunia) is associated with increased SF-36 domain scores and confirms the role of pain as a major determinant of physical and psychosocial functioning. Although postoperative digestive function evolves variably and there are cases of worsened KESS or decreased GIQLI, the overall benefits on HRQoL remain evident, supporting the predominance of pain relief in recovery perception. The combined use of VAS, KESS, GIQLI, and SF-36 allows for a standardized and multidimensional evaluation of postoperative progress.

Chapter 8: Conclusions and personal contributions

Deep colorectal endometriosis is a severe, potentially disabling pathology, characterized by pelvic pain, digestive dysfunction, and a marked impairment of quality of life. The present thesis brings together three observational clinical studies conducted on a prospective cohort of 488 patients, which multidimensionally assess the impact of the disease and surgical treatment on pain, digestive symptoms, and health-related quality of life (HRQoL). Methodological rigor is supported by standardized pre- and postoperative follow-up, the large cohort size, validation of the SF-36 questionnaire in this population, and the use of appropriate statistical analyses.

Study 1 fulfilled its objective of characterizing the clinical and functional profile of patients with deep colorectal endometriosis. Cohort analysis highlighted the severity of pain and digestive symptomatology and demonstrated, through comparison of pre- and postoperative VAS, KESS, and GIQLI scores, a significant functional improvement one year after surgical intervention.

In Study 2, the use of the SF-36 questionnaire enabled a standardized and validated assessment of quality of life in patients with deep colorectal endometriosis. Psychometric analyses demonstrated good internal consistency and a stable domain structure, both preoperatively and at one year postoperatively. The evolution of SF-36 scores showed a significant improvement in both physical and mental dimensions of quality of life after surgical treatment, confirming the sensitivity of the instrument to clinical changes and its relevance for monitoring postoperative recovery in this pathology.

The analysis performed in Study 3 highlighted the central role of pelvic pain in shaping quality-of-life perception in patients operated on for colorectal endometriosis. Significant correlations between VAS scores and all SF-36 domains, observed both before and after surgery, indicate that pain intensity represents the main determinant of HRQoL. At the same time, persistence or worsening of digestive symptoms had a negative impact on certain quality-of-life dimensions, without compromising the overall benefit of surgery, suggesting that pain relief remains the dominant factor in the perception of postoperative recovery.

Overall, the results support the global benefit of surgical treatment and the need for a multidisciplinary approach, as well as the importance of standardized evaluation using validated instruments (VAS, KESS, GIQLI, SF-36), outlining future research directions regarding long-term follow-up and personalization of therapeutic strategies.

Personal contributions

The general part of the thesis consisted of an in-depth and multidisciplinary analysis of the specialized literature on deep colorectal endometriosis. The pathophysiological mechanisms of the disease were reviewed, with emphasis on the etiopathogenesis of fibrosis, chronic pain, and infertility, as well as current staging and classification methods. In addition, validated instruments for quality-of-life assessment were analyzed, highlighting the impact of endometriosis surgery on functional, psychosocial, and reproductive dimensions. The influence of the disease on fertility and pregnancy outcomes was also addressed. This approach constituted the theoretical basis for the development of clinical research and the formulation of hypotheses oriented toward a patient-centered approach. Thus, the following elements of originality were included:

a. A review article on the impact of deep endometriosis on pregnancy, demonstrated through maternal–fetal consequences and their pathophysiological mechanisms (Bibliographic reference 360);
b. The impact of deep endometriosis on quality of life analyzed from an integrative perspective, with emphasis on severe pain and its physical and psycho-emotional consequences, illustrated by an original case report describing excessive heat use as a method of self-management of pelvic pain, complicated by erythema ab igne (Bibliographic reference 252). This case highlights the risks of uncontrolled chronic pain and the need for a multidisciplinary therapeutic approach, including educational and psychological components.
c. Figures 1.1–1.6 represent original creations, developed using the BioRender software.

The personal contributions of the doctoral thesis consist of three original studies, published within the original article with Bibliographic reference 401:

1. In the first study, I investigated the determinants of postoperative quality of life in patients with deep colorectal endometriosis. I defined the clinical and paraclinical characteristics of the cohort of 488 patients according to inclusion and exclusion criteria, performed statistical analyses with tables, graphs, and figures, and demonstrated that:
   a. There was a significant postoperative decrease in VAS scores using paired-sample t-tests: for dysmenorrhea without treatment, from a mean of 8.4 to 2.1 ($p < 0.001$), and with treatment from 4.7 to 2.9 ($p < 0.001$), 95% confidence interval (CI 95%) (Subchapter 5.3.4);
   b. A significant postoperative decrease in VAS scores for dyspareunia without treatment, from a mean of 5.6 to 1.9 ($p < 0.001$), CI 95%, confirming the effectiveness of surgical intervention on pain symptoms (Subchapter 5.3.4);
   c. The mean KESS score decreased from 10.6 to 9.1 ($p < 0.001$), CI 95%, indicating an important improvement in constipation symptoms (Subchapter 5.3.4);
   d. The mean GIQLI score increased significantly from 76.6 to 90.5 ($p < 0.001$), CI 95%, reflecting a significant overall improvement in perceived quality of life after treatment (Subchapter 5.3.4).
2. In Study 2, I performed validation of the SF-36 questionnaire in patients with deep colorectal endometriosis, representing the first formal application and verification of this

quality-of-life assessment instrument in this pathology. The study confirmed that SF-36 is a reliable and sensitive instrument to postoperative changes, highlighting significant increases in quality-of-life scores one year after surgery in most evaluated domains. I demonstrated that:

a. Internal consistency analysis using Cronbach's α ranged between 0.75 and 0.92 preoperatively and between 0.82 and 0.92 postoperatively. The highest values were recorded for PF (0.922 pre/0.921 post), BP (0.850/0.910), and MH (0.865/0.890), confirming very good internal reliability. Domains with lower values, RP and RE, remained within acceptable ranges (0.75–0.89), supporting clinical usability (Subchapter 6.3.1);

b. Comparative pre- and postoperative analysis of SF-36 scores using paired-sample t-tests showed statistically significant increases ($p < 0.001$), CI 95%, across all eight domains (Subchapter 6.3.2);

c. Composite scales also showed major improvements: PCS increased by 19.5 points and MCS by 15.3 points (both $p < 0.001$), CI 95%, suggesting a significant surgical impact on both physical and psychological dimensions of quality of life (Subchapter 6.3.2);

d. Comparison of postoperative scores with French population norms (as an external reference) demonstrated a notable convergence across all domains, indicating relevant functional and psychological recovery at one year after treatment (Subchapter 6.3.2).

3. In Study 3, I analyzed the relationship between pain reduction and quality-of-life improvement, as well as the influence of residual digestive disorders on postoperative recovery, and demonstrated that patients show a significantly positive overall perception of their general condition:

a. A direct correlation was observed between decreases in VAS pain scores (dysmenorrhea and dyspareunia) and increases in all eight SF-36 domains, with Pearson coefficients ranging from 0.25 to 0.41 ($p < 0.001$), confirming the central role of pain relief in restoring well-being (Subchapter 7.3.1);

b. Although a subgroup of patients presented worsening intestinal transit symptoms (reflected by higher KESS or lower GIQLI scores), overall quality of life improved at one year postoperatively (Subchapter 7.3.2);

c. In patients with worsened KESS scores, all SF-36 domains showed statistically

significant increases ($p < 0.001$), except for the VT domain ($p = 0.002$) (Subchapter 7.3.2);

d. Despite worsened GIQLI scores, the BP and PCS domains showed statistically significant improvements, $p < 0.006$ and $p < 0.047$, respectively (Subchapter 7.3.2).

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2 **Scurtu F,** Scurtu LG, Bauşic AIG, Petca A, Mehedinţu C. Erythema ab igne-A Potential Cutaneous Marker of Chronic Heat Use in Patients with Endometriosis: A Narrative Literature Review and a Case Report. Life (Basel). 2025 Sep 29;15(10):1533. doi: 10.3390/life15101533. PMID: 41157206; PMCID: PMC12565542. FI=3,4, https://pmc.ncbi.nlm.nih.gov/articles/PMC12565542/ (Capitolul 1 , pag. 35)

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1. Bauşic A, Coroleucă C, Coroleucă C, Comandaşu D, Matasariu R, Manu A, **Frincu F**, Mehedinţu C, Brătilă E. Transvaginal Ultrasound vs. Magnetic Resonance Imaging (MRI) Value in Endometriosis Diagnosis. Diagnostics (Basel). 2022 Jul 21;12(7):1767. doi: 10.3390/diagnostics12071767. PMID: 35885670; PMCID: PMC9315729. FI=3,6. https://pmc.ncbi.nlm.nih.gov/articles/PMC9315729/ (Capitolul 3, pag. 45)
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3. Noditi AR, Bostan IS, **Scurtu F**, Ionescu D, Mehedintu AM, Petca A, Mehedintu C, Bostan M, Rotaru AM. Analysis of the Biopsychosocial Impacts Associated with Endometriosis to Improve Patient Care. J Clin Med. 2025 Mar 21;14(7):2158. doi: 10.3390/jcm14072158. PMID: 40217609; PMCID: PMC11989268. FI=2,9, https://pmc.ncbi.nlm.nih.gov/articles/PMC11989268/ (Capitolul 1, pag. 35)

- **Full-text articles published in BDI-indexed journals:**

1 **Frincu F**; Mehedințu C; Brătilă E; Iftene L; Bratu O; Spânu D; Socea B; Rotaru A.M., New perspectives in the pathogenesis of endometriosis – potential treatment strategies targeting the smart adult stem cells, Research & Science Today. 2019 Supplement S2, p88-101. 14p, ISSN-E: 2344-0007 / ISSN-L: 2344-0007 https://share.google/yv9h4VrB066SpDWKO (Capitolul 1, pag. 26)

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• Posters presented at National and International Congresses

▪ **Frincu F**, Ionescu G, Cazachevici A, Rotaru AM, Antonovici M, Iftene L, Mehedințu C Premiul I - O nouă strategie – Laparoscopie asistată prin Neuro-Navigație (LANN) în sprijinul tratamentului endometriozei profund infiltrative latero-pelvice (EPI-LP) - Al II-lea Congres național al societății de endometrioză și infertilitate est-europeană 2019 Sinaia

▪ **Frincu F**, Coroleucă B, Brătilă E, Mehedințu C - Study of postoperative pain in patients with pelvic endometriosis – SEUD Congress Montreal 2019

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