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# EFFECTS OF ENDOMETRIOSIS ON QUALITY OF LIFE

(Benefit of combined hystero-laparoscopic surgery on quality of life and fertility performance in endometriosis)

Doctoral (PhD) thesis

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## 1. INTRODUCTION

Endometriosis is a common, progressive, chronic disease with detrimental effects on affected women. It is a mostly benign but potentially debilitating gynecological disorder with rare malignant transformation [1]. Endometriosis is estimated to affect 10–15% of the female population of reproductive age [2, 3]. It is an estrogen-dependent disorder characterized by the growth of endometrium-like tissue outside the uterine cavity. Organs distant from the pelvis can be involved, such as the lungs and skin [4,5,6]. These displaced or relocated ectopic endometriotic lesions are predominately located in the pelvic cavity and can involve the ovaries, rectovaginal septum, peritoneal surfaces, uterine bladder, bowels, ligaments, pelvic sidewall structures, and the Fallopian tubes.

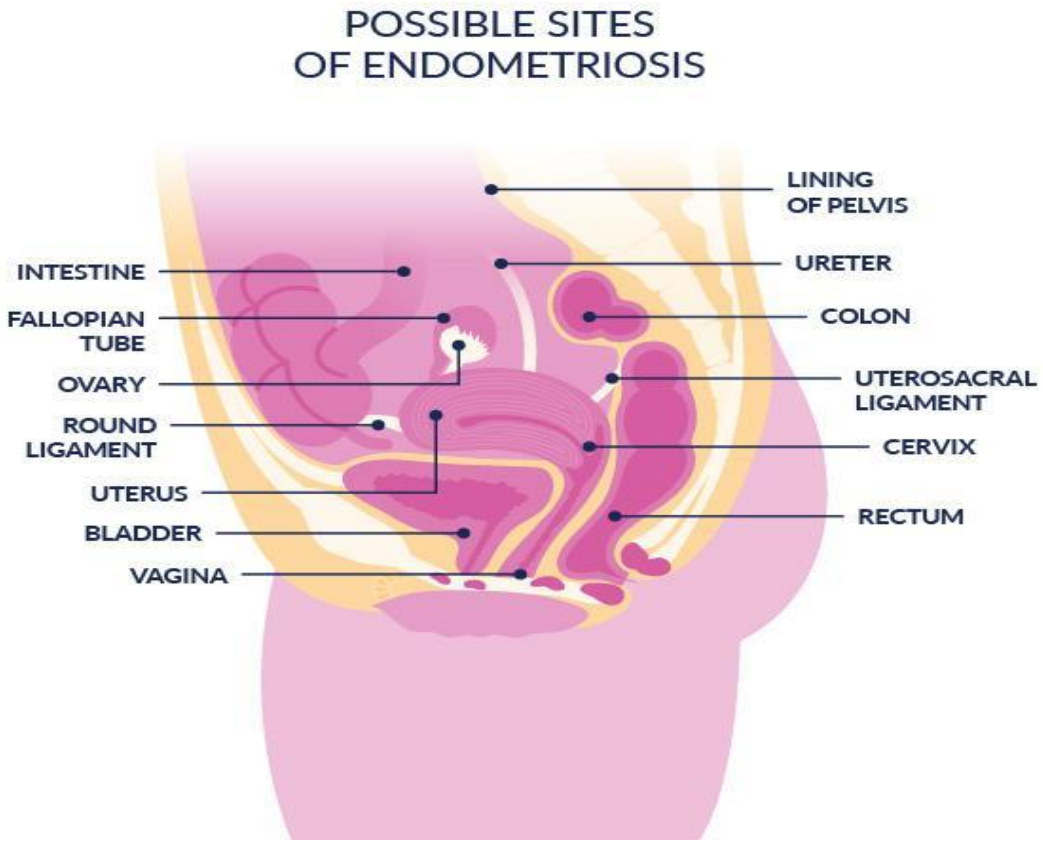



Figure 1: Possible sites of endometriosis (Dr. Lane et al. Adelaide Obstetrics & Fertility).

The quality of life (QoL) of women with symptomatic endometriosis is markedly reduced by subfertility or infertility, chronic pelvic pain, dysmenorrhea (painful periods), and dyspareunia (pain during sexual intercourse) [7, 8]. Endometriosis is estimated to affect 20–50% of the female population with fertility issues (subfertility

or infertility) [9, 10] and 40–60% of women with dysmenorrhea [11]. The complexity of its pathogenesis has made endometriosis difficult to identify using universally standard biomarkers; several attempts have been made with little or no success [12]. The major challenge of the disease is the delay in diagnosis, which frequently requires invasive procedures, such as laparoscopy, and—less frequently—diagnostic laparotomy [13, 14]. The severity of the disease reflects the resultant extent of pelvic adhesions and distortion of the pelvic anatomy, which can both lead to subfertility and infertility [4]. Endometriosis is categorized into stages by scoring systems developed by the American Fertility Society in 1979. The American Society for Reproductive Medicine (ASRM) classification of endometriosis is referred to by many authors as a useful tool for predicting *in vitro* fertilization (IVF) success and fertility performance [15]. Furthermore, the European Society for Human Reproduction and Embryology (ESHRE) suggests that patients with lesions classified as "moderately severe" or "severe" have a higher likelihood of success with IVF as the first line of treatment [16, 17, 18]. Several treatment modalities have been developed over the decades: symptomatic treatment of pain with nonsteroidal anti-inflammatory drugs (NSAIDs), other painkillers, oral contraceptive pills, progestogen-releasing intrauterine contraceptive devices (hormonal IUCDs), and agonists of gonadotropin-releasing hormone (GnRH). The complexity of the pathogenesis of endometriosis and the lack of clear-cut target molecules makes the development of therapeutics difficult. Currently, the only successful treatment modality for severe endometriosis consists of surgical removal of visible lesions with or without adjuvant medical therapy. Recurrence is relatively frequent depending on the surgical expertise and is estimated to range from 4.2–75% within 2 years; therefore, the need for repeated surgery is common [19, 20].

This dissertation aims to investigate the effectiveness of laparoscopic surgery on improving QoL, GeneralWB, and fertility performance in patients with endometriosis. Furthermore, its objectives are to test some of the hypotheses regarding the pathogenesis of endometriosis, such as the implantation theory (retrograde menstruation), the dietetic effect, and genetic disposition.

Endometriosis was first described in 1860 as "adenomyoma" by Karl Freiherr von Rokitansky, an Austrian pathologist. The first formal description of the disease was made by Dr. John Sampson in his paper describing 13 cases in which the presence of

endometrial tissue was noticed during abdominal surgery [1, 21]. Earlier, in 1690, Daniel Shroen recorded several detailed descriptions of the disease [21]. There are reports with medical implications of the disease dating back approximately 4,000 years. Some women presenting with symptoms similar to those of endometriosis were considered to be demon-possessed, witches, or mad; these women were regarded with contempt by society, rejected, and sometimes murdered. 2,500 years ago, Hippocratic doctors also documented a similar medical condition, which was merely referred to as "chronic pain". Thomas Sydenham and others referred to women presenting with these symptoms as "hysterics" [1, 14, 21]. The attitudes of male medical professionals in the early days, the insufficient technology at the time, and the complexity of endometriosis resulted in the delayed discovery of the disease. Therefore, the affected women were in a state of agony for most of their lives, which may support the development of some of the behaviors termed as "possessed" [4, 21].

Accurate and reliable figures for endometriosis prevalence are unascertained. The statistics regarding the disease are controversial; they may vary from country to country, and they largely depend on the quality of healthcare, which is not uniform across countries. Centered on the few reliable data, the prevalence of endometriosis can be assumed to be around 3.5–10.8%. The following figures have been estimated in different countries: 6–10% in the USA, 7% in Canada, 10% in the UK, 10% in Hungary, and 3.7% in Australia [14, 22-24]. The age group with the highest prevalence is women aged 40–44 years in Italy (18.6%), as reported by Morassutto et al. [14, 25-27].

Approximately 176 million women worldwide have endometriosis [28]. The disease is also discovered in asymptomatic women undergoing tubal ligation, and figures range from 3% to 43% [29, 30].

Endometriosis is principally a disease of reproductive-aged women; it is also found in post-menopausal women receiving hormone replacement therapy and in adolescents [31-33]. Endometriosis has no ethnic, racial, cultural, social class, or geographical predilection as it is present in every environment. Studies have shown that a high prevalence of endometriosis was observed in women with infertility and chronic pelvic pain (20–90%) [34-36].

### 1.1. Theories on the pathogenesis of endometriosis

Endometriosis is among the most common diseases with no unifying theory regarding its etiology. Endometriosis has remained mystifyingly elusive, with multiple hypotheses each contributing to characterize the disease as multifactorial in etiology and pathogenetically complex. The number of theories proposed to explain the pathogenesis of endometriosis has increased over the decades.

#### 1.1.1. Retrograde menstruation (transplantation)

The retrograde menstruation theory is widely accepted; it is the oldest theory regarding the formation of ectopic endometrium in endometriosis. The theory was first proposed by Sampson in the mid-1920s (1927) [37].

The retrograde menstruation theory explains that, during menstruation, some endometrial tissue flows backward through the Fallopian tubes into the peritoneal cavity, implanting on the peritoneal surface (lining of the abdominal cavity). This tissue later invades the surrounding tissues, causing inflammatory reactions and leading to painful symptoms and deformity [38].

Although retrograde menstruation is presumed to occur in 70–90% of women [39], Koninckx reported that the larger volume of retrograde menstrual fluid in the pelvises of patients with endometriosis as compared with healthy women could increase their risk of endometriotic lesion implantation [40].

Other studies have reported the presence of peritoneal endometrial cells in women during the early follicular phase and menstruation [41, 42]. Although this has been the leading theory for many decades, it is evident that the incidence and prevalence of endometriosis is lower than the frequency of retrograde menstruation, which suggests etiological multiplicity of the disease, with not only one factor being involved but a series of disorders in other systems (e.g., immunological, molecular, or genetic defects) [43]. Sampson's theory was further reinforced by the observation that many conditions could result in obstruction of menstrual flow. Such obstructing genital anomalies include imperforate hymen, non-communicating rudimentary uterine horns, vaginal agenesis, and iatrogenic cervical stenosis—all of which increase retrograde menstruation and the risk of endometriosis [44]. A higher incidence of endometriosis is observed in women with more frequent and longer menstrual periods than in those with a normal cycle and duration [45]. In retrograde menstruation, the survival of endometrial cells in a hypoxic microenvironment may require involvement of pro-angiogenic factors. Hypoxia promotes the expression of downstream genes involved in

implantation and the persistence of ectopic endometrium; the failure of the immune system to clear implants from the peritoneal surface also plays a role in disease progression (Giudice & Kao, 2004) [4].

### 1.1.2. Altered cellular immunity.

Several theories have been postulated over the decades to verify the role of implantation and defective clearance of endometrial cells from the pelvic floor in facilitating the development of endometriosis. It is an acknowledged occurrence that retrograde menstruation is relatively common, with most women (75–90%) experiencing some degree of retrograde menstruation [46]; however, not every woman with retrograde menstruation develops endometriosis. It has been suggested that endometriosis is the consequence of an inappropriate immune defense response, reduced immunologic clearance of viable endometrial cells (reduced natural killer cell [NK] and macrophage activity [47]), or that the pelvic and peritoneal inflammation is a consequence of the disease [48, 49]. The immunological pathogenesis of endometriosis has two dimensions: (i) reduced NK and macrophage activity; and (ii) immune tolerance of ectopic endometrial and stromal cells, leading to complete system failure essential in the development of endometriosis.

There is significant evidence to suggest that endometriosis is associated with a state of latent or subclinical inflammation, characterized by increased peritoneal fluid volume, white blood cell concentration, and levels of inflammatory cytokine, growth factors, and angiogenesis-promoting substances [50, 51]. However, in cell-mediated immunity, the core function of the NKs is to eliminate cells of an origin other than the intraperitoneal cells (e.g., infected cells, ectopic endometrial cells, tumor cells). Local and systemic variations in NK function and decreased NK-mediated cytotoxicity have been reported in women with endometriosis [52]. All these factors contribute to the elimination of endometrial cells in the pelvis. However, some studies have reported that NKs have an altered phenotype in women with endometriosis, with increased expression of the cytotoxic cell surface receptor CD16 and NK receptor NKp46, a phenomenon that might play a role in endometriosis-associated infertility [53].

Eisenberg et al. [54] reported an increase in the numbers and activation of peritoneal macrophages, pro-inflammatory chemoattractant cytokines for monocytes, macrophages, and granulocytes in women with endometriosis [55]. Moreover,

interleukin 1 (IL-1) was reported by Taylor [56] as having angiogenetic potential through vascular endothelial growth factor (VEGF) and interleukin 6 (IL-6) activation. Several processes and factors are involved in enhancing the establishment of endometriotic lesions that can escape immune surveillance, such as intercellular adhesion molecule 1 (ICAM-1), which conciliates immune cell-to-cell synergy, and the Fas–Fas ligand system, which mediates the cell death of activated immune cells in a pro-inflammatory environment, such as the peritoneal fluid of women with endometriosis [56].

### 1.1.3. Coelomic metaplasia (transformation theory)

The transformation of coelomic epithelium to endometrial tissue has been proposed as the mechanism for the genesis of endometriosis, i.e., endometriosis originates from abnormally differentiated extrauterine cells. This theory, heralded by Gruenwald et al. [57], postulates that endometriosis is derived from metaplasia of specialized cells present in the mesothelial lining of the visceral and abdominal peritoneum. In support of this theory, Dinulescu et al. [58] conducted a study involving genetic induction of ovarian endometriosis in mice and reported that ovarian endometriotic lesions may arise directly from the ovarian surface epithelium through a metaplastic differentiation process induced by activation of an oncogenic K-Ras allele. Vercellini et al. [59] suggested that the theory of coelomic metaplasia could be supported for ovarian endometriosis development, as the coelomic epithelium lining the peritoneum and ovary undergoes metaplastic transformation. Regarding endometriosis on the surface, the survival of the endometrial implants could be explained by altered endometrial gene transcription and increased endometrial invasion induced by the early endometriotic lesion (Nair et al.), and by the failure of the immune system to clear implants from the peritoneal surface [4, 60]. Scholars believe that, for this transformation to be successful, some hormonal or immunological factors could be responsible for the stimulation of a normal peritoneal cell to form endometrium-like tissues [46, 61]. Furthermore, the coelomic metaplasia theory could explain the incidence of endometriosis in prepubertal girls; in this age group, endometrial growth-stimulating estrogen is absent, and this condition could be differentiated from the disease found in women of reproductive age [62].

Recent molecular genetic findings on endometriosis and the normal endometrium have suggested a modified model in which circulating epithelial progenitor or stem cells

intended to regenerate uterine endometrium after menstruation may become overactive and trapped outside the uterus [63]. These trapped epithelium-committed progenitor cells form nascent glands through clonal expansion and recruit polyclonal stromal cells, leading to the establishment of deep infiltrating endometriosis [46, 63]. Once developed, the ectopic tissue is subject to immune surveillance, resulting in chronic inflammation. However, the inflammatory response orchestrated by nuclear factor-κB (NF-κB) signaling is exacerbated by aberrations in the estrogen receptor β and progesterone receptor pathways, which are also affected by local inflammation, resulting in a dysregulated inflammatory–hormonal loop [64]. Glandular epithelium within endometriotic tissue harbors cancer-associated mutations that are often detected in endometriosis-related ovarian cancers. Recent advances have illuminated the origin and pathogenesis of endometriosis and have provided new avenues for research that promise to improve the early diagnosis and management of endometriosis [62].

### 1.1.4. Steroid metabolism dysfunction and progesterone regulation

Historically, endometriosis was considered to be regulated or modulated by estrogen. Studies have shown that progesterone dysfunction or incompetence is also involved in the pathogenesis of endometriosis [65]. Steroid hormones play a significant role in the manifestation of endometriosis, as the disease is commonly present during the reproductive age; however, there are some exceptions, and younger and even older women are affected [60, 65]. A study conducted by Kao et al. in 2003 reported the deregulation of many target genes vital to implantation in women with endometriosis, and many of the genes correlated with progesterone receptors and metabolism [63]. Furthermore, both eutopic endometrium and ectopic lesions are regulated by ovarian hormones. The ectopic lesions also exhibit increased responsiveness to estrogen, which may enhance the development of endometriosis [66].

The activated progesterone receptor plays a vital role in regulating tissue remodeling in the uterus that is necessary for menstruation or pregnancy. However, dysfunction of these progesterone regulatory processes—aggravated by the chronic inflammatory state caused by endometriosis—results in a condition known as “progesterone resistance” [20, 60]. Progesterone resistance could involve the progesterone receptor (PR) isoforms PR-A and PR-B, in addition to downstream molecules, such as transforming growth factor (TGF), retinoic acid, c-myc, or the co-activators of the

receptor itself [20]. Remarkable reduction in PR-A and PR-B levels have been observed in endometriotic tissue [5].

### 1.1.5 Genetic background

Studies have shown that some factors responsible for the onset of endometriosis are heritable [5, 67]. A sevenfold risk of developing the disease has been reported in women with an affected mother or sister [68]. Reports have shown an increased incidence of endometriosis among monozygotic twins, and correlation has also been observed in the stage of the disease [69, 70].

Many studies have suggested that genetic polymorphisms are among the factors involved in the development of endometriosis. Endometriosis is inherited by a polygenic model, as evidenced by the identification of a Mendelian inheritance pattern, which indicates a form of multifactorial inheritance. Inheritance is likely to involve multiple specific loci and chromosomal regions, which some studies have reported to be associated with the corresponding endometriosis phenotype [70, 71].

Inherited and acquired factors could facilitate the attachment of ectopic endometrial cells to the peritoneal epithelium and the evasion of these lesions from immune clearance [46]. Burney et al. reported in 2013 that genes assumed to be involved in cytokine-related inflammation, steroid and hormone receptors, and matrix degradation may be differentially expressed in women with endometriosis [72]. Recently, genome-wide association studies (GWAS) have revealed several genes that are possibly involved in the pathogenesis of endometriosis. European and Japanese GWAS have shown a significant association between the LD block on chromosome 1 near the cyclin-dependent kinase inhibitor 2B antisense RNA (CDKN2BAS) and the wingless-type MMTV integration site family 4 (WNT4) gene [73].

The epigenetic research model has recently gained wide acceptance. It is characterized by a reversible condition, influenced by age and lifestyle factors, which underlies a wide range of pathologies. The most frequent and well-documented epigenetic mechanism is DNA methylation, followed by histone modification and regulation of chromatin modification. This research model demonstrates that a single endometriotic lesion is monoclonal and—based on gene expression profiling studies—a large number of genes are dysregulated in endometriosis [74, 75].

The first documentation of epigenetic alterations in endometriosis was the HOXA10 gene, which showed hypermethylation in the endometria of women with endometriosis (Wu et al., 2005) [76]. However, evidence supports the estimate that endometriosis is approximately 51% heritable; the identification of a specific gene consistently associated with endometriosis is complex, with predictive potential in identifying high-risk women [77, 78].

### 1.1.6. Oxidative stress

The oxidative stress theory describes excessive presence or overload of iron released from the pathway that is caused by the destruction of erythrocytes that contain the iron-binding protein hemoglobin, or a deficiency in peritoneal iron metabolism. This iron is associated with the local destruction of the peritoneal mesothelium, leading to the adhesion of ectopic endometrial cells [79]. Furthermore, an association with increased oxidation of lipoproteins is observed, where reactive oxygen species (ROS) cause lipid peroxidation that leads to DNA damage in endometrial cells [80]. A study showed that oxidative activity and ROS were higher than average in patients with endometriosis. The excess chemical changes observed in oxidative stress and in the presence of ROS could cause tissue damage and induce rapid cellular division [79], thereby recruiting lymphocytes and activated macrophages that produce cytokines that induce the oxidation of enzymes and promote endothelial growth [81]. Accumulation of ROS may contribute to the propagation and maintenance of endometriosis and its associated symptoms [80]. Finally, several cellular pathways have been identified by which oxidative stress and ROS can induce endometriotic lesion proliferation, such as the mitogen-activated protein kinase (MAPK) and the extracellular signal-related kinase (ERK) pathways. The activation of these pathways leads to increased levels of c-Fos and c-Jun, which are proto-oncogenes that are associated with high-grade lesions [79].

### 1.1.7. Environmental factors

Studies have shown that some environmental toxins, such as dioxin, behave similarly to estrogen by interacting with the estrogen receptor and are involved in the etiology of endometriosis [82]. However, the mechanism by which dioxin and similar substances 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and polychlorinated biphenyls (PCBs) affect endometrial physiology remains unclear as it is difficult to assess exposure to these chemicals in the intrauterine period, in childhood, and in adulthood.

The limitations for reproducing their effect and the possible consequences remain unclear [66]. In support of this theory, a study published in 2013 reported a high concentration of organochlorine pesticides (OCPs) in the blood of 248 women with endometriosis [82]. The study revealed a possible link between high concentrations of two OCPs—β-hexachlorocyclohexane (β-HCH) and dechlorane (Mirex)—and an increased risk of endometriosis; ovarian endometriosis was found to have a stronger association with the β-HCH [83-85].

## 2. SYMPTOMATOLOGY OF ENDOMETRIOSIS

The symptomatology of endometriosis is unclear and complex. There is no single symptom or complaint with a sensitivity and specificity close to 100%. Several studies have reported diverse symptoms [7, 126-128]. Pelvic pain is a common complaint among women with endometriosis. Singularly, it is proven insufficient as an indicator of endometriosis by many authors as it can be associated with other gynecological (and non-gynecological) conditions [129-132]. Other medical conditions, such as pelvic inflammatory disease (PID), ovarian cysts, and irritable bowel syndrome (IBS), can mimic the symptoms of endometriosis [133-135]. When these pain-related symptoms persist, are progressive (i.e., worsen over time), or coexist with other related symptoms, the likelihood of association with endometriosis increases [7, 135-137].

The development of painful symptoms varies with time; typically, initial menstrual pain (dysmenorrhea) may progress to non-menstrual pelvic pain, which is dominant among women diagnosed with endometriosis. Symptoms associated with endometriosis are usually intertwined, as they are mostly uncommon. The other, less common symptoms of endometriosis include severe menstrual cramps unresponsive to NSAIDs, long-term lower back and pelvic pain, periods lasting longer than 7 days, heavy menstrual bleeding, intermenstrual bleeding, bowel, and urinary problems including pain, diarrhea, constipation and bloating, bloody stools or urine, nausea, vomiting, and fatigue [19]. A possible implication and complication of endometriosis is infertility, affecting 30–50% of those with the condition [19, 138].

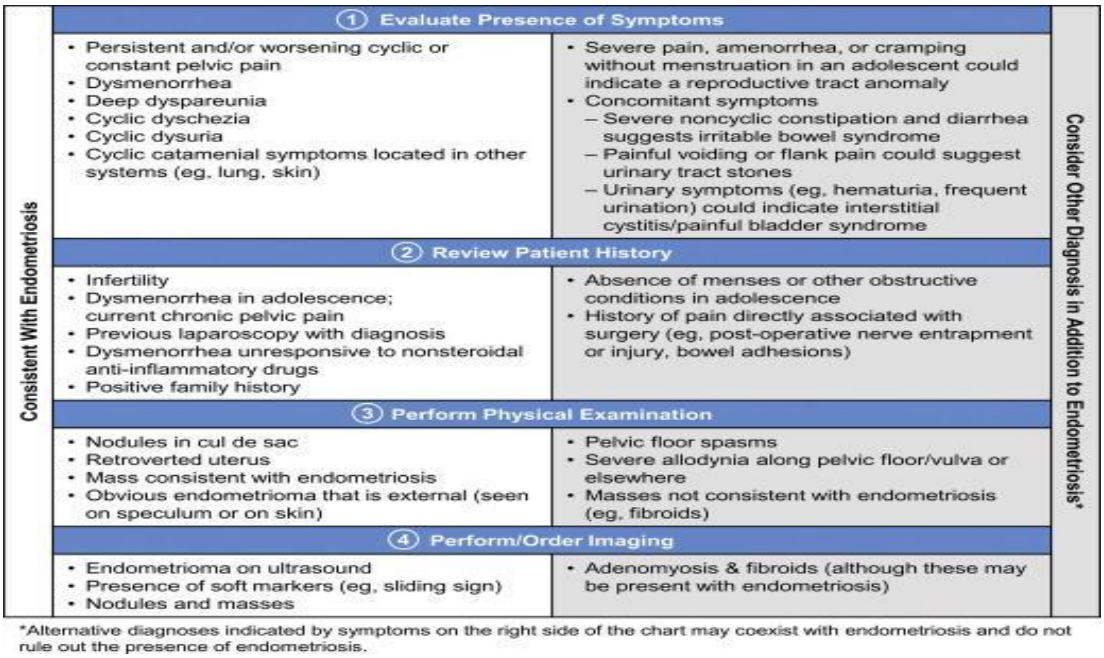



Figure 2. Non-specific and specific symptoms associated with endometriosis (Agarwal. Clinical diagnosis of endometriosis. Am J Obstet Gynecol (2019) [7]).

The evaluation of symptoms, complaints, and their severity indicates the likelihood of endometriosis in a patient. However, caution is required before dismissing NSAID-responsive pain as simple dysmenorrhea; early symptoms of endometriosis may be responsive to these agents.

## 3. GENERAL IMPACT OF ENDOMETRIOSIS

Endometriosis affects a substantial percentage of the female population, mainly in their prime, and its impact is considered to be high. Some of the pitfalls of the management of this disease are a lack of proper understanding, lack of awareness, and the multifaceted presentation to health professionals [86, 87]. Among other pitfalls are the general inadequate social health education policies put in place by health personnel and authorities that lead to delayed diagnosis. Significant strides have been made, but they are still taking too long [86, 88]; however, there is increasing knowledge and understanding of the disease [86, 87]. The main challenges of the disease include subfertility, infertility, and its debilitating symptoms, which include persistent chronic lower pelvic pain and other forms of pain—dependent or independent on menstruation—with adverse psychological outcomes that affect work productivity and learning. Sexuality and sexual life are seriously affected in most patients. Overall, patients experience a significantly reduced QoL [89].

The impact of endometriosis involves three intertwined aspects that negatively influence the QoL of women with endometriosis: infertility (reduced reproductive capacity), socio-economic impact, and QoL.

### 3.1. Impact on fertility

Although there has not been any absolute proven mechanism on how exactly it occurs, an association between endometriosis and subfertility is widely acknowledged based on epidemiological, retrospective, and cross-sectional studies on women and non-human primate research [86, 89]. According to studies conducted by Giudice [90], endometriosis negatively affects fertility. The average monthly fecundity rate (MFR) in women is 15–20% (MFR 0.150.2), while women with untreated endometriosis have an estimated MFR of <0.05 (2–10%) [91]. Other authors have an estimated prevalence of between 2% and 10% in women in the general population and a staggering 20–50% in the female population with fertility issues [92, 93].

#### 3.1.1. Chronic inflammation

Endometrial tissue localization outside the uterine cavity might cause a chronic inflammatory state that generates a favorable environment for adhesion development, as reported by Seli et al. and Moradi et al. [94-97].

#### 3.1.2. Tuboperitoneal distortion

Peritubal adhesions are common in patients with endometriosis, mainly when the ovaries are involved. These adhesions can affect the tubo-ovarian, tuboperitoneal, or Douglas pouch peritoneal walls, adhering the tubes to neighboring organs or pelvic sidewall, and may appear slight, moderate, or dense when visualized intraoperatively. Damaged tubal function caused by adhesions not only inhibits sperm mobility toward the ampullary region, but also impairs oocyte collection by the fimbriae. Moreover, severely damaged tubes can increase the incidence of ectopic pregnancy. Studies have shown a detrimental effect of tubal adhesions on fertility [96, 98].

#### 3.1.3. Hormonal changes on implantation

Studies have shown that there is a higher concentration of steroid hormones in the peritoneal fluid after ovulation in normal women than in women with luteinized unruptured follicle (LUF) syndrome. LUF syndrome is most frequently observed in women with endometriosis. Furthermore, studies have shown an association between endometriosis and LUF syndrome, accompanied by a low-grade inflammatory reaction

within the peritoneal space, as indicated by a relatively large number of macrophages and their by-products [96, 99, 100].

There is a suboptimal luteinizing hormone (LH) level surge with concomitant impaired ovulation in patients with endometriosis that is triggered by gonadotropin-surge attenuating factor (GnSAF) [101].

Another observation is the presence of progesterone resistance, causing decreased fertilizing capacity [100, 101].

### 3.1.4. Decrease in ovarian reserve.

Ovarian reserve depletion remains the main problem in endometriosis. Ovarian reserve is determined either by measuring anti-Mullerian hormone (AMH) pre- and post-surgery or by measuring the number of follicles or ovary size via ultrasound. Ovarian reserve depletion might originate primarily from ovarian endometriosis itself or from subsequent ovarian surgery.

Endometriomas can affect ovarian reserve by impairing circulation in the ovarian cortex due to compression, leading to follicle loss; the inflammatory environment within the cyst walls may also leading to follicular damage [102]. The destruction of ovarian tissue could be partial or complete, with or without a viable oocyte on the affected ovary. The left ovary is reported to be more frequently involved. Endometriosis can also affect the ovarian capsule, enhancing the formation of adhesions with the surrounding tissue. Furthermore, the chronic inflammatory process may induce the development of LUF syndrome, which could reduce ovulation. In addition to the decrease in reserve oocytes, embryo quality can also be affected, which can lead to decreased pregnancy rates in spontaneous gestation and IVF or intracytoplasmic sperm injection (ICSI) cycles. Some studies have also shown that patients with endometriosis have a reduced number of preovulatory follicles, follicular growth, dominant follicle size, and follicular estradiol concentration in their ovaries [103-105].

The other cause of ovarian reserve depletion is a direct result of the surgical destruction of ovarian tissue [104]. Endometriomas can be removed by stripping, ablation, combined techniques, or complete removal of the affected ovary [105, 106]. Each of the surgical procedures may invariably cause loss of ovarian tissues, including viable follicles. Studies reported that baseline anti-Mullerian hormone (AMH) values were significantly lower in individuals with endometrioma than in a control group

[107, 108]. Furthermore, bilateral endometriomas had a significantly greater rate of decline, and the rate of AMH decline was positively correlated with baseline preoperative AMH values and the size of the removed endometrioma [107, 108]. Moreover, Urman et al. stated that AMH was a better indicator for postoperative assessment of ovarian reserve, while Esinler et al. believed that endometriomas ≤3 cm in diameter did not have a deleterious effect on ovarian reserve in ICSI cycles [109, 110].

### 3.2. Pain-related symptoms (reduced or absent sexual activity)

Infertility creates complex psychological dysfunction in women's lives. In many cultures, infertile women are forced out of their marriages, resulting broken homes; it instigates antisocial behaviors and depression. Adequate and harmonic sexual activity is among the prerequisites for good fertility outcomes. With the advent of artificial reproductive techniques (ART), some of these obstacles have been alleviated [111]. Sexual function is a vital aspect of health, general well-being, and QoL. Sexual activities are influenced by both medical conditions and healthcare interventions, especially when gynecological disorders—such as endometriosis—are involved [112]. Dyspareunia is among the main factors that affect sexual functioning, and the prevalence of this symptom is reported to be between 50% and 75% in women who suffer from endometriosis. Sexual functioning is a central and complex phenomenon, driven by social, psychological, and biochemical factors. Consequently, the pain associated with endometriosis might further affect sexual function and the quality of a sexual relationship [113].

Dyspareunia can alter a woman's perspective on life enough to avoid engaging in sexual intercourse; in severe situations, a loss of self-esteem or destruction of relationships with partners can lead to a complete cessation of sexual activities, which could hamper fertility [113]. Endometriosis negatively affects different domains of sexual function and health. It is among the most highlighted impacts on well-being and QoL in a marital setup. Studies have shown that women with deep infiltrating endometriosis of the uterosacral ligament and vagina complain of a higher incidence of dyspareunia [114, 115]. The impact of deep dyspareunia on sexual dysfunction is significant [115, 116].

### 3.3. Impact on socioeconomic life

Endometriosis is a complex medical condition with a multifaceted presentation. The pain-associated symptoms of endometriosis can be so frustrating and exhausting that they can compel sufferers to self-isolate; it limits involvement in certain physical and social activities. Weekends and work-free days are about indulging in a person's favorite activities, such as visiting restaurants, bowling, parties, beach barbecues, and outings with friends and family members. Social life can be impaired significantly due to the exhaustion from inadequate rest due to pain, and a flare-up can force the sufferer to remain in bed at home; therefore, relationships are affected, resulting in social decline over time [117]. The cost of medications and hospital treatment results in financial constraints, limiting spending for other social activities [118]. The cost of the burden of illness is enormous, with most costs generated by reductions in productivity, loss of working hours, and medical expenses. Although it is difficult to ascertain the exact financial implications for individuals and society, a study conducted by Simoens et al. in 2012 estimated the average cost of endometriosis of about €9,579 per woman/year; in the breakdown, an average of €6,298 was a loss in productivity, and an average €3,113 was spent directly on healthcare [117]. In another study conducted by Armour et al. in 2019, they estimated an economic burden to the system in Australia of $6.50 billion annually [119]. These financial burdens are due to loss of productivity, absenteeism, and health costs, and affect spending in other areas of life, such as entertainment, sports, and social activities.

### 3.4. Impact on quality of life and well-being

The psychological, social, and clinical impacts of endometriosis are significant, and the effect of pain on the general well-being and QoL of patients is multidimensional [97, 120]. Painful symptoms of endometriosis have a direct impact on sufferers' physical activity, their ability to play roles and work, social activities, sexual relationships, mental and psychological health, and energy [121]. In addition to the pain associated with direct impacts, other factors, such as infertility, affect mental health and personalities [88, 122-126]. The strong psychological and emotional impact of endometriosis also has adverse effects on an individual's self-image and can lead to a loss of feeling physically strong, impaired fertility, and can even lead to broken homes. Moreover, the depressive mental state encountered in people with endometriosis aggravates a feeling of guilt and distress in the workplace caused by the pain and infertility. Studies on the QoL of women affected by endometriosis have

suggested that QoL and General WB are significantly altered in many aspects—such as infertility, severe dysmenorrhea, and dyspareunia—which not only influences fertility performance but also compromises work capacity, with lost days at work and possible surgery-related complications and costs [88, 124, 125].

Currently, the exact quantifiable financial burden of endometriosis cannot be accurately noted due to many independent factors influencing healthcare globally: cultural, educational, and developmental differences, the priority of health-sector financing, and attitude towards healthcare. A study conducted by Simeons et al. in 2012 estimated the overall annual cost of endometriosis in several European countries: €14.2 billion in the UK, €17.8 billion in Germany, and €2.3 billion in Hungary [86]. Overall, the cost burden for the United States of America is estimated to be €70.9 billion annually. A study conducted by Armours et al. in 2019 reported an estimated cost of about $6.50 billion in Australia, of which the majority (75–84%) of costs were due solely to lost days at work [119, 122, 126].

The health and socioeconomic challenges affecting women with endometriosis are partly due to diagnostic delay, which ranges between 5 and 10 years in symptomatic women [88, 115]. Reasons for delaying diagnosis include cultural habits regarding healthcare-seeking behaviors, normalization or trivialization of painful symptoms, intermittent suppression of symptoms by contraceptives, or misdiagnosis due to lack of knowledge from healthcare providers [126]. Recent studies have shown that endometriosis affected work in 51% of the investigated women, and 50% of the women reported that it had a profound impact on their relationships [127].

Numerous studies estimate that most of the sufferers encounter symptoms associated with endometriosis either in combination or as a single symptom, such as dysmenorrhea (65–75%), dyspareunia (50–70%), lower abdominal pain (60–85%), and infertility (50–65%) [88, 90, 115, 121].

To strengthen some of the facts attributed to endometriosis, Simoens et al. conducted a prospective multicenter study in 10 countries in 2012 that assessed the costs and QoL factors related to endometriosis. Pain and discomfort were reported by 56% of the study participants, anxiety, or depression by 36%, and 29% of the participants reported difficulty with usual activities [121].

Worldwide, an estimated 176 million women at aged 15 to 49 years suffer persistently from endometriosis [128]. Therefore, endometriosis carries a reasonable socioeconomic burden [129].

## 4. DIAGNOSIS

The currently available diagnostic procedures are limited to those that have been used for decades, such as patient medical history, clinical physical examination, radiological examinations (e.g., vaginal, rectal, and abdominal ultrasound, magnetic resonance imaging [MRI]). A definite diagnosis is currently made only by laparoscopy and appropriate biopsy followed by histopathology examination.

### 4.1. Endoscopy findings

Extrapelvic manifestations of endometriosis are infrequent (0.7–2.5%). Some of these extrapelvic implants are detectable with the naked eye on the skin, urinary tract, gastrointestinal tract, or vulva; some are discovered during other medical investigations [139, 140-142].

Pelvic and intra-abdominal endometriosis is usually revealed during laparoscopy by direct imagining of suspicious lesions. This method is accepted as the gold standard for diagnosis. A few cases are diagnosed through laparotomy or hysteroscopy; the latter procedure is used to investigate for intrauterine endometriosis [143-145].

During hysteroscopy in young women, meticulous attention is needed to rule out endometriosis implants (black-blue-dark brown spots in the cavity [Figure 3]). More importantly, during laparoscopy or laparotomy, pelvic and abdominal areas are investigated for the presence of endometriosis [42, 146-148].

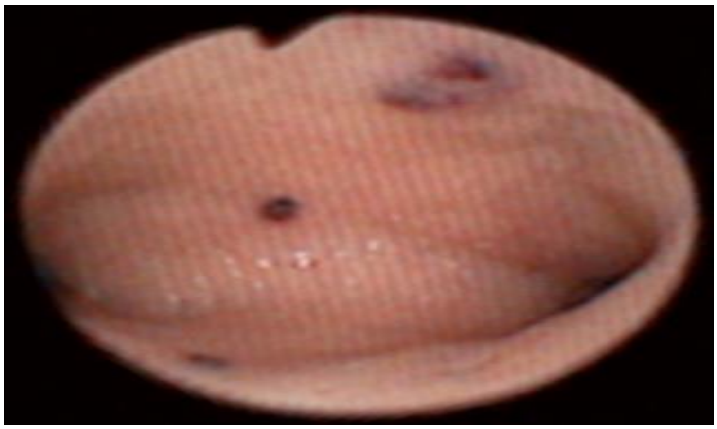


Figure 3. A hysteroscopic picture of endometriosis, as seen in the cavity.

Endoscopic surgery provides an opportunity to document the disease by type, location, and extent of all lesions and adhesions [149, 150]. Pelvic and intra-abdominal endometriotic lesions differ from stage to stage and by their presenting sites.

Superficial ovarian endometriosis and ovarian endometriotic cysts are frequently located on the lateral aspect of the ovary and are associated with retraction, pigmentation, and adhesion to the pelvic sidewall. Ovarian endometriotic cysts (endometriomas) usually contain a thick and viscous, dark brown fluid (chocolate-like). Endometrioma fluid contains hemosiderin derived from previous intra-ovarian hemorrhage; such fluid can also be present in other conditions, such as hemorrhagic corpus luteum cysts or neoplastic cysts. Other presentations, as seen in Figure 4, include involvement of the superficial peritoneum. The lesions appear in several forms and coloration, with features such as the typical “powder-burn” or “gunshot” lesions on the serosa surfaces of the peritoneum, or black, dark brown, or bluish nodules or small cysts containing old hemorrhage surrounded by a variable degree of fibrosis [26, 151]. Other uncharacteristic features can be observed, including red implants (petechial, vesicular, polypoid, hemorrhagic, red flame-like), serous or clear vesicles, and sometimes white plaques or scarring, yellow-brown discoloration of the peritoneum, and tubo-ovarian adhesion.

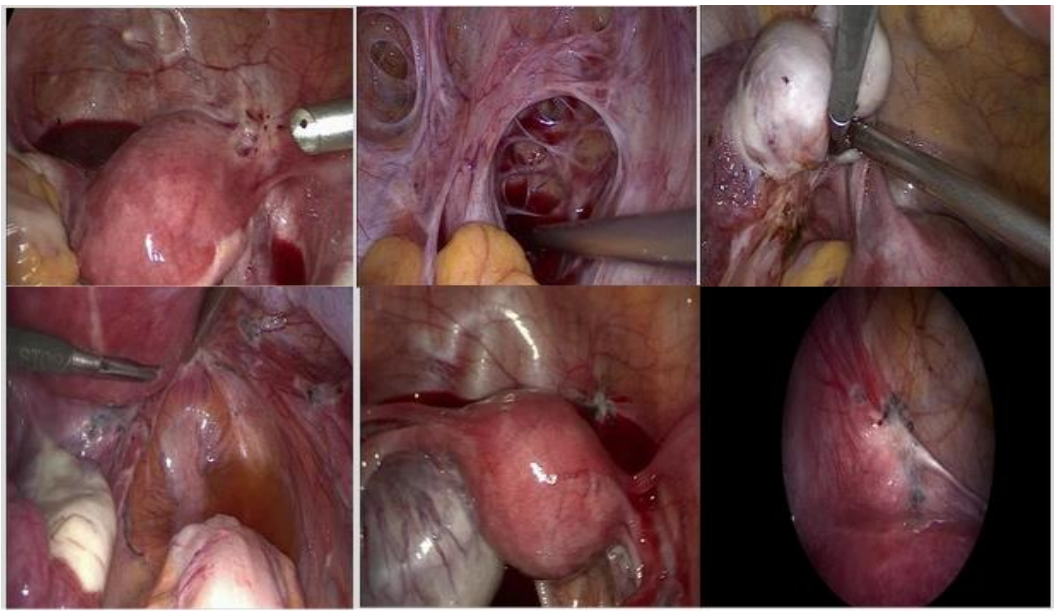


Figure 4. Common presentations of endometriosis, with subtle lesions, serous and clear vesicles, and deep infiltrating endometriosis of the recto-vaginal septum and rectum. (By Ekine A.A., 2020, Róbert Private Hospital)

### 4.2. Histological confirmation

The diagnosis of endometriosis is based upon surgical findings and imagining followed by histological confirmation of the extracted tissues. Studies have shown that histological findings do not always correlate with surgical findings; however, Moen et

al. reported that approximately 51% of patients who underwent surgery received histological confirmation [155]. In another study by Mettler et al., biopsies confirmed the presence of endometriosis in 84.1% of patients [156]; 100% of "red" lesions, 92% of "black" lesions, and 31% of "white" lesions were confirmed as endometriosis. The most accurate diagnosis was made in lesions on the parietal peritoneum of the pelvis (100%); however, only 66.7% of cases were confirmed in the ovarian fossa and 60.1% of cases at the uterosacral ligaments and posterior surface of the broad ligament. Confirmation rates from lesions on the ovarian surface, bowel serosa, and vesicouterine fold were 48%, 40%, and 13%, respectively [20]. Confirmation rates in additional studies varied from 42% to 99%. A possible reason for discrepancies between surgical and histological findings might be the presence of fibrosis, as shown in Figure 5 [157, 158].

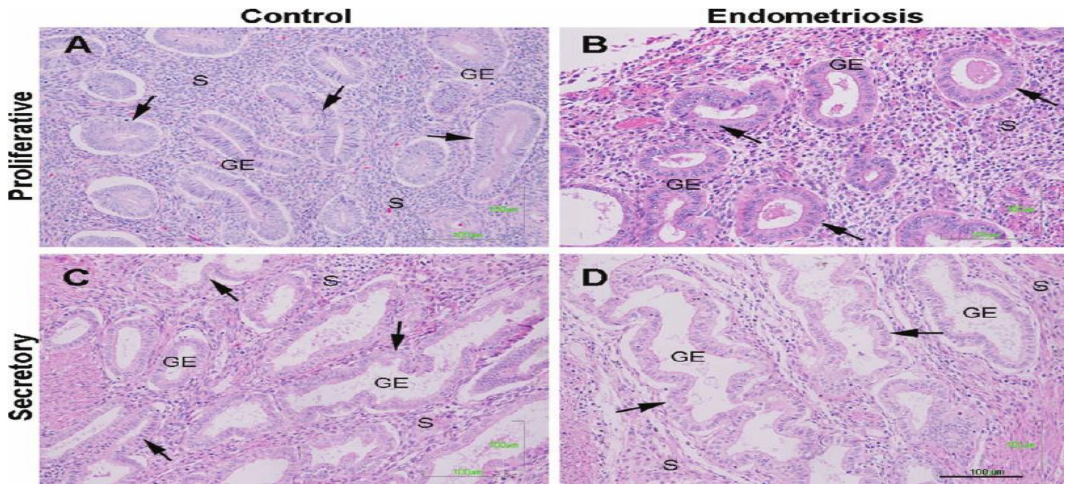



Figure 5. Histological findings of normal endometrial tissue and endometriosis. Source: Francisco J. Valdez-Morales (2014).[Glandular epithelium (GE), normal stroma (S) (A and C). Eutopic endometrium with endometriosis (B and D). Arrows show typical GE proliferative (A and B) and secretory (C and D) phases in the control and endometriotic endometrium, respectively. Scale bar 1⁄4 100 mm. Biopsy samples were stained with hematoxylin-eosin]

## 5. CONSERVATIVE MANAGEMENT

Management options in endometriosis must be tailored according to the multifaceted clinical presentations and their effect on QoL. The condition might persist despite sufficient surgical or medical treatment. The complexity of symptoms requires proper counseling and, in some cases, multidisciplinary management [62].

The objective purpose of endometriosis treatment is to alleviate symptoms, restore, preserve, or improve fertility, and to ensure normal organ function. Endometriosis is a

disease with a high recurrence rate, and the recurrence of endometriosis depends on treatment modules and expertise. Studies have reported recurrence rates ranging from 4.5% to 50% within 2 years of surgery [19, 78, 159-164].

### 5.1. Medical therapy

#### 5.1.1. Hormones

Pathophysiological evidence shows that endometriosis is stimulated by hormones produced in the ovaries, and hormonal suppression of ovarian function is an effective treatment. Hormonal management is not suitable for women who wish to become pregnant. Hormonal treatments in endometriosis are oral progestins, combined contraceptive pills or patches, progestin containing intrauterine devices, GnRH analogues, androgenic substances, and aromatase inhibitors that prevent ovulation [165]. GnRH analogues are potent inhibitors of the hypothalamus-hypophyseal-gonadal axis and can markedly influence endometriosis symptoms; however, their side effects can be severe [166]. Side effects of progestins include spotting, weight gain, reduced sexual desire, breast tenderness, and headaches [167-170]. Effective androgenic compounds, like Danazol, are capable of decreasing pain; however, they have many severe side effects [170]. The use of an oral contraceptive regimen is useful in reducing symptoms and may delay progression of endometriosis [166].

#### 5.1.2. Other drugs (NSAIDs)

The pain-related symptoms associated with endometriosis demand frequent use of painkillers; the most common drugs are NSAIDs. These drugs account for approximately 10% of the total financial burden of endometriosis [171-174]. However, the constant use of these drugs is not without potential complications; long-standing use can adversely affect the gastrointestinal tract, renal function, and other systems [175].

### 5.2. Physiotherapy

The role of physiotherapy in the treatment of endometriosis focuses on the following modalities: pelvic floor strengthening; internal and external trigger point management, manual myofascial therapy, stretching and flexibility exercises, spinal mobilization, and nerve glides [165, 201, 202].

Other studies have established regular physical activities and physiotherapy as having a favorable impact on women’s QoL [128, 165, 203, 204]. The decision to treat patients diagnosed with endometriosis is based on the presentation of musculoskeletal

and non-musculoskeletal symptoms [4, 5, 58, 205]. Regular physical exercise appears to have a protective effect against diseases that involve inflammatory processes as it induces an increase in the systemic levels of cytokines with anti-inflammatory and antioxidant properties and reduces estrogen levels [165, 204, 206].

### 5.3. Acupuncture Therapy

A study conducted by Yang Xu et al. reported that acupuncture reduced pain and serum CA-125 levels, regardless of the control intervention used [165, 207]. Other studies also reported positive effects of acupuncture use in endometriosis [128, 165, 208, 209]. Acupuncture is primarily an adjuvant therapy because it focuses on symptom management rather than a permanent treatment for the disease.

### 5.4. Psychotherapy

Endometriosis is associated with debilitating symptoms, such as dyspareunia, dysmenorrhea, dysuria, and infertility. These symptoms reduce a woman's self-esteem and general well-being. Many women require psychotherapy due to the physical, psychological, and economic burden of the disease. Studies have reported the positive impact of psychotherapy in the management of endometriosis [165, 210-212].

### 5.5. Prevention

The complexity of the pathogenesis and multifaceted presentation of the disease has made it almost impossible to formulate an adequate preventive strategy. There is insufficient evidence to support measures such as physical activity or exercise, diet, and the use of contraceptive pills at an early age as being preventive [4, 30, 204, 213]; however, more investigations are needed to validate the effectiveness of these preventive measures.

## 6. SURGICAL PROCEDURES

Many studies have shown that surgical removal of endometrial implants and endometriomas of the ovaries appears to relieve pain in mild or severe endometriosis [176, 177]. Other research suggested that removing endometrial implants during laparoscopy can improve fertility outcomes [178, 179]. Little research has been conducted to confirm which of the surgical approaches is most effective in treating endometriosis. Several studies have reported a possible impact on QoL after laparoscopy [19, 180].

Generally, surgical removal of endometriotic lesions relieves symptoms and restores a normal anatomical state. Surgical treatment can involve laparotomy or laparoscopy as both procedures are efficient. Laparoscopy is the superior treatment option and is associated with shorter hospital stays, less post-surgical pain, and a shorter recovery time [181, 182].

All stages of endometriosis are usually effectively treated via excision and/or ablation. Cystectomy for endometrioma is a preferred treatment option to reduce pain or restore fertility. Cystectomy also provides a sample for histological confirmation of the disease [182, 183].

### 6.1. Treatment of ovarian endometriosis associated with pain and infertility.

Different surgical techniques have been used in the management of ovarian endometrioma: fenestration, drainage, fenestration and ablation, and cystectomy. The historically preferred surgical procedure is cystectomy. This involves opening the ovarian cortex, ascertaining the cyst wall, and stripping it from the healthy ovarian tissue. Some patients exhibit no physical symptoms despite the presence of an endometrioma and may instead benefit from conservative therapy. Surgical treatment is usually encouraged as the treatment for pelvic pain, dyspareunia, and to improve sexual function and potentially improve the likelihood of spontaneous conception [184, 185].

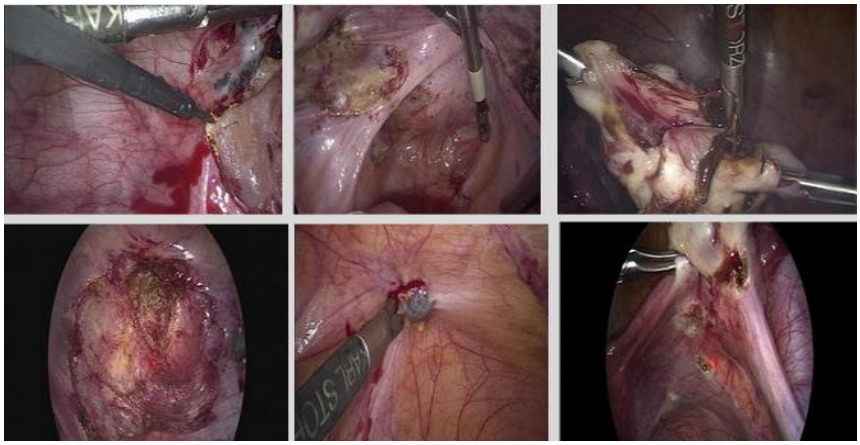


Figure 6. Images of different laparoscopic surgical procedures performed at Róbert Private Hospital (Ekine A.A.).

Some reviews report a clear improvement in spontaneous and assisted fertility after cystectomy as compared with fenestration or electrocautery; however, the benefits associated with IVF outcomes are less evident. Other noticeable benefits are reduced

recurrence and increased ovarian response to gonadotropin use during ART [186]. Studies have also demonstrated a benefit for spontaneous conceptions [180, 187-189].

### 6.2. Other surgical options

The cardinal symptom of endometriosis is pain. Pain is the main indication for surgical treatment after various primary conservative treatments. Surgical management of endometriosis comprises three essential techniques: removal or destruction (excision) of endometriotic lesions, interruption of nerve pathways, and lysis of adhesion. The application of these techniques has evolved from open laparotomy to minimally invasive laparoscopic or robotic surgery. The recovery time and morbidity are much lower following laparoscopy; however, other benefits and efficacy have not been established between the two surgical procedures [181, 200].

Severe, deep infiltrating endometriosis (DIE) is the presence of endometriosis at 5 mm or greater depth from the peritoneal surface and can involve the uterosacral ligaments, vagina, bowel, bladder, ureters, or other organs [190, 200]. Many studies have suggested that an increase in the intensity of symptoms is correlated with the severity of the disease [191, 192, 200]. Several surgical techniques have been employed in the management of DIE: shaving off the endometriotic nodule, disc excision, and segmental bowel resection with end-to-end anastomosis. Every surgical treatment appears to significantly reduce pain, with higher complication rates associated with bowel resection [193, 194, 200]. However, fertility outcomes following surgery for DIE are less clear and there is no robust evidence to suggest a significant benefit [195, 200]. Other surgical options are available when women have completed their family planning or if other forms of conservative management fail, such as total or subtotal hysterectomy with bilateral salpingo-oophorectomy. [196-198, 200]. Surgical treatment of DIE reduces pain and improves QoL [196, 197, 200].

## 7. HYPOTHESES

1. We suppose that there might be a possible link between patient history of cesarean section and an increased likelihood of the development of endometriosis.
2. We suppose that combined hysteroscopic and laparoscopic endometriosis surgery significantly improves fertility outcomes in patients with endometriosis.
3. We suppose that combined hysterolaparoscopy may significantly improve the QoL of endometriosis patients. We believe that the validated EHP-36 instrument, along

with the VAS and the NRS-11, are useful tools in the evaluation of the QoL of endometriosis patients.

## 8. RESEARCH STUDIES

### 8.1. Study I: Isthmocele and its probable link with endometriosis.

#### 8.1.1. Background

Isthmocele is an iatrogenic gynecological disorder characterized by thinning of the uterine wall and bulging at the site of uterotomy performed during prior cesarean section. It is frequently associated with abnormal uterine bleeding, suprapubic pain, and chronic vaginal discharge. Isthmocele can cause secondary infertility, although the mechanism is still poorly understood. There is a paucity of literature regarding the possible link between isthmocele and the development of endometriosis or adenomyosis [214, 215].

#### 8.1.2. Materials and methods

The study was conducted at the Endoscopic Surgical Unit, Department of Obstetrics and Gynecology, Róbert Private Hospital, Budapest, Hungary. The study protocol was approved by the ethical committee of Róbert Private Hospital (RRC-RMK) 001-3/2017. Using the hospital database, we conducted a retrospective analysis of data from 34 patients with post-cesarean isthmocele. After initial screening, 28 patients agreed to surgical management, and all underwent combined hysteroscopic and laparoscopic repair, except for one patient who opted for only hysteroscopy repair. Patients were followed up between 3$^{rd}$. January 2013 and 30$^{th}$. June 2016. Inclusion criteria were: (a) a history of cesarean section, (b) the presence of a V- or U-shaped area of an echoic space (with or without fluid) of at least 2 mm at the site of the cesarean section scar, (c) thinning of the myometrial wall of the anterior portion of the uterus, (d) vascular hyperplasia and blood clots in the vicinity of the defect, (e) lack of related symptoms or definite diagnosis of endometriosis before the cesarean section in the history, and (f) lack of previous diagnosis of any form of infertility. Exclusion criteria were: (a) congenital abdominal wall dysplasia, (b) isthmocele resulting from other postoperative abdominal incisional hernia, (c) previous myomectomy, and (d) refusal of consent.

Laparoscopic and hysteroscopic surgical procedures were performed in the post-menstrual cycle phase under general anesthesia. Patients were placed in the Trendelenburg (head down) position. Hysteroscopic evaluation of the endometrial

cavity was performed to exclude or treat other pathologies in the uterine cavity, and to identify the presence of isthmocele, which appeared partially white, thus allowing the confirmation of the pathology in addition to its location, size, and relationship with the bladder (Figure 7). Hysteroscopy was followed by careful laparoscopic inspection of the abdominal cavity to evaluate the presence of other pathologies, including endometriosis, uterine fibroids, or intra-abdominal adhesion (Figure 7). If such pathologies were found, endometriotic lesions were excised and sent for histopathological examination to confirm the diagnosis. A monopolar hook was used to open the isthmocele. Then, *in toto* resection was made, the uterine wound was trimmed, and 2-0 absorbable suture was placed to perform the full-thickness repair. The resected specimen was sent for a histopathological examination. The vesicouterine peritoneal fold was repaired. Histology reports were evaluated. For statistical analysis, we used a multiple binary logistic regression model (using age as a control). A p-value $<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 24 (IBM Corp, Armonk, NY, USA).

### 8.1.3. Results

The mean age of the patients was $36.9 \pm 4.5$ years, with a range of 23–42 years. Of the 28 patients, 20 (71.4%) had undergone a single previous cesarean section, while 8 patients (28.6%) had undergone ≥2 cesarean sections (Table 1). A total of 25 patients (89.3%) had different forms of bleeding disorders, 18 patients (64.3%) experienced chronic menstrual pain, 13 patients (46.4%) had recurrent vaginitis, 23 patients (82.1%) had chronic supra-pubic or lower abdominal pain, and 17 patients (60.7%) were diagnosed with secondary infertility (Table 1). Lysis of pelvic adhesions were performed in 15 patients (53.6%), and we performed endometrial polyp resection in 4 patients (14.3%). A total of 2 patients (7.1%) had myoma and underwent myomectomy. Endometriosis of different sites was found in 16 patients (57.1%) (Table 2a-b, Figure 7). The stages of endometriosis ranged between stage I and III, as classified by the ASRM. There was a significant reduction of symptoms and improvement of the patients' general health from the first month after isthmocele surgery as compared with prior to surgery (Table 2a-b). Of 17 patients, 14 (82.4%) underwent cesarean section within 24 months of surgery.

| 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 ±2years - ±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 cesarean section delivery | 17 | 39.3% |
| History of > 2 cesarean section delivery | 11 | 71.4% |
| Cesarean section incision closure (single layer) | 20 | 57.1% |
| Size of isthmocele (<6-15x>6xl5mm) | 16 | 25.0% |
| Size of isthmocele (<15-20x>15×20mm) | 7 | 17.9% |
| Size of isthmocele (>20×25mm) | 5 | 17.9% |
| Endo-myometrium thickness (<3mm) | 16 | 57.1% |
| Endo-myometrium thickness (>3mm) | 12 | 42.9% |

Table 1. 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% |

| 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 ±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.

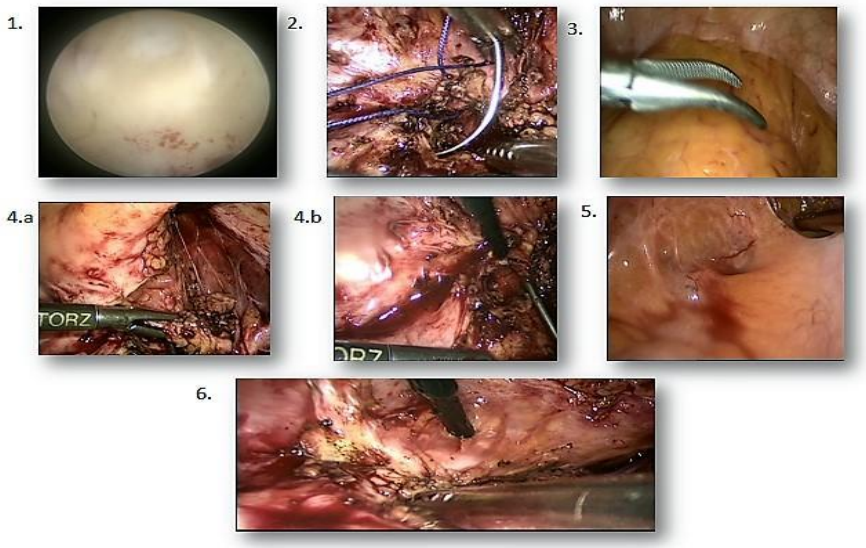



Figure 7. Images of different surgical stages of hysterolaparoscopic repair of isthmocele at Róbert Hospital (Ekine A.A.).

1: hysteroscopy image showing the area of the scar; 2: closure of scar tissue; 3: adhesion/attachment of scar tissue to bladder peritoneum; 4a/b: scar tissue preparation; 5: areas affected by endometriosis; 6: uterine wound during surgical procedures.

### 8.1.4. Discussion

Complications of cesarean section may arise due to poor alignment, single-layer uterine closure technique, poor wound healing, dysplastic endometrial capillary dilatation, and inflammatory tissue infiltration, increasing the risk of the expansion of the uterine incision [216, 217]. While the frequency of fibroid was not statistically significant, the frequency of intra-abdominal adhesion was statistically significant at 53.6% (15/28). This finding could be explained as a probable postoperative complication of abdominal surgery (Figure 6). However, unlike intra-abdominal adhesion, endometriosis is not expected to be a possible late complication of abdominal surgery such as cesarean section [217]. However, we observed a relatively high incidence of endometriosis during combined hysterolaparoscopic management of isthmocele of 57.1% (16/28). This is likely not an accidental phenomenon and should raise questions about the correlation and possible link between cesarean section or isthmocele and the onset of endometriosis [216, 217]. This observation could support the well-known transplantation theory. One possible explanation is that transport of endometriotic cells occurs via lymphogenous or hematogenous pathways [216-219]. Other options include direct extension of adenomyotic nodules through the thin uterine wall or by direct iatrogenic dissemination of endometrial cells following poor alignment of tissues during closure or by curettage during cesarean section [220, 221].

Furthermore, dissemination of endometrial cells through the isthmocele due to prolonged stagnation of menstrual fluid may be a possible cause. Although the exact mechanism is not yet understood, our finding strongly supports the implantation theory of endometriosis (Figure 7).

### 8.2. Study II: Benefits of hysterolaparoscopy in endometriosis-related infertility

#### 8.2.1. Background

It is well known that women in their prime childbearing age (between 25 and 40 years) are the most likely to be affected by endometriosis [222]. The possible association between the disease and infertility is becoming more apparent. The fecundity rate is about 0.15–0.20 per month among average couples, whereas women with endometriosis have a reported range of 0.02–0.1 per month [223]. Endometriosis affects millions of women worldwide, although the actual prevalence is unknown [222, 224]. Some authors estimate the prevalence of isthmocele to be between 2% and 10% for women in the general population and a staggering 20–50% of the female population with infertility [9, 10, 14]. Infertility causes loss of self-esteem in women, while endometriosis-associated infertility constitutes a significant burden on the QoL of women, their families, and the healthcare system [88, 225]. Studies have combined hysteroscopy and laparoscopy in patients with endometriosis-related infertility with varying degrees of success [10, 222, 226, 227]. This study aimed to determine the post-surgical performance of patients regarding fertility, with or without other endometriosis-related symptoms.

#### 8.2.2. Materials and methods

A retrospective, single-center study was conducted at the Endoscopic and IVF Unit of the Róbert Private Hospital, Budapest, from 1$^{st}$. June 2010 to 30$^{th}$. June 2018, based on the hospital database. Ethical approval was obtained from the hospital ethical committee (RRC-RMK) 001-3/2017. The study sample comprised 533 infertile women who had received prior infertility treatments—either artificial insemination (AI) or IVF—on at least one occasion. A decision for surgical management was made based on the symptoms and signs suggestive of endometriosis, previous medical history, ultrasonography findings, and results from other diagnostic procedures, including MRI, computed tomography (CT), and serum markers. Patients diagnosed with different stages of endometriosis were enrolled in the study. Exclusion criteria were Pelvic inflammatory disease (PID), polycystic ovary syndrome (PCOS),

adhesion from previous surgical interventions, and infection. All patients underwent combined hysterolaparoscopic surgical treatment between 1st. January 2010 and 31st. December 2016. Endometriosis stage was evaluated according to the revised American Fertility Society (rAFS) scoring system. The size, penetration depth, and location of the lesions were precisely recorded to ensure proper staging. During surgery, all visible endometriotic lesions were removed. Post-surgical follow-up lasted for a maximum of 2 years. Finally, 455 patients were eligible to complete the study. Immediately after surgery, patients without apparent post-surgical anatomical abnormalities were advised to conceive naturally, while those with proven complete tubal obliteration or those who failed to become pregnant 12 months after surgery were offered IVF. Patients were followed up for a maximum of 24 months; during this period, we collected relevant clinical data using personal and electronic communication forms. The determined study variables included age, parity, type of infertility, duration of infertility, stage of endometriosis, mode of conception, pregnancy outcome, and other presenting symptoms (dysmenorrhea, dyspareunia, chronic pelvic pain, and urinary symptoms). Ultrasonography findings, such as the presence of endometrioma, adenomyosis, tenderness, adnexal masses, and mobility of the uterus, were also recorded. Statistical analysis included the chi-square test for categorical data and the two-sample t-test for continuous variables using SPSS software version 24. A multiple binary logistic regression model was used to ascertain the relationship between pregnancy occurrence and the investigated variables by controlling for age (≤35 and >35 years). Data were expressed either as mean ± standard deviation, or frequency, percentage, or cumulative percentage. Meanwhile, the associations between age, stage of the disease, mode of conception, laparoscopic surgical management, and fertility performance were assessed. We adopted a multiple binary logistic regression model to determine the statistical relationship (using age as a control). A p-value <0.05 was considered statistically significant.

### 8.2.3. Results

The average age range of the subjects was 25–46 years, with a mean of 34.3 ± 4.1 years. The overall cumulative pregnancy rate was 81.3% (370/455). The live birth rate was 94.2% (Figure 8 and 9, Table 3–5). There were no statistical differences between age, cycle length, duration of menstruation, and stage of endometriosis of the women becoming pregnant or remaining infertile after surgery (Chi-square-test 6.28; df=3; p=0.099) (Figure 8 and 9, Table 3). A marked difference was observed in successful

conception rate after surgery, with 85 remaining non-pregnant and 370 becoming pregnant (p=0.001) (Table 4). Moreover, there was a significant difference in type of conception (spontaneous vs. ART) following surgery between age groups ≤35 years or >35 years (74.1% [40/54] vs. 91.3% [73/80]; p=0.007; OR=3.7; 95% CI=1.4–9.8) (Table 5). There was no statistical difference between pregnancy rates among those who underwent or did not undergo pre-surgery ART in both studied age groups (≤35 years vs. >35 years) (Tables 4 and 5). However, patients who underwent post-surgery ART had a significantly higher chance of becoming pregnant (OR=2.2; 95% CI =1.2–3.6) (Tables 3 and 4). Among those who received preoperative ART in the >35-years age group, there was no statistically significant difference in the type of conception (spontaneous vs. ART) following surgery (83.0% [73/88] vs. 73.6% [39/53]; p=0.111). There was no significant difference between the effect of various types of surgical procedures on postoperative fertility performance (Table 4).

| **Characteristics** | **Category** | **Total (n=455)** | | **Number of pregnancies (n=85)** | | **Pregnancy (n=370)** | | **Chi2 test** |
|---|---|---|---|---|---|---|---|---|
| | | N | (Col. %) | N | (Row%) | N | (Row %) | p |
| 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 endometriosis | 1 | 61 | 13.4% | 12 | 19.7% | 49 | 80.3% | 0.138 |
| | 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.

The study examined the relationship between various demographic and clinical characteristics and the history of pregnancy in a sample of 455 women diagnosed with endometriosis. The characteristics analyzed included age, length of menstrual cycle, duration of menstruation, and stage of endometriosis. The sample was divided into two groups: those who had experienced pregnancy (n = 370) and those who had not (n = 85).

- **Age:**

The age of participants ranged from 25 to 46 years. The distribution across 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 had experienced pregnancy was highest in the 31-35 age group (86.0%) and lowest in the 25-30 age group (81.3%). However, the Chi-square test revealed no statistically significant association between age and pregnancy history ($\chi^2$ (3) = 0.5799, p =0.99).

- **Length of Menstrual Cycle:**

The length of the menstrual cycle was categorized into ≤24 days (20.4%), 25-35 days (74.3%), and 36+ days (5.3%).

The highest proportion of women who had been pregnant was in the 36+ days category (91.7%), but the Chi-square test indicated no significant association between the length of the menstrual cycle and pregnancy history ($\chi^2$ (2) = 1.5188, p =0.409).

- **Length of Menstruation:**

The duration of menstruation was categorized into <4 days (27.5%), 5-6 days (48.1%), and 7+ days (24.4%).

The highest proportion of women who had been pregnant was in the <4 days category (85.6%). However, the Chi-square test showed no significant association between the duration of menstruation and pregnancy history ($\chi^2$ (2) = 0.7655, p =0.318).

Stage of Endometriosis:

The stages of endometriosis were classified as Stage 1 (13.4%), Stage 2 (29.0%), Stage 3 (35.6%), and Stage 4 (22.0%).

The highest proportion of women who had been pregnant was in Stage 3 (86.4%). The Chi-square test, however, indicated no significant association between the stage of endometriosis and pregnancy history ($\chi^2$ (3) = 0.7474, p = 0.138).

The analysis revealed that there were no statistically significant associations between the history of pregnancy and the demographic and clinical characteristics studied, including age, length of menstrual cycle, duration of menstruation, and stage of endometriosis.

| Type of laparoscopic surgical procedures | No pregnancy | | Pregnancy | | Total |
|---|---|---|---|---|---|
| | N | (Row%) | N | (Row%) | |
| Laser not used | 29 | 16.8% | 144 | 83.2% | 173 |
| Co2 laser evaporation technique used | 13 | 24.1% | 41 | 75.9% | 54 |
| Electrocoagulation excision of deep infiltrating endometriosis lesions & adhesiolysis | 6 | 20.7% | 23 | 79.3% | 29 |
| Electrocoagulation excision of superficial peritoneal & deep infiltrating lesion & endometrioma stripping& adhesiolysis | 13 | 13.7% | 82 | 86.3% | 95 |
| Cauterization of bilateral ovarian endometriosis & Electrocoagulation excision of superficial peritoneal & deep infiltrating lesion & adhesiolysis | 2 | 16.7% | 10 | 83.3% | 12 |
| Endometrioma stripping & adhesiolysis & cauterization of ovary endometriosis | 10 | 23.8% | 32 | 76.2% | 42 |
| Electrocoagulation excision of superficial peritoneal lesion & adhesiolysis | 2 | 28.6% | 5 | 71.4% | 7 |
| Electrocoagulation excision of superficial peritoneal lesion & deep infiltrating lesion & adhesiolysis | 12 | 27.9% | 31 | 72.1% | 43 |

Table 4. Types of laparoscopic surgical procedures performed on patients with endometriosis-related infertility.

The study examined the relationship between the type of laparoscopic surgical procedure performed for endometriosis and subsequent pregnancy outcomes. The procedures were categorized into various types based on the surgical techniques and extent of lesion treatment. The sample included a total of 455 cases, with the distribution of pregnancy outcomes (pregnancy vs. no pregnancy) reported for each procedure type.

- Laser Not Used: Out of 173 cases where laser was not used, 29 (16.8%) did not result in pregnancy, while 144 (83.2%) did.
- CO2 Laser Evaporation Technique: In the 54 cases where the CO2 laser evaporation technique was used, 13 (24.1%) did not lead to pregnancy, and 41 (75.9%) did.
- Electrocoagulation Excision of Deep Infiltrating Endometriosis Lesions (EEDL) & Adhesiolysis: Of the 29 cases involving EEDL and adhesiolysis, 6 (20.7%) did not result in pregnancy, while 23 (79.3%) did.
- Electrocoagulation Excision of Superficial Peritoneal (EEPL) & Deep Infiltrating Lesion & Endometrioma Stripping & Adhesiolysis: In this category, 13 out of 95 cases (13.7%) did not result in pregnancy, whereas 82 cases (86.3%) did.
- Cauterization of Bilateral Ovarian Endometriosis & EEPL & EEDL & Adhesiolysis: Of the 12 cases in this category, 2 (16.7%) did not lead to pregnancy, and 10 (83.3%) did.

- Endometrioma Stripping & Adhesiolysis & Cauterization of Ovary Endometriosis: In this group, 10 out of 42 cases (23.8%) did not result in pregnancy, while 32 (76.2%) did.
- EEPL & Adhesiolysis: Out of 7 cases, 2 (28.6%) did not result in pregnancy, and 5 (71.4%) did.
- EEPL & EEDL & Adhesiolysis: In this category, 12 out of 43 cases (27.9%) did not lead to pregnancy, while 31 (72.1%) did.

The data suggest variability in pregnancy outcomes following different laparoscopic surgical procedures for endometriosis. The highest percentage of pregnancies was observed in cases where laser was not used (83.2%), and the lowest in cases involving electrocoagulation excision of superficial peritoneal & deep infiltrating lesion & endometrioma stripping & adhesiolysis (86.3%).

| **Post-surgical fertility performance among women 25 – 35-years-old with infertility – related endometriosis** | | | | |
|---|---|---|---|---|
| **Preoperative ART** | **Postoperative ART treatment** | **No pregnancy** | **Pregnancy** | **Total** |
| | | **N(Row%)** | **N(Row%)** | **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(Row%) | N(Row%) | 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.

The study investigated the post-surgical fertility performance among women aged 25 to 35 years with infertility-related endometriosis. The focus was on the impact of preoperative and postoperative Assisted Reproductive Technology (ART) on fertility

outcomes. The sample consisted of 270 cases, divided based on their utilization of ART before and after surgery and their subsequent pregnancy outcomes.

- Preoperative ART Not Used: Among the women who did not use preoperative ART, 92 did not undergo postoperative ART, with 15 (16.3%) of these cases not resulting in pregnancy and 77 (83.7%) resulting in pregnancy. In contrast, 44 women used postoperative ART, with 6 (13.6%) not achieving pregnancy and 38 (86.4%) achieving pregnancy. Overall, in the group not using preoperative ART, 21 (15.4%) did not achieve pregnancy, while 115 (84.6%) did.
- Preoperative ART Used: In the group that used preoperative ART, 54 did not undergo postoperative ART, with 14 (25.9%) not resulting in pregnancy and 40 (74.1%) resulting in pregnancy. Among those who used both preoperative and postoperative ART, 7 (8.8%) did not achieve pregnancy, while 73 (91.2%) did. Overall, in the group using preoperative ART, 21 (15.7%) did not achieve pregnancy, while 113 (84.3%) did.
- Total: Combining both groups, the total number of cases not resulting in pregnancy was 42 (15.6%), while those achieving pregnancy were 228 (84.4%).

The findings indicate that most women aged 25 to 35 years with infertility-related endometriosis achieved pregnancy post-surgery, regardless of the use of ART either before or after surgery. Notably, the highest pregnancy rate (91.2%) was observed among women who utilized both preoperative and postoperative ART, suggesting a potential benefit of continuous ART intervention in this subgroup.

The study further examined the post-surgical fertility performance among women aged 36 to 46 years with infertility-related endometriosis. Similar to the younger cohort, this group was analyzed based on their use of preoperative and postoperative Assisted Reproductive Technology (ART) and their subsequent pregnancy outcomes. The sample included 185 cases.

- Preoperative ART Not Used: Among women who did not use preoperative ART, 26 did not undergo postoperative ART, with 11 (42.3%) of these cases not resulting in pregnancy and 15 (57.7%) resulting in pregnancy. In contrast, 18 women used postoperative ART, with 3 (16.7%) not achieving pregnancy and 15 (83.3%) achieving pregnancy. Overall, in the group not using preoperative ART, 14 (31.8%) did not achieve pregnancy, while 30 (68.2%) did.
- Preoperative ART Used: In the group that used preoperative ART, 53 did not undergo postoperative ART, with 14 (26.4%) not resulting in pregnancy and 39 (73.6%)

resulting in pregnancy. Among those who used both preoperative and postoperative ART, 15 (17.0%) did not achieve pregnancy, while 73 (83.0%) did. Overall, in the group using preoperative ART, 29 (20.6%) did not achieve pregnancy, while 112 (79.4%) did.

- Total: Combining both groups, the total number of cases not resulting in pregnancy was 43 (23.2%), while those achieving pregnancy were 142 (76.8%).

The results indicate that in the older age group of women with infertility-related endometriosis (36 to 46 years), a significant proportion achieved pregnancy post-surgery, with a notable impact observed from the use of ART. The highest pregnancy rate (83.0%) was observed among women who utilized both preoperative and postoperative ART, suggesting the effectiveness of ART in enhancing fertility outcomes in this age group.

| Age groups | Pregnancy | No pregnancy |
|---|---|---|
| 25-30 (n=91) | 81% | 19% |
| 31-35 (n=179) | 86% | 14% |
| 36-40 (n=159) | 78% | 22% |
| 41-46 (n=26) | 69% | 31% |

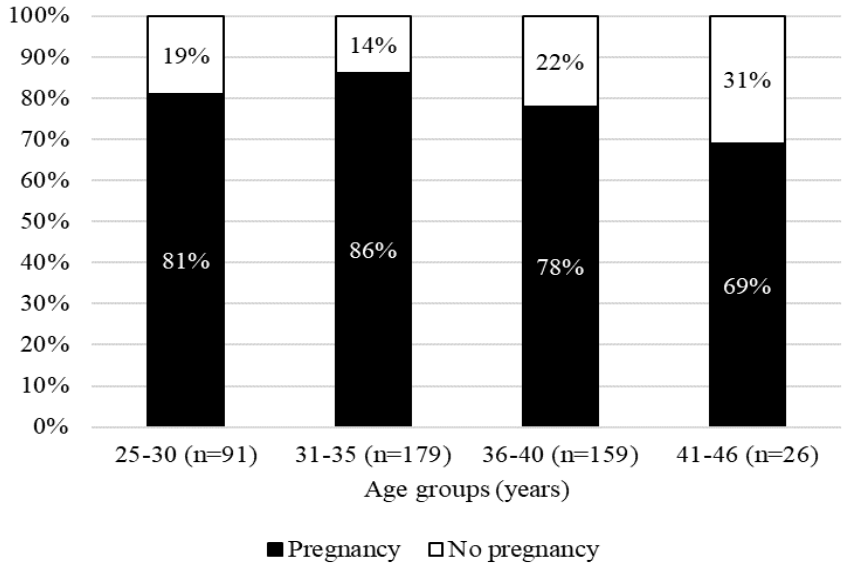



Figure 8. Effect of laparoscopic surgery on fertility performance by age in Study II.

The study examined the relationship between age and pregnancy outcomes in a sample of women with endometriosis. The participants were categorized into four age groups: 25-30 (n=91), 31-35 (n=179), 36-40 (n=159), and 41-46 (n=26). The frequency of pregnancy and no pregnancy outcomes was reported for each age group.

- Age Group 25-30: Out of 91 women, 81% achieved pregnancy, while 19% did not.
- Age Group 31-35: In this group of 179 women, a slightly higher pregnancy rate was observed, with 86% achieving pregnancy and 14% not achieving pregnancy.
- Age Group 36-40: Among the 159 women in this age group, the pregnancy rate was 78%, with 22% not achieving pregnancy.
- Age Group 41-46: The oldest age group, consisting of 26 women, had the lowest pregnancy rate, with 69% achieving pregnancy and 31% not achieving pregnancy.

The Chi-square test was conducted to determine if there was a statistically significant difference in pregnancy rates across the different age groups. The Chi-square value was calculated to be 6.282, with a p-value of 0.099.

The analysis suggests a trend where the likelihood of achieving pregnancy decreases with increasing age among women with endometriosis. The highest pregnancy rate was observed in the 31-35 age group, and the lowest in the 41-46 age group. However, the Chi-square test indicated that these differences across age groups were not statistically significant ($\chi^2 = 6.2816$, $p = 0.0987$). This implies that while there appears to be a trend of decreasing pregnancy rates with age, the differences observed in this sample are not strong enough to rule out the possibility that they occurred by chance.

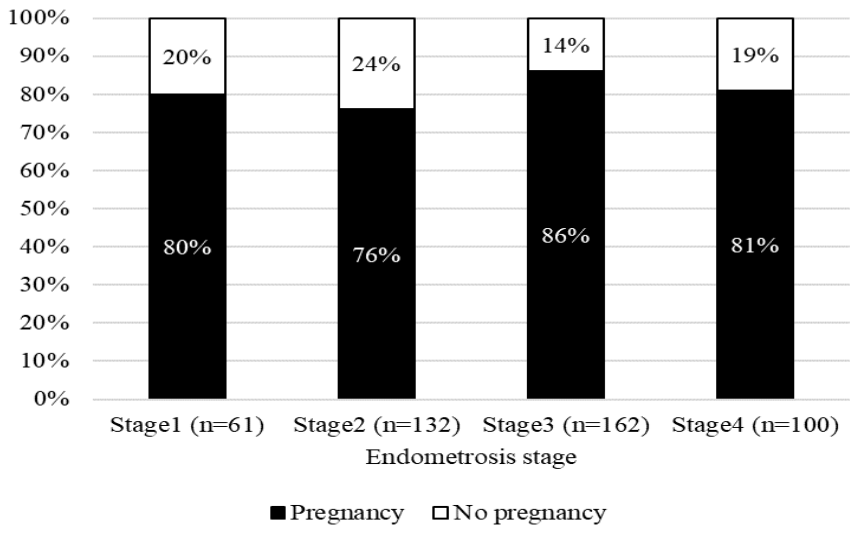



Figure 9. Effect of laparoscopic surgery on fertility performance by stage of endometriosis in Study II.

The study investigated the relationship between the stage of endometriosis and pregnancy outcomes. Participants were categorized into four groups based on the stage of endometriosis: Stage 1 (n=61), Stage 2 (n=132), Stage 3 (n=162), and Stage 4

(n=100). The frequency of pregnancy and no pregnancy outcomes was reported for each stage.

- Stage 1 Endometriosis: Out of 61 women with Stage 1 endometriosis, 80% achieved pregnancy, while 20% did not.
- Stage 2 Endometriosis: In this group of 132 women, 76% achieved pregnancy, and 24% did not achieve pregnancy.
- Stage 3 Endometriosis: Among the 162 women in this stage, a higher pregnancy rate was observed, with 86% achieving pregnancy and 14% not achieving pregnancy.
- Stage 4 Endometriosis: In the most advanced stage, Stage 4, consisting of 100 women, 81% achieved pregnancy, and 19% did not.

The analysis suggests a variation in pregnancy rates across different stages of endometriosis, with the highest pregnancy rate observed in Stage 3 (86%) and the lowest in Stage 2 (76%). However, the Chi-square test indicated that these differences across stages were not statistically significant ($\chi^2 = 5.5081$, $p = 0.1382$). This implies that while there appears to be a variation in pregnancy rates across different stages of endometriosis, the differences observed in this sample are not strong enough to rule out the possibility that they occurred by chance.

### 8.2.4. Discussion

Infertility affects women around the world, and the socio-cultural stigma that surrounds it varies and can often result in family breakdown [228-230]. Many studies have shown an association between endometriosis and infertility. The combined hysteroscopic–laparoscopic surgical treatment of endometriosis-related infertility improves fertility performance; therefore, it is considered one of the best options currently available, irrespective of the few shortcomings associated with the procedure. Furthermore, well-timed ART has also been proven to enhance the reproductive performance of affected women [231-233]. Our results demonstrated the significant benefits of hysterolaparoscopic management of endometriosis-related infertility. Our goal for the applied surgical technique was to eradicate all active endometriotic lesions. In our study, the pregnancy rate improved considerably after surgery, reaching 81.3%, with a live birth rate of 94.2%. We also observed that the stage of endometriosis did not significantly influence fertility performance. We propose that fertility performance is more dependent on surgical expertise and patient age rather than on the stage of endometriosis. Consistent with our results, a review conducted by Jacobson et al. concluded that the laparoscopic treatment of minimal and

mild endometriosis improved pregnancy and live birth rates [230, 233]. Fuchs et al. recorded a high pregnancy rate (65%) within an 8.5-month postoperative follow-up period, of which 86.9% of pregnancies resulted in deliveries [232-234]. For minimal and mild endometriosis-related infertility, clinicians commonly share the opinion that laparoscopic surgery may increase the likelihood of future pregnancy and live birth [10, 18, 235]. Another study reported a pregnancy rate of 81.6% and a live birth rate of 43.7% in stage I and II endometriosis, respectively, and a 56.7% pregnancy rate and 40.3% live birth rate was recorded in patients with stage III and IV endometriosis, respectively, after ICSI [228, 236]. However, with a relatively smaller study population, Słabuszewska-Jóźwiak et al. reported that 20.75% of patients became pregnant spontaneously and concluded their pregnancy with live birth, without ART in the first 6 months of follow-up [34]. Nardo et al. reported a cumulative pregnancy rate of 23.2% after laparoscopic treatment with the Helica Thermal Coagulator for minimal and mild endometriosis [236]. Both study outcomes were similar to ours, as we reported an overall spontaneous pregnancy rate of 28.8% during the follow-up period. However, our study had a broader patient population by including all stages of endometriosis [235, 237-239]. A systematic review highlighted the beneficial effect of laparoscopic surgery for the treatment of subfertility related to minimal and mild endometriosis [231, 240-242]. Several studies concluded that the overall pregnancy outcomes improved after laparoscopic surgical intervention regarding endometriosis-related infertility, regardless of the stage of endometriosis [91, 231, 232, 244]. Many authors reported that the ASRM's classification of endometriosis was a useful tool in predicting IVF success and fertility performance [240]. Furthermore, the ESHRE suggests that lesions classified as moderately severe to severe have a better chance with IVF as the first line of treatment [9, 34, 241]. However, in our study, there was no statistically significant difference in fertility outcome regarding different stages of endometriosis, with expectant management or with IVF, even without any anatomical deficiencies.

Explanation of the relatively improved fertility performance observed in this study may be provided by the application of combined hysteroscopic-laparoscopic surgery. Surgical expertise is another crucial factor, in addition to others, such as study population, environment, and the efficiency of IVF centers. Hysteroscopy is an efficient tool in the evaluation and correction of intrauterine and intra-tubal abnormalities. The direct imagining of the tubal os, chromopertubation, and peritubal

adhesiolysis via laparoscopy enhances the likelihood of pregnancy as compared with painful hysterosalpingography (HSG) or hysterosalpingo-contrast-sonography (HYCOSY) [34, 235,245]. Similarly to other centers, we routinely apply various surgical approaches ranging from electro-cauterization of visible endometriotic implants, excision or stripping of ovarian endometriomas, and laser coagulation, adhesiolysis, and adenomyomectomy [34, 234, 246, 247]. The hysterolaparoscopic surgical procedure plays an integral role as it enables the surgeon to treat or correct anatomical abnormalities found in the uterine cavity, including uterine fibroid, Asherman syndrome and synechia, polyps, uterine septum, isthmocele (scar defect or niche), ovarian cysts, or chronic PID; these conditions were present in our study in 17.8%, 0.8%, 5.4%, 6.6%, 1.0%, 0.8%, and 1.8% of cases, respectively. Similar findings were reported by Sreekanth [246]. In our study, approximately 52.2% of patients had tubal patency restoration via Peritubal adhesiolysis, 3.5% had unilateral tubal patency, 4.6% had a total tubal blockage, and only 39.7% had normal tubal function. Godinjak et al. reported bilateral tubal occlusion in 18 patients (5%) and unilateral tubal occlusion in 30 patients (8.33%) [247]. Our data were also comparable to those of Alborzi et al. who reported 66 spontaneous pregnancies (33.1%) and 5 pregnancies (25%) through intrauterine insemination [227, 248-250]. However, we must highlight that there are limitations of such studies because of patient desire, patient withdrawal of consent during the study, heterogeneity of study subjects, and loss to follow-up. Other limitations were the retrospective nature of the study, population size, and potential pitfalls in data collection. Nevertheless, we believe that improved fertility outcome after a combined hysterolaparoscopic approach in infertile patients is beyond doubt.

### 8.3. Study III: Effectiveness of combined hysterolaparoscopy on quality of life of endometriosis patients

#### 8.3.1. Background

Worldwide, endometriosis is reported to affect up to 10% of women of reproductive age [21, 96]. Symptoms associated with endometriosis vary and are dependent on localization, stage of the disease, individual pain threshold, and individual goals and needs [3, 9, 21]. Endometriotic tissues outside the uterine cavity behave like eutopic endometrium and are cyclically influenced by sex hormones [251-253]. Endometriosis causes chronic inflammatory reactions that can result in scar tissue formation,

adhesion, and eventual displacement or distortion of lower pelvic reproductive organs [96, 254]. Usually, the disease is accompanied by increased peritoneal fluid concentrations of biochemical substances, such as prostaglandins, proteases, and inflammatory cytokines, including IL-1, IL6, and TNFα [159, 254-256]. Angiogenic cytokines, such as IL-8 and VEGF, are secreted from the distorted reproductive organs and adhesion [159, 254, 256]; this milieu favors the presence of specific symptoms.
Sometimes, endometriosis is associated with mood swings and depression, which can occasionally lead to self-destructive lifestyles. Frequently reported symptoms are chronic pelvic pain, waist pain, dysmenorrhea, and dyspareunia; more severe symptoms include dysuria and gastrointestinal dysfunction, such as bloating and dyschezia [252-254]. Subsequently, changes in the anatomical and biochemical environment can adversely affect pelvic organ function, leading to infertility [159, 255-257].

The purpose of our investigation was to evaluate whether hysterolaparoscopy in patients with impaired QoL caused by endometriosis could lead to significant improvements.

### 8.3.2. Materials and methods

We conducted a single-center analysis on the impact of laparoscopic surgery on the QoL of patients with endometriosis at Róbert Private Hospital, Budapest. The study had two arms: the first arm was a retrospective cohort analysis from 1st. January 2010 to 31st. December 2016; and the second arm was based on a prospective cohort investigation between 1st. January 2017 and 31st. December 2018 using the Endometriosis Health Profile 30 (EHP-30) questionnaire, visual analogue scale (VAS), and Numeric Rating Scale (NRS-11) instruments. Both data for retrospective studies and prospective study questionnaires were retrieved or collected personally. In both arms, the cohorts consisted of patients of reproductive age who complained of endometriosis-related symptoms and underwent laparoscopy. In the first arm, a random sample comprising 777 patients with histologically confirmed endometriosis was recruited. In the second arm, 87 patients with histologically confirmed endometriosis and relevant symptoms were recruited. Access to the hospital database was approved by the hospital ethics committee (RRC-RMK) 001-3/2017. Exclusion criteria were PCOS; PID; current use of drugs that could affect cognition and mood; and primary medical conditions, such as neurologic, psychiatric, gastrointestinal,

urologic, and orthopedic diseases. In the first arm, we applied a standard questionnaire 3, 6, and 12 months after surgery to collect information from women on the following groups of variables: age, type of pain-related symptoms (i.e., dysmenorrhea, dyspareunia, chronic pelvic pain, or urinary symptoms), general history, history of previous gynecological surgery, mode of diagnosis, type of surgery, stage of endometriosis, surgical outcome, infertility, pregnancy outcome, and other relevant ultrasound findings, such as the presence of polyps, septum, and adhesion. In the second arm, the EHP-36 questionnaire was applied to measure demographics, physical and mental health, emotional problems, and general perception of health and QoL.

Moreover, the VAS and the NRS-11 were employed to measure painful distress associated with endometriosis. We commenced with "0" representing no pain and "10" representing the least bearable pain. None of the patients received preoperative adjuvant therapy. Questionnaires were completed before and after surgical interventions. Post-surgical follow-up was performed in the first 6 months, 12 months, and 24 months after surgery via postal questionnaire using email and by direct telephone conversation. Other complementary information was used to test for a possible association of symptoms with lifestyle, nutrition, and genetic predisposition. The questionnaire was pretested with the aid of voluntary hospital staff and the average time needed to complete the questionnaire was noted. A decision for surgical management was made based on the symptoms and signs suggestive of endometriosis, past medical history, ultrasound findings, and results of other investigative procedures, including clinical examination, MRI, CT, and serum markers (Figure 10).

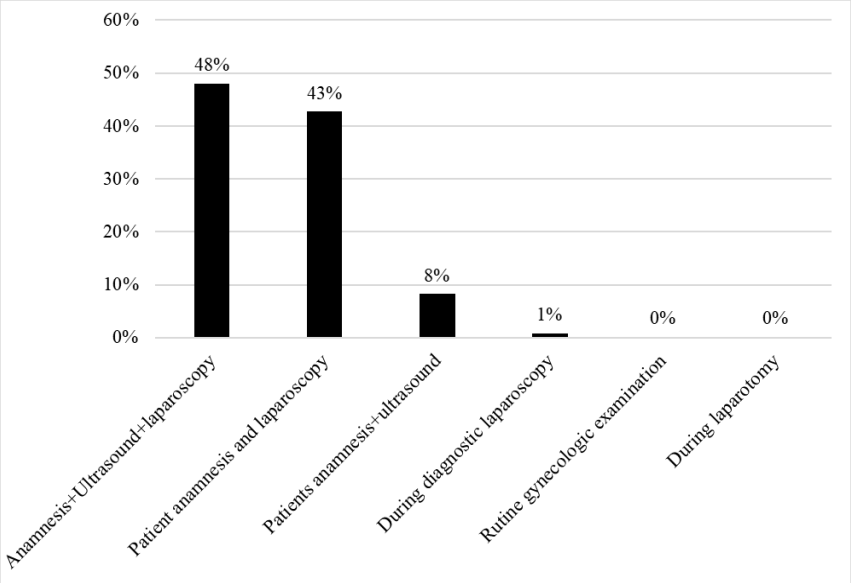



Figure 10. Mode of discovery of endometriosis in women in Study III/a.

Laparoscopic surgeries were performed by experienced surgeons, ensuring that identical surgical approaches were used in both arms of the study. Following the operations, a standard operative report was completed to provide relevant nonoperative information. The severity of endometriosis was staged according to the American Fertility Society revised definition [258, 259]. In all patients, endometriotic lesions were laparoscopically removed by excision, electrocauterization, vaporization, or excision by laser, and were sent for histological examination. Only patients with histologically confirmed endometriosis were eligible to continue the study. Postoperative follow-up lasted for 1–2 years (until 31$^{st}$. December 2018). Participants who became pregnant during the study period were followed up until term or the end of pregnancy. Those with complaints other than infertility, such as chronic pelvic pain, dysmenorrhea, dyspareunia, dysuria, and dyschezia, were followed up for 12 months. During each visit, patients underwent general gynecological and ultrasound evaluations for symptom or disease recurrence.

Data obtained from patients were statistically analyzed using SPSS software version 24 and the Stata program v.11. Correlations between age, stage and laparoscopic surgical management were assessed using the chi-square test and Fisher exact test for categorical data. We investigated continuous variables using the independent-sample t-test, non-parametric Mann–Whitney U test, or the two-sample t-test, where appropriate. Multiple logistic and linear regression analyses were performed to investigate associations between variables and outcomes, adjusting for potential confounders independently associated with exposure and sequel of interest in univariate analysis. We used the multiple binary logistic regression model to determine statistical relationships, using age as a control. For comparison of the emotional characteristics of study individuals before and after surgery according to the timing of the follow-up (6, 12, and 24 months), we used the Mauchly variance homogeneity test and MANOVA. A p-value $<0.05$ was considered nominally significant. Results are expressed as mean ± standard deviation, frequency, percentage, or cumulative percentage.

### 8.3.3. Results

In the first arm of the study, all patients were Caucasian, and the mean age of the patients was 34.3 ± 5.1 years (18–53 years). The mean age at menarche was 13.1 ± 1.4 years, the mean duration of menstruation was 5.9 ± 2.1 days, the average age at the

onset of endometriosis-related symptoms was 29.1 ± 4.3 years, and the duration from onset of symptoms to the diagnosis of endometriosis was 5.1 ± 2.9 years (Table 6).
The distribution of different stages of endometriosis was stage I in 15% (113/777) of patients, stage II in 31% (243/777) of patients, stage III in 34% (264/777) of patients, and stage IV in 20% (157/777) of patients (Table 6). The most frequently encountered complaints were dyspareunia 80% (621/777) and dysmenorrhea 74% (574/777). Among the 534 patients (69%) who initially complained about infertility, 49 did not wish to conceive after surgery (Figure 11).

The coexistence of symptoms appeared to be significant for the following variables: dysmenorrhea and obstipation, dysmenorrhea, and obtuse pain, crushing pain and obtuse pain, and sharp pain and obtuse pain (Table 7, Figure 11 and 12).

| Age | | 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) | Stage 1 | 113 | 14.5% | 14.5% |
| | Stage 2 | 243 | 31.3% | 45.8% |
| | Stage 3 | 264 | 34.0% | 79.8% |
| | Stage 4 | 157 | 20.2% | 100.0% |
| Total | | 777 | 100.0% | 100.0% |

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

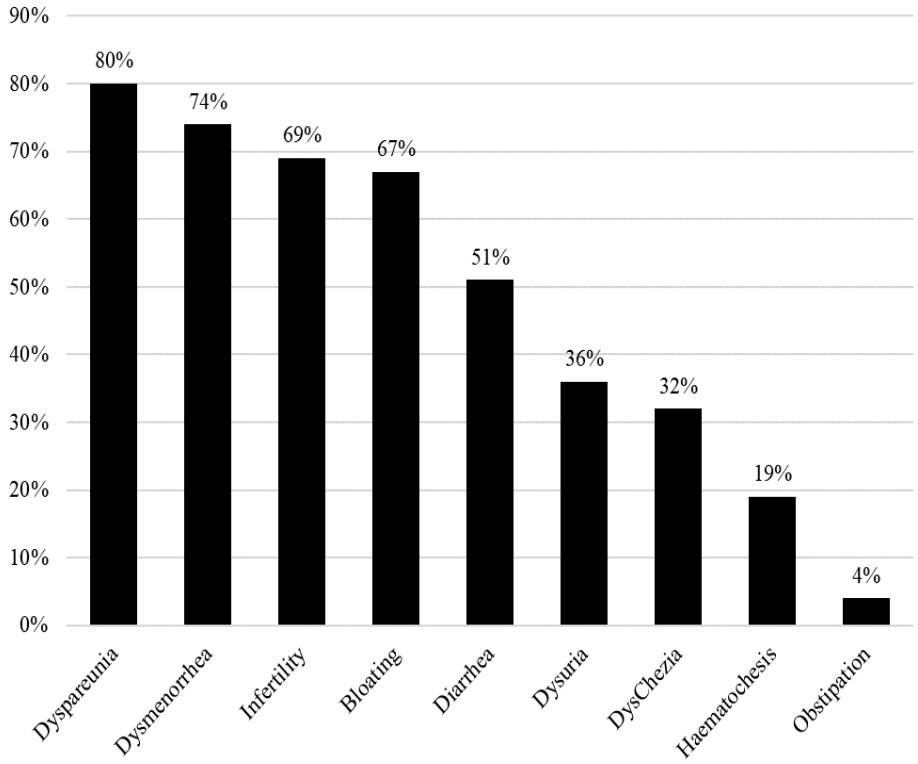



Figure 11. Distribution of endometriosis-related symptoms in Study III/a.

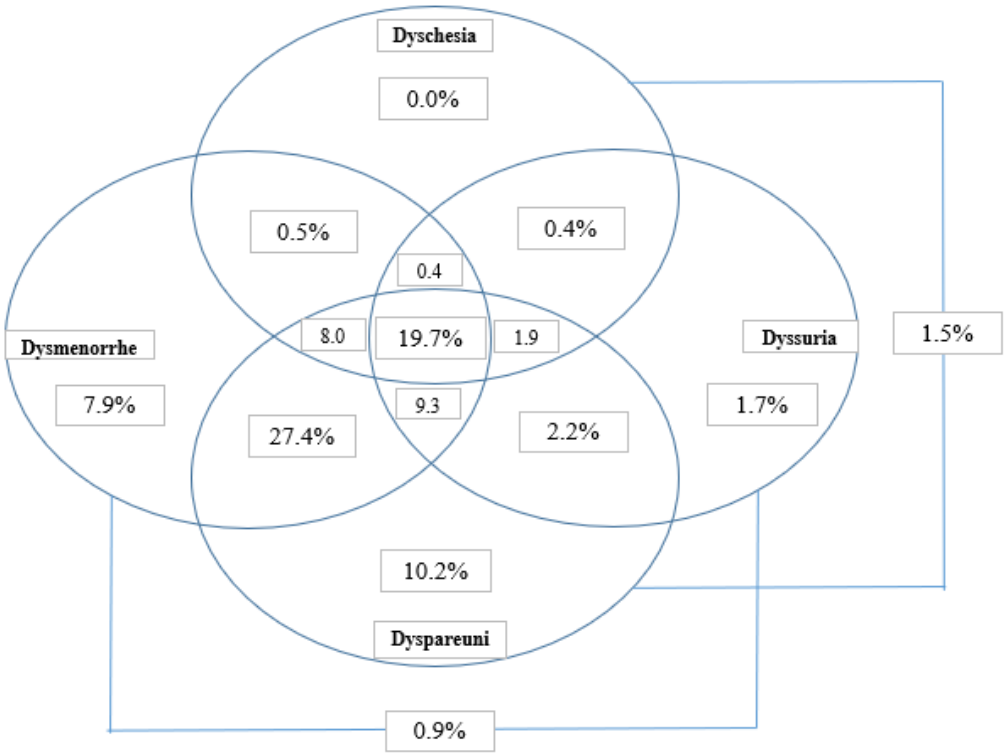



Figure 12. The prevalence and overlap of pain-related symptoms in women with endometriosis, as diagnosed surgically in Study III/a.

| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Dysmenorrhea | | | | | | | | | | |
| 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 |

Table 7. Relationship between type of pain and symptoms in patients with endometriosis in Study III/a

[*P<0.001. In the case of dysmenorrhea, the most probable type of pain was crushing pain. In the case of dyschezia, there was no typical pain, as all three types occurred. In the case of dyspareunia, the most probable type of pain was sharp pain. In the case of dysuria, there was no typical pain, as all three occurred.]

Among different anatomical locations, the recto-vaginal septum and the left ovary were the most affected sites, with involvement of 59% (458/777) and 45% (349/777), respectively (Figure 13).

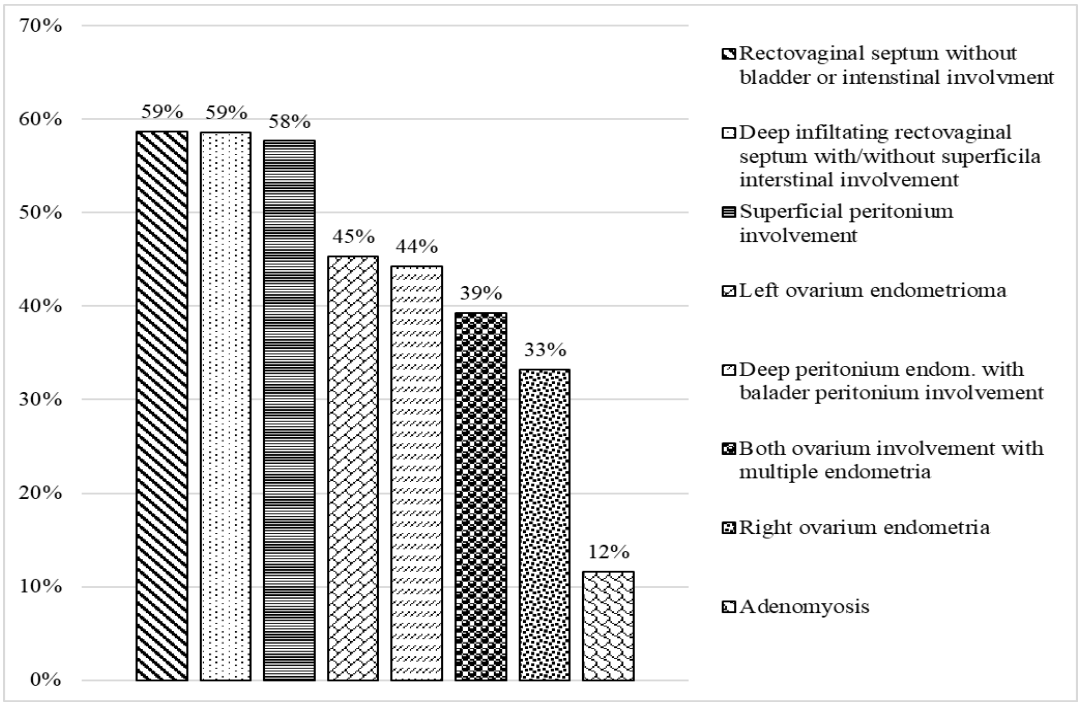



Figure 13. Frequent localization of endometriosis in Study III/a.

Unexpectedly, the incidence of previous gynecological surgery was high at 44.4% (345/777), which may present an opportunity for further evaluation or study (Figure 14).

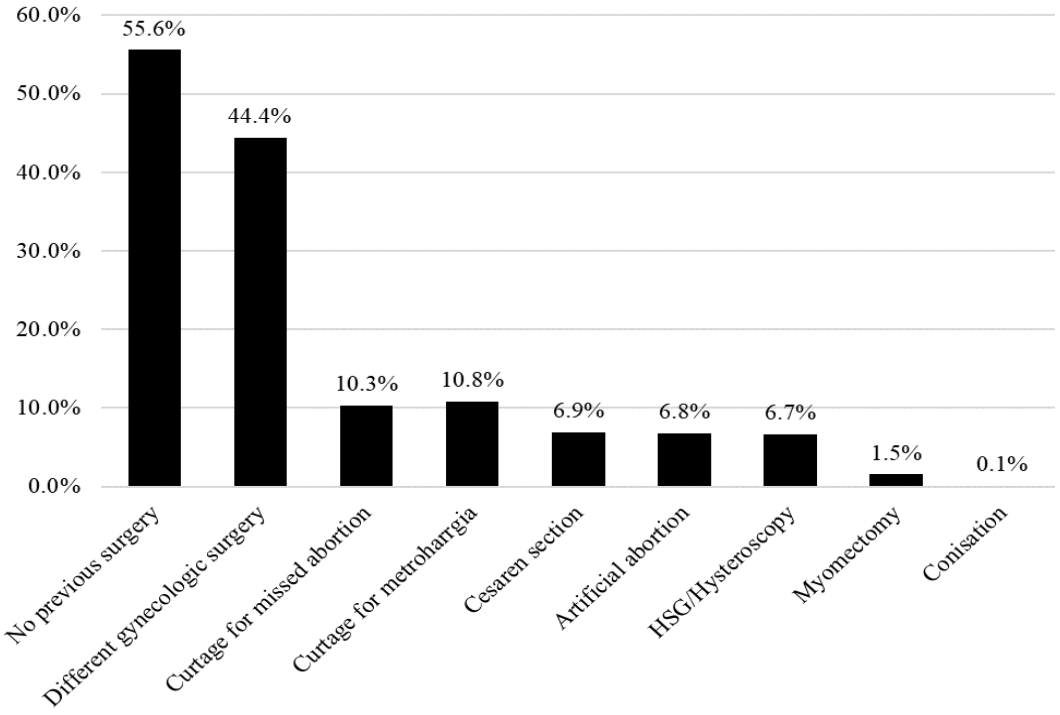



Figure 14: The incidence of other previous gynecological surgery prior to onset of endometriosis symptoms in women in Study III/a

[More than half of the patients (55.6%) had no surgical history, 44.4% had different gynecological surgery, and 1 in 9 patients (10.9%) had curettage for missed abortion and curettage for metrorrhagia (10.8%). Frequency of cesarean section (6.9%), artificial abortion (6.8%), and HSG/hysteroscopy (6.7%) was low. Frequency of myomectomy and conization were negligible.]

More complex symptomatology was observed with right ovary involvement, while deep infiltration found either underneath the peritoneum or within the recto-vaginal septum appeared second (Table 8). There was a significant improvement in QoL at 3, 6, and 12 months after surgery, and most of the patients reported significant to complete cessation of symptoms (Table 9 and Figure 15).

The rate of successful live births was 94.2% (327/347) and the rate of pregnancy loss was 5.8%. Overall, there was gradual improvement in the QoL of the women. There was a significant relationship between improvement rate and the time of visit; patients

reported increasing improvement over time. The moderate improvement rate alone decreased, but this also strengthened the degree of progress, as the other two improvement factors ("significant" and "complete") were "at the expense of" the change. Significant to complete improvement in QoL was observed, recorded as 57–59% on the first follow-up visit and 74–85% on the final visit (after 1st. the year), and all woman reported a significant level of improvement (p=0.0005) (Table 9, Figure 15 and 17). Patients reported improvement in QoL as follows: 41/421 moderate, 196/421 significant, and 184/421 as complete at 12 months of follow-up, at the first 3 months (250/455), 6 months (341/455), and at 12 months 432/reported this positive change. Only 23/455 were non-respondents concerning fertility performance and QoL.

Table 8 in Study III/a presents the relationship between the type of pain experienced and the localization of endometriosis in the study participants. The types of pain assessed include dysmenorrhea (painful menstruation), dyschezia (pain during defecation), dyspareunia (pain during sexual intercourse), bloating (abdominal swelling), obstipation (intestinal obstruction), diarrhea, dysuria (painful urination), and bloody defecation. The localization of endometriosis considered are the right ovary, left ovary, superficial peritoneal involvement, deep involvement of the ovary with multiple unilateral or bilateral endometriosis, deep peritoneal endometriosis with bladder peritoneum involvement, deep recto-vaginal septum endometriosis with intestinal peritoneal involvement, and deep recto-vaginal septum (RVS-B-R) without bowel involvement.

- Right Ovary: Participants with endometriosis in the right ovary reported experiencing all types of pain assessed in the study.
- Left Ovary: Endometriosis in the left ovary was associated with dysmenorrhea, bloating, and dysuria.
- Superficial Peritoneal Involvement: No specific types of pain were reported for superficial peritoneal involvement.
- Deep Involvement of the Ovary with Multiple Unilateral or Bilateral Endometriosis: Participants with this type of endometriosis reported experiencing all types of pain assessed.
- Deep Peritoneal Endometriosis with Bladder Peritoneum Involvement: This condition was associated with all types of pain assessed in the study.

- Deep Recto-vaginal Septum Endometriosis with Intestinal Peritoneal Involvement: Participants with this type of endometriosis also reported experiencing all types of pain assessed.
- Deep Recto-vaginal Septum (RVS-B-R) Without Bowel Involvement: This condition was associated with dyschezia, dyspareunia, bloating, obstipation, diarrhea, dysuria, and bloody defecation.

| **Localization** | **Dysmenorrhea** | **Dys-Chezia** | **Dys-pareunia** | **Bloating (abdominal swelling)** | **Obstipation (intestinal obstruction)** | **Diar-rhea** | **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 peritoneum involvement | X | X | X | X | X | X | X | X |
| Deep recto-vaginal septum endometriosis with intestinal peritoneal involvement | X | X | X | X | X | X | X | X |
| Deep recto vaginal septum; RVS-B-R without bowel involvement | | X | X | X | X | X | X | X |

Table 8. Relationship between type of pain and localization of endometriosis in study III/a.

The findings from Study III/a, indicate a significant relationship between the localization of endometriosis and the type of pain experienced by participants. Notably, deep involvement of endometriosis, whether in the ovaries, peritoneum, or recto-vaginal septum, was associated with a broader range of pain symptoms, including dysmenorrhea, dyspareunia, bloating, obstipation, diarrhea, dysuria, and bloody defecation. In contrast, superficial peritoneal involvement did not report specific pain types in this study.

These results highlight the diverse and often severe symptomatology associated with different localization of endometriosis. The presence of pain in multiple locations and of various types underscores the complexity of diagnosing and managing endometriosis. It also emphasizes the need for a comprehensive and individualized approach to treatment, considering the specific localization and symptom patterns in each case.

| 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% |

Table 9. Comparison of the improvement in symptoms after surgery across the different stages of follow-up in patients with endometriosis in Study III/a.

At the first 3-month follow-up, the Chi-square test revealed a statistically significant association between the level of symptom improvement and the follow-up period, $\chi^2$ (2) = 12.524, p = 0.002. This indicates that the differences in symptom improvement levels among patients are not due to chance. At the 6-month follow-up, the Chi-square test again, showed a statistically significant association, $\chi^2$ (2) = 9.988, p = 0.007. This suggests that the variation in symptom improvement observed among patients at this stage is statistically significant and unlikely to be due to random variation. At the 12-month follow-up, the Chi-square test results were $\chi^2$ (2) = 20.988, with a p-value of less than 0.001. This indicates a very strong statistical significance, suggesting that the differences in symptom improvement levels among patients at one-year post-surgery are highly unlikely to be due to chance.

Across all three follow-up periods (3, 6, and 12 months), the Chi-square tests consistently indicate statistically significant differences in symptom improvement among patients with endometriosis who underwent surgery. These results suggest that the level of improvement in symptoms varies significantly among patients over time, underscoring the importance of individualized postoperative care and monitoring.

| Symptoms | First month visit | Sixth month visit | First year visit |
|---|---|---|---|
| Dysmenorrhea | <0.001 | <0.001 | <0.001 |
| Dyschezia | <0.001 | <0.001 | <0.001 |
| Dyspareunia | <0.001 | <0.001 | <0.001 |
| Blooting (abdominal swelling) | <0.001 | <0.001 | <0.001 |
| Obstipation (intestinal obstruction) | 0.585 | 0.700 | 0.701 |
| Diarrhea | <0.001 | <0.001 | <0.001 |
| Dysuria | <0.001 | <0.001 | <0.001 |
| Bloody defecation | <0.001 | <0.001 | <0.001 |
| Crushing pain | <0.001 | <0.001 | <0.001 |
| Obtuse pain | 0.006 | <0.001 | <0.001 |
| Sharp pain | <0.001 | <0.001 | <0.001 |

Table 10. Improvement of individual endometriosis-related symptoms and quality of life 12 months after surgery in Study III/a.

| | | | | | 95% confidence interval | | |
|---|---|---|---|---|---|---|---|
| Visit | 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 of symptoms 50- 60% | 30.418 | 1 | <0.001 | 0.052 | 0.012 | 0.220 |
| | Significant improvement of symptoms 70- 80% | 0.823 | 1 | 0.364 | 1.152 | 0.012 | 0.220 |
| | Complete improvement os symptoms 90- 100% | 2.125 | 1 | 0.145 | 1.254 | 0.925 | 1.702 |
| 6 months | Moderate improvement of symptoms 50- 60% | 29.912 | 1 | <0.001 | 0.000 | 0.000 | 0.000 |
| | Significant improvement of 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 of symptoms 50- 60% | 32.478 | 1 | <0.001 | 0.000 | 0.000 | 0.000 |
| | Significant improvement of 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 90-100% | 65.441 | 1 | <0.001 | 3.837 | 2.749 | 5.356 |

Table 11. Post-surgery well-being and quality of life of endometriosis patients in Study III/a.

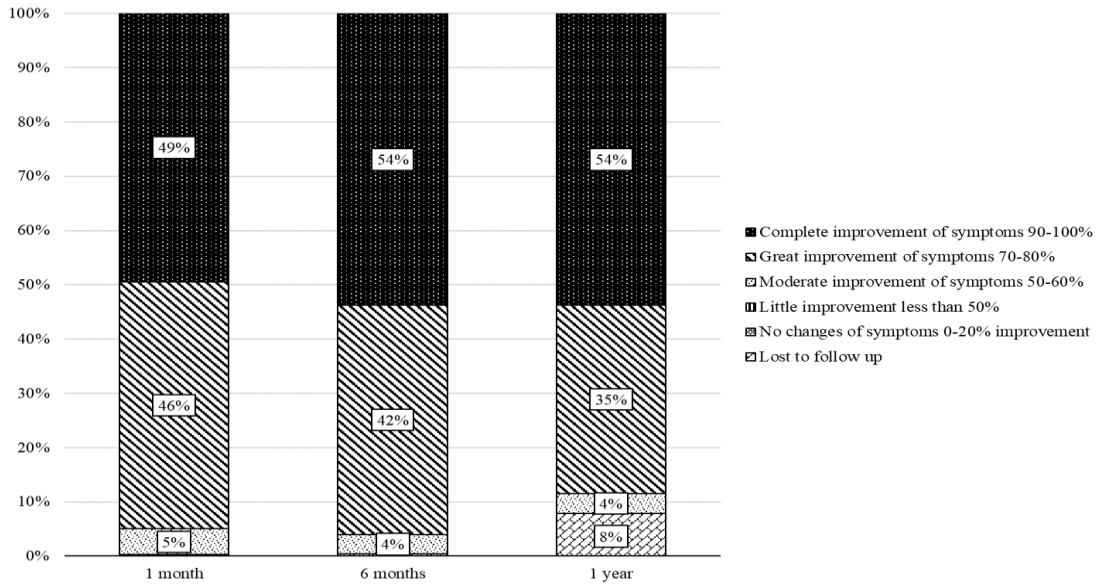



Figure 15. The post-surgical outcome regarding general well-being during the follow-up period beyond 12 months in Study III/a.

The study employed the Wilcoxon Signed-Rank Test to compare the improvement in symptoms of patients with endometriosis at various follow-up intervals post-surgery: 1 month, 6 months, 1 year, and beyond 1 year. The improvement was categorized as: no changes of symptoms (0-20% improvement), little improvement (less than 50%), moderate improvement (50-60%), significant improvement (70-80%), and complete improvement (90-100%).

At the 1-month follow-up, 49% of patients reported complete improvement (90-100%), and 46% reported significant improvement (70-80%). By the 6-month follow-up, the percentage of patients reporting complete improvement increased slightly to 54%, while those reporting significant improvement decreased to 42%. At the 1-year mark, the percentages remained stable for complete improvement (54%) but decreased for significant improvement (35%). Beyond 1 year, the proportion of patients reporting complete improvement decreased to 42%, and significant improvement further decreased to 26%.

The Wilcoxon Signed-Rank Test results indicated statistically significant differences between the follow-up periods:

- 6 Months vs. 1 Month:

There was a statistically significant difference in the improvement of symptoms between the 1-month and 6-month follow-ups, with a greater improvement observed at 6 months. ($Z = 6.714$, Asymptotic Significance (2-tailed) $< 0.001$.)

- 1 Year vs. 6 Months:

The improvement in symptoms was significantly different between the 6-month and 1-year follow-ups, indicating continued improvement over time. (Z = 3.81, Asymptotic Significance (2-tailed) < 0.001.)

- 1 Year vs. 1 Month:

A statistically significant difference was observed in symptom improvement between the 1-month and 1-year follow-ups, suggesting substantial improvement over the first-year post-surgery. (Z = 7.362, Asymptotic Significance (2-tailed) < 0.001.)

The findings indicate a significant improvement in symptoms of endometriosis in the first year following surgery, with the most notable improvements observed between the 1-month and 6-month follow-ups. The level of improvement appears to stabilize or slightly decrease beyond one-year post-surgery. These results underscore the effectiveness of the surgical intervention in the short term and highlight the need for ongoing monitoring and management of symptoms in the long term.

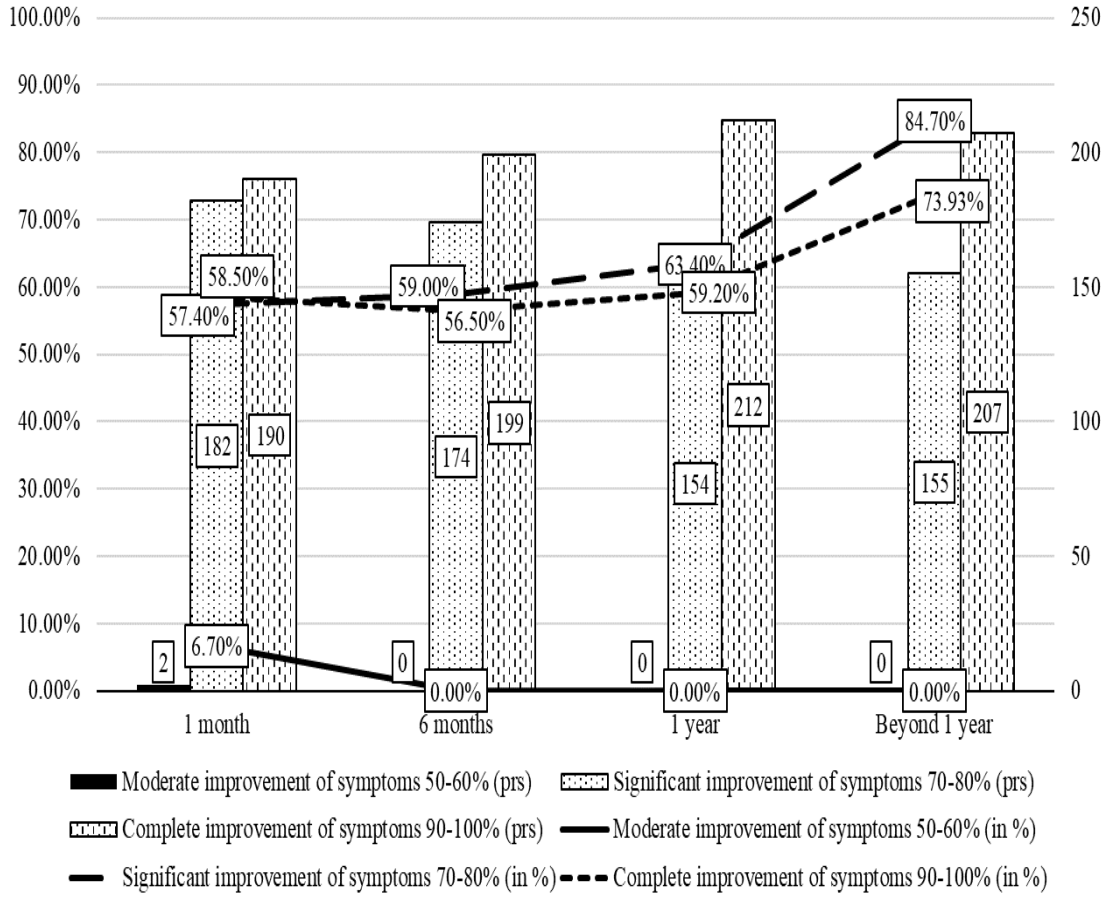



Figure 16. Relationship between well-being and infertility following surgery in Study. III/a.

(There was a significant correlation between the rate of improvement and pregnancy after 1 month (Cramer's V = 0.218; $\chi 2$ (3) = 31.847; p <0.001) and 6 months after surgery (Cramer's V = 0.213; $\chi 2$ (2) = 30.302; p <0.001), 1 year after the intervention (Cramer's V = 0.232; $\chi 2$ (2) = 33.510; p <0.001), and on a visit later than 1 year (Cramer's V = 0.303; $\chi 2$ (2) = 43.513; p <0.001).

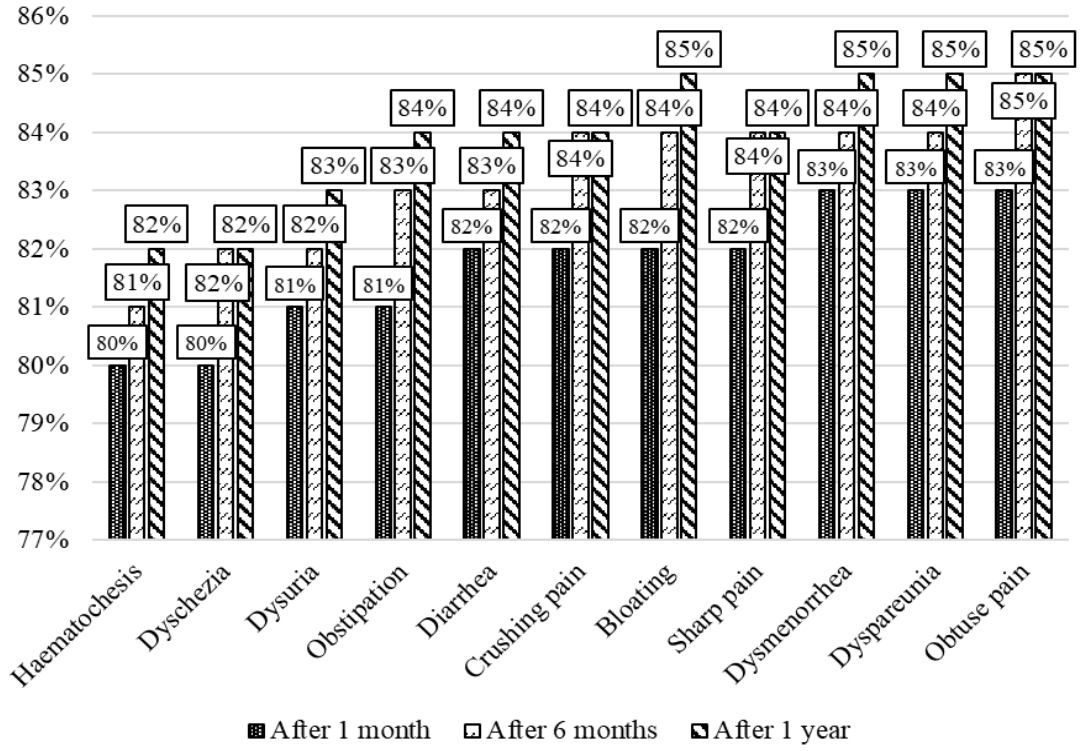



Figure 17. Effect of surgery on the quality of life during follow-up in Study III/a

The study assessed the well-being of respondents with various complaints associated with endometriosis, measured at three different time points post-treatment: after 1 month, 6 months, and 1 year. Well-being was quantified on a scale from 0% (worst) to 100% (best). The complaints evaluated included hematochezia, dyschezia, dysuria, obstipation, diarrhea, crushing pain, bloating, sharp pain, dysmenorrhea, dyspareunia, and obtuse pain.

- Hematochezia: Well-being scores improved marginally from 80% after 1 month to 81% after 6 months, and to 82% after 1 year.
- Dyschezia: Scores for dyschezia showed a slight improvement from 80% after 1 month to 82% after both 6 months and 1 year.

- Dysuria: Well-being scores increased from 81% after 1 month to 82% after 6 months, and further to 83% after 1 year.
- Obstipation: Scores improved from 81% after 1 month to 83% after 6 months, and to 84% after 1 year.
- Diarrhea: There was an improvement in well-being from 82% after 1 month to 83% after 6 months, and to 84% after 1 year.
- Crushing Pain: Scores increased from 82% after 1 month to 84% after both 6 months and 1 year.
- Bloating: Well-being scores improved from 82% after 1 month to 84% after 6 months, and to 85% after 1 year.
- Sharp Pain: Scores for sharp pain showed an improvement from 82% after 1 month to 84% after both 6 months and 1 year.
- Dysmenorrhea: Well-being scores increased from 83% after 1 month to 84% after 6 months, and to 85% after 1 year.
- Dyspareunia: Scores improved from 83% after 1 month to 84% after 6 months, and to 85% after 1 year.
- Obtuse Pain: Well-being scores for obtuse pain showed an improvement from 83% after 1 month to 85% after both 6 months and 1 year.

The findings indicate a gradual improvement in the well-being of respondents across all complaints over the course of one year following treatment. The most notable improvements were observed in symptoms such as bloating, dysmenorrhea, dyspareunia, and obtuse pain, where well-being scores increased by 3 percentage points over the year. While the improvements in well-being for each symptom were modest, the consistent upward trend across all complaints is encouraging.

These results suggest that the treatment provided had a positive impact on the well-being of patients with various endometriosis-related complaints. The gradual nature of improvement underscores the importance of ongoing management and support for individuals with endometriosis. It also highlights the chronic and often fluctuating course of endometriosis symptoms, necessitating long-term strategies for symptom management and patient support.

In the second arm of the study, all patients were Caucasian. A higher level of education and higher income category was reported in 81.6% of the enrolled patients.

The mean age at diagnosis was 34.2 ± 5.97 years (22–48 years). The mean duration of infertility was 3.8 ± 2.1 years. The mean duration between symptom onset and diagnosis was 9.7 ± 0.35 years. The most reported complaints or symptoms were infertility in 70.1%, dysmenorrhea in 82.8%, dyspareunia in 60.9%, bloating in 93.1%, and urinary discomfort in 49.4% (Table 12). During surgery, the involvement of the left ovary as a single affected organ was more frequently observed (42.5%), while recto-vaginal septum involvement or superficial peritoneal implants were found in 55.2% and 66.7%, respectively. The third stage of endometriosis was the most frequently observed (48.3%).

NRS-11 scale data analyses revealed a mean preoperative pain score of 6–10 (moderate to severe pain) in 85/87 patients (94.8%). Postoperative pain perception improved to an average 0–2 score (none or slight periodic discomfort) in 71/87 patients (81.6%). Before surgery, the average VAS score was 8–10 (moderate to severe pain) in 82/87 patients (94.3%). Postoperative VAS score declined to 0.47–0.89 (minimal to no pain) in 81/87 patients (93.1%) (Figure 19). The completion rate was 100%, except for three cases of pregnancy. Post surgically, all patients reported significant changes and improvements in QoL (Table 13, Figure 18).

When considering different types of complaints associated with endometriosis in the study, we found that the most frequent complaint was pricking pain/discomfort, while the least frequent was rectal bleeding (Table 13). When considering QoL indicators, we found a marked improvement in all indices (Table 14, Figure 20).

All the Mauchly variance homogeneity tests proved heteroscedasticity. Regarding MANOVA testing for the differences among the changes in emotions over time, all tests showed significant decreases in all depressing problems and emotions after surgery (Table 13, Figure 18).

| General Characteristics of women with endometriosis in this study (n=87) | | | |
|---|---|---|---|
| Mean Age at menarche (years) | | 13.2 ± 1.293 (9–17) | |
| Mean Age at diagnosis of endometriosis (years) | | 34.2 ± 5.97 (20–48) | |
| Mean Age at the onset of symptoms relating to endometriosis (years | | 24.5 ± 5.71 (15–37) | |
| Duration of infertility (years) | | 3.8 ± 2.1 | |
| Duration of symptoms before diagnosis (years) | | 9.7 ± 0.35 | |
| Characteristics | Types | Number (n) | Percentage (%) |
| Localization of endometriosis | Superficial/Deep left ovary involvement | 37 | 42.6 |
| | Deep right ovary involvement | 14 | 16.2 |
| | Bilateral ovary involvement | 27 | 31 |
| | Superficial (RVS)/Deep rectovaginal septum involvement | 62 | 71.3 |
| | Superficial bladder involvement | 48 | 55.2 |
| | Deep bladder involvement | 10 | 11.5 |
| | Intestinal involvement | 13 | 14.9 |
| | Superficial peritoneal involvement | 58 | 66.7 |
| | Adenomyosis | 10 | 11.5 |
| Other surgical procedures | Adhesiolysis | 61 | 70.1 |
| | Bladder resection | 8 | 9.2 |
| | Dixon operation | 2 | 2.3 |
| | Relapse of endometriosis | 5 | 5.7 |
| Stages of endometriosis | 1 | 3 | 4.9 |
| | 2 | 12 | 19.7 |
| | 3 | 29 | 47.5 |
| | 4 | 17 | 27.9 |
| Other complication | Endometrioid carcinoma | 1 | 1.6 |
| Fertility | Preoperative infertility issue | 61 | 70.1 |
| Mode of pregnancy | Spontaneous pregnancy | 23 | 37.7 |
| | IVF-ET | 9 | 14.1 |
| Outcome of pregnancy | Spontaneous delivery | 17 | 53.1 |
| | Cesarean section | 7 | 21.9 |
| | Missed abortion | 4 | 12.5 |
| | Lost to follow up | 3 | 9.4 |
| Preoperative pain score (NRS–11) | Moderate to severe pain | 85 | 94.8 |
| Postoperative pain score (NRS–11) | Mild to no pain | 71 | 81.6 |
| Preoperative VAS score | Moderate to severe pain | 82 | 94.3 |
| Postoperative VAS score | Minimal to no pain | 81 | 93.1 |
| Additional factors | Family history of endometriosis | ** | 15 |
| | High red meat/fish | ** | *** |
| | Smoking (≥5 cigarettes/day) | 17 | 19.5 |
| | Alcohol consumption (beer/wine regularly) | 8 | 9.2 |
| | Alcohol consumption (gin/whisky regularly) | 14 | 16.1 |
| | Coffee consumption (>1 cup/daily) | 29 | 33.5 |
| Menstrual history | Bleeding disorder (metrorrhagia) | 57 | 66 |
| | Cycle dysfunction (spotting) | 43 | 49 |
| Miscellaneous issues | Use of sanitary napkins (solely to more regularly) | 63 | 72 |

Table 12. General characteristics of women with endometriosis in Study III/b.

| Emotion | Test | Value | F | Hypothesis df | Error df | Sig. |
|---|---|---|---|---|---|---|
| Exhausting emotionally | Wilks' Lambda | 0.129 | 189.285 | 3 | 84 | <0.001 |
| Sickening emotionally | Wilks' Lambda | 0.275 | 73.854 | 3 | 84 | <0.001 |
| Unbearable emotionally | Wilks' Lambda | 0.117 | 211.495 | 3 | 84 | <0.001 |
| Miserable emotionally | Wilks' Lambda | 0.136 | 176.23 | 3 | 83 | <0.001 |
| Torturing emotionally | Wilks' Lambda | 0.115 | 215.733 | 3 | 84 | <0.001 |
| Depressing emotionally | Wilks' Lambda | 0.123 | 198.814 | 3 | 84 | <0.001 |
| Affect your work negatively | Wilks' Lambda | 0.165 | 141.547 | 3 | 84 | <0.001 |
| Affect your learning negatively | Wilks' Lambda | 0.188 | 121.096 | 3 | 84 | <0.001 |

Table 13. Comparison of emotional assessment of individuals before and after surgery according to the timing of follow-up (6, 12, and 24 months) in Study III/b.

| **Women' s emotional, socioeconomic and physical state assessment before surgery** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Assessment | Very bad (0-20%) 7-16 score | | Bad (20-50%) 5-7 score | | Satisfactory (60-70%) 3-5 score | | Good (80-100%) 0-3 score | |
| Characteristics | n | % | n | % | n | % | n | % |
| Quality of life | 47 | 54.0% | 31 | 35.6% | 8 | 9.2% | 1 | 1.1% |
| General wellbeing | 48 | 55.2% | 33 | 37.9% | 6 | 6.9% | NA | NA |
| Sexual problems (dyspareuma) | 34 | 39.1% | 22 | 25.3% | 19 | 21.8% | 12 | 13.8% |
| Urinary-problems | 5 | 5.7% | 25 | 28.7% | 12 | 13.8% | 45 | 51.7% |
| All painful complaints associated with endometriosis | 53 | 60.9% | 34 | 39.1% | NA | NA | NA | NA |
| Dyschezia | 8 | 9.2% | 30 | 34.5% | 19 | 21.8% | 30 | 34.5% |
| | | | | | | | | |
| Characteristics | No improvement /relapse/ (0-20%) 7-10 score | | Little improvement (20-50%) 5-7 score | | Moderate improyement (60-70%) 3-5 score | | Significant/Complete improyement (80-100%) 0-3 score | |
| | n | % | n | % | n | % | n | % |
| Quality of life | 5 | 5.7% | 1 | 1.1% | 2 | 2.3% | 79 | 90.8% |
| General wellbeing | 1 | 1.1% | 4 | 4.5% | 19 | 21.8% | 63 | 72.4% |
| Sexual problems (dyspareuma) | 2 | 2.2% | 6 | 6.8% | 4 | 4.6% | 75 | 86.2% |
| Urman-problems | NA | NA | 1 | 1.1% | 6 | 6.9% | 80 | 92.0% |
| All painful complaints associated with endometriosis | 2 | 2.2% | 5 | 5.7% | 9 | 10.3% | 71 | 81.6% |
| Dyschezia | NA | NA | 2 | 2.2% | 8 | 9.1% | 77 | 88.5% |

Table 14. Improvement in quality of life and general well-being after surgery in women with endometriosis in Study III/b.

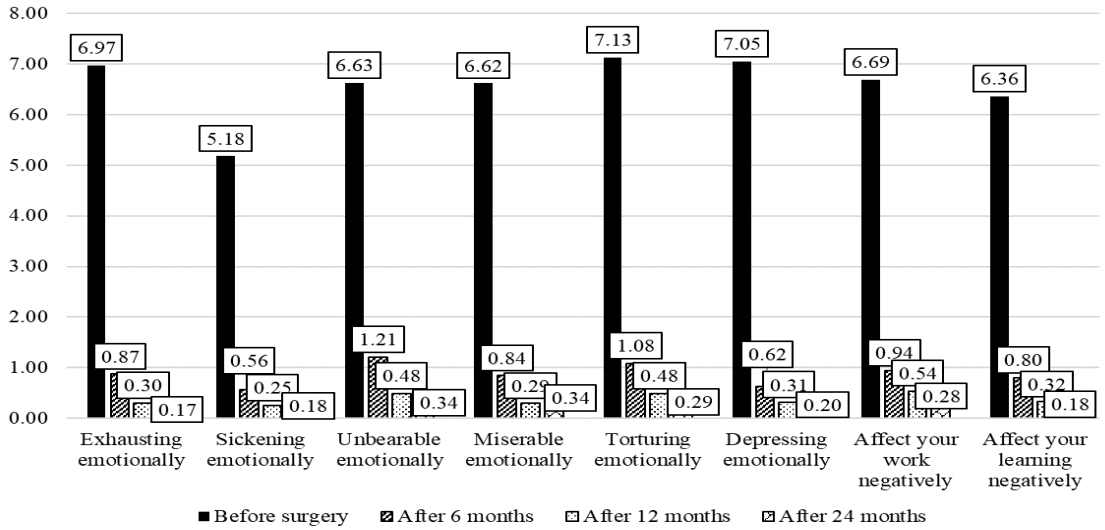
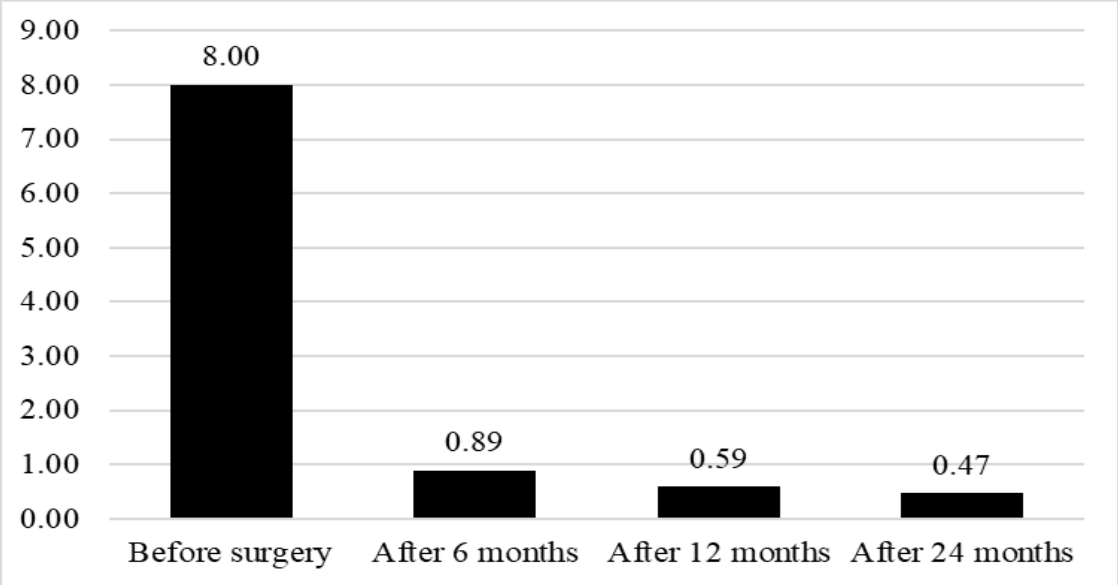



Figure 18. Psychological-emotional assessment of individuals before and after surgery according to different follow-up intervals (April to June 2 and 24 months) in Study III/b.




| 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 |

Figure 19. Comparison of NRS-11 and VAS scores before and after surgery according to the timing of follow-up (6, 12, and 24 months) in Study III/b.

[Because the Mauchly variance homogeneity test proved heteroscedasticity (chi-squared (5) =113.835, p<0.001), we also used MANOVA for testing the differences among the pain rating changes over time. The MANOVA tests proved a significant decrease in all pain after surgery]

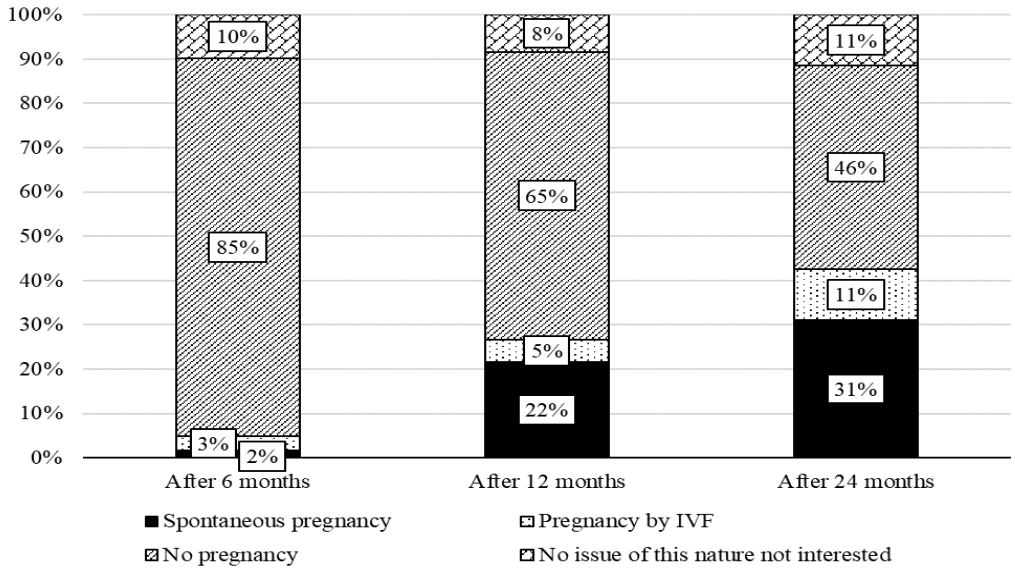
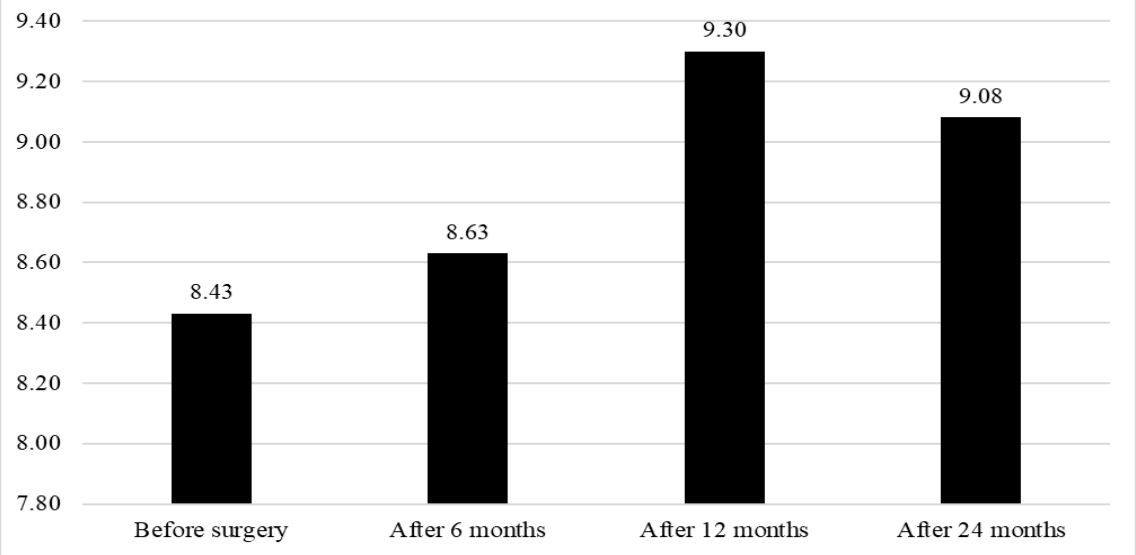



Figure 20. EHP-36 scores before and after surgery at different follow-up intervals (6, 12, and 24 months) in Study III/b.




| Tests | Value | F | Hypothesis df | Error df | Sig. |
|---|---|---|---|---|---|
| Pillai's Trace | 0.526 | 31.02 | 3 | 84 | <0.001 |
| Wilks' Lambda | 0.474 | 31.02 | 3 | 84 | <0.001 |
| Hotelling's Multivariate Trace | 1.108 | 31.02 | 3 | 84 | <0.001 |
| Roy's Largest Root | 1.108 | 31.02 | 3 | 84 | <0.001 |

Figure 21. EHP-36 scores before and after surgery at different follow-up intervals (6, 12, and 24 months) in Study III/b.

### 8.3.4. Discussion

Our study focused on the potential positive effects of hysterolaparoscopy on the QoL of patients suffering from endometriosis. The economic burden that endometriosis imposes on individuals and society is significant [97]. In 2012, an endometriosis survey in the UK revealed that approximately 1.6 million women were affected, with an estimated financial burden of £10.6 billion [86, 260, 261]. In Australia, approximately 550,000 women have endometriosis, costing £2.75 billion [119, 262, 263]. In the United States, approximately 7.6 million women are affected, with financial implications of approximately £52.1 billion per year due to loss of work and healthcare costs [260, 261]. The accurate prevalence and subsequent economic burden of the disease Hungary remains unknown, although a multicenter study estimated an affected population of approximately 184,000 women, with an estimated cost of €1.6 billion per year [86, 262, 263].

In the first arm of our study, the average age of the patients and the duration of diagnosis were similar to those reported in other studies [24, 86]. Interestingly, the left side of the lower pelvis seemed to be involved more frequently, likely owing to the intra-abdominal fluid circulation pattern, which is in a clockwise direction and stops at the pouch of Douglas [40, 264-266]. This circulation may increase the possibility of implantation of endometriotic cells in an asymmetric pattern [267]. In concordance with other studies, our results demonstrated a possible direct association of endometriosis with dysmenorrhea, dyspareunia, chronic pelvic pain, and infertility [24, 192, 268]. Endometriosis can significantly lower QoL for women. In our study, almost 95% of women had substantial or complete resolution of symptoms at 1 month postoperatively. This result is higher than those of similar studies reporting on QoL and sexual performance after laparoscopic surgical treatment for endometriosis [235, 269-271]. Furthermore, combined hysterolaparoscopy had positive effects on QoL, regardless of the stage of the disease. Our results were in line with those of Mabrouk et al. [176]. Other studies focusing on endpoints, such as dysmenorrhea, dyspareunia, pelvic pain, dyschezia, and dysuria, have also highlighted the beneficial effect of endoscopic surgery on symptom relief [37, 271]. Further improvement in women's well-being and QoL is achievable with the help of combined hysterolaparoscopy [240, 259].

The second arm of our study demonstrated the usefulness of EHP-36, VAS, and NRS-11 questionnaires in evaluating the QoL of patients with endometriosis. Interestingly, in this arm, the mean age of onset of initial symptoms was 24.5 ± 5.71 years, similar to

other studies that demonstrated the first symptom onset between 20 and 29 years of age [273, 274]. In the first arm of the study, we found the mean age for first symptoms to be 29.1 years. This finding does not contradict the literature, and this value overlaps with the standard deviation of our first arm data (29.1 ± 4.3 years). We believe that there is a shift in general awareness of endometriosis in society, and within decades we will likely experience significantly earlier detection rates, partly due to earlier personal detection of alarming signs and symptoms and due to better public education and awareness. Furthermore, in the second arm of our study, the average age of diagnosis was 34.2 ± 5.97 years (20–48 years). This value is in line with our findings in the first arm of the study. The question might be raised, as to why there might be a longer duration between onset of first symptoms and definitive diagnosis in the second arm. Because of the difference between the study samples of the two arms, we were not yet able to draw firm conclusions. This field requires further studies involving a larger number of participants. The negative effect of endometriosis on physical well-being significantly improved after surgery, as demonstrated by VAS and NRS pain score analyses (8.0 ± 2.11 score before surgery vs. 0.47 ± 1.25 score after surgery). It is an improvement that is in line with the results of a study conducted by Alborzi et al. in 2017, where the initial score of 8.23 ± 2.03 decreased to 4.46 ± 2.47 in 93% of patients [250]. The positive effect of surgery on socio-emotional well-being that was detected by the modified EHP-36 questionnaire was like the results of earlier studies [127, 275, 276].

In summary, the EHP-36 instrument, in addition to the VAS and NRS-11, is a useful tool in the evaluation of the QoL of patients experiencing the misery of endometriosis, especially in a comparative setting applied pre- and postoperatively.

## 9. SUMMARY OF RESULTS

Our study comprised two major parts. In the first part, three retrospective studies involved collection of patients' information from the hospital database. Study I recorded 28 women with post-cesarean section isthmocele who underwent combined hysteroscopic and laparoscopic repair. Return of fertility after surgery was 82.4% (n=14/17). Endometriosis was found in 16 patients (57.1%), which is high in patients in this group who had no previous history of endometriosis prior to the cesarean section. Overall, patient satisfaction was 92.9% (26/28) in terms of improved QoL. In Study II, records were collected of 455 patients with endometriosis-related infertility who were managed with combined radical laparoscopy surgery and ART between

2010 and 2018. Fertility return was 81.3% (370/455), with 94.2% (327/347) live births and 5.8% (20/347) pregnancy loss. Pregnancy occurred spontaneously in 39.5% (146/370) of patients, in 3.8% (14/370) of women after AIH, and in 56.8% (210/370) after IVF-ET, with patients aged ≤35 years having a higher chance of conception post-surgery (84% vs. 77%, respectively [p=0.039]). Comparatively, this effect was 91.3% vs. 74.1% (p=0.007; OR=3.7; 95% CI=1.4–9.8) among the ≤35- and >35-year-old age groups, respectively. There was no significant difference in reproductive performance in difference stages of endometriosis.

Study III was based on the records of 777 patients with endometriosis who underwent combined radical hysteroscopy–laparoscopy surgery, incorporated with occasional ART treatment for those with infertility issues. The postoperative QoL improved significantly, with 46–49% having moderate to significant improvement, and 35–54% achieving complete resolution of symptoms (p<0.0005). This improvement was achieved in the areas corresponding to 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 requested to complete a modified EHP-36 questionnaire pre- and post-surgery to assess their perspective on endometriosis in terms of their QoL, General WB, and fertility. Women underwent combined radical hysteroscopy–laparoscopy surgery based on their conditions and disorders, such as infertility, in which case operative or diagnostic hysteroscopy was always included. There was a significant improvement in the QoL in this group (p<0.001). The VAS for pain score decreased from 8 ± 2.11 (86.0%), moderate to severe pain, preoperatively, and to 0.47 ± 1.24 (93.1%) negligible to no pain, postoperatively (p <0.001). Of those women with infertility, 58.45% (32/61) became pregnant. Analysis showed a loss to follow-up, with 77.4% (24/31) live births. Postoperative general well-being was rated “very good” or “good” in 94.2% (82/87) of participants. There was a significant improvement observed in sexual life, with 86.2% (75/87) of women rating it as “good” or “very good” (p<0.001).

## 10. ANSWERS TO OUR HYPOTHESES

1. Our results demonstrate a link between history of cesarean section and an increased likelihood of development of endometriosis, supporting our first hypothesis.

2. Our results demonstrate that combined hysteroscopic and laparoscopic endometriosis surgery significantly improved fertility outcomes in patients with endometriosis, supporting our second hypothesis.

3. Our data showed that combined hysterolaparoscopy significantly improved the QoL of endometriosis patients. Furthermore, our results proved that the validated EHP-36 instrument, along with the VAS and the NRS-11, were useful tools in the evaluation of the QoL of endometriosis patients, supporting our third hypothesis.

## 11. GENERAL DISCUSSION

Endometriosis remains a plague in the lives of many women worldwide. The negative effects of the disease range from direct daily health challenges to socio-cultural, socioeconomic, and QoL impairment. Our study provided positive evidence that early meticulous radical laparoscopy surgery significantly improves QoL. The combination of hysteroscopy and assisted ART was found to improve overall fertility performance. We demonstrated a positive impact on the QoL with laparoscopy surgical excision of endometriotic lesions, as was reported in previous studies [10, 15, 17, 217]. Our first study demonstrated a controversial view relating to the role of prior surgery on the uterus and the possible association with the onset of the disease in support of the implantation hypothesis [36, 54, 55]. Our study demonstrated incredibly high frequency of the disease in this group of patients, with 57.14% (16/28) cases supporting our hypotheses ($p<0.05$). Doubts were raised about the possibility of prior cesarean section (scar defect) being one of the contributing factors to the onset of endometriotic lesions. The mechanism is unknown; however, it could be triggered by direct implantation or by diffusion due to prolonged stagnation of menstrual fluid trapped in the scarred pouch-like structure. Other possibilities, like the inability of the defensive mechanism to remove endometrial tissues disseminated during cesarean section, require consideration. The postoperative outcomes were satisfactory, with 80% for infertility, 95.65% for LAP, 100% for vaginal discharge, 94.44% for dysmenorrhea, and 100% for PMBD; these results are more favorable or similar to studies by Changdong Li et al. and Cuilan Li et al. [278, 279].

Our second study demonstrated post-surgical fertility performance with or without ART. The current prevalence of endometriosis is approximately 1–2 per 10 women [56, 75, 140]. Our study demonstrated that early expert minimal surgical treatment of endometriosis-related infertility and timely introduction of ART is currently the most feasible option, and supports our hypotheses [233, 234]. The result showed that the

pregnancy rate improved dramatically after surgery (370/455, 81.3%), with a live birth rate of 88.1% (326/370). Our study also demonstrated that the stage of endometriosis did not significantly influence fertility performance, while age had a significant influence on fertility. This observation is similar to reviews conducted by Jacobson et al. and others [233, 236, 238-240]. The positive outcomes may have resulted from the individualized combined hysterolaparoscopic surgical approach. The inclusion of hysteroscopy was necessary because uterine abnormalities and other tubal abnormalities contribute to approximately 30–35% of female infertility issues [155, 237]. All based on patient desire, the recurrence ratio was low. The expectant management option was initially applied before the recommendation of ART was considered [237]. Patients with primary infertility made up 55.2% (278/504), while secondary infertility made up 30.9% (156/504). The results from this study showed that meticulous and timely surgical management of endometriosis improves fertility performance irrespective of the age, stage, or duration of infertility.

Endometriosis can cause constant debilitating pain, broken homes, loss of jobs, economic burden, and infertility [44]. Many studies have reported financial burdens: about £10.6 billion in healthcare costs in the UK (2012), about £2.75 billion in Australia, and $52.1 billion per year in the USA [241, 280]. A study conducted by Bokor et al. estimated €1.6 billion per year, accumulated from out-of-pocket (OoP) and national health insurance policies [62,70]. Our study showed direct association of endometriosis with dysmenorrhea, chronic pelvic pain (CPP), dyspareunia, and other sexual aberrations, which may affect fertility [114, 217, 243]. Our study demonstrated that hysterolaparoscopic surgery significantly positively influenced fertility, as 81.3% of patients in all stages of endometriosis became pregnant, with a successful live birth rate of 94.2%; these findings are like a study by Kuivasaari et al. [236]. Our study also showed that QoL improved significantly, as close to 95% of women had substantial or complete resolution of symptoms at 1 month postoperatively; these findings are similar to a study conducted by Ferrero et al. and Denny E et al. [97, 98]. We observed a progressive improvement in all indices of the patient's needs as time elapsed, even more favorable than in the previous studies [106, 224, 226].

The most common sites were deep infiltrating recto-vaginal septum endometriosis, left ovarian fossa and endometrioma, and right ovarium fossa. Our study demonstrated the

correlation between the localization of the endometriosis and the degree and type of presenting pain-associated symptoms. Our last study demonstrated the usefulness of the EHP-36, VAS, and another questionnaire in evaluating the QoL and General WB in patients with endometriosis before and after radical laparoscopic surgery. Our findings were similar to other studies in this regard [258, 259]. The study exposed some of the unbearable suffering that women with endometriosis encounter daily (e.g., self-reported depression and anxiety). Post-surgical follow-up outcomes demonstrated significant improvements in all areas (all $p < 0.001$) (Table 13–15, Figure 18–21).

The average pain score gradually decreased from $8.0 \pm 2.11$ points before surgery to $0.47 \pm 1.25$ points after surgery, higher than that reported in a study conducted by Alborzi et al. [263-265]. Our study demonstrated significant improvement in reducing or eliminating those agonizing physical, emotional, and socioeconomic deprivation caused by endometriosis; close to 93.1% of patients reported improvement in their QoL. Other studies have not reported outcomes superior to those of our study [263, 266]. Fertility outcomes also improved, as 52.5% of patients became pregnant; 61% had presented with infertility issues. This observation represents an improvement as compared with other similar studies [110, 271]. Our study did not demonstrate any significant association between cigarette smoking or alcohol consumption and endometriosis, in concordance with studies conducted by Bravi et al. in 2014 and Thylan in 1995 [273, 274]. We could not confirm any associated eating habits and/or types of food, or a direct link between other medical conditions and endometriosis. However, more women reported drinking because of the impact of endometriosis on their lives, and we observed a slight correlation of 15% with family (genetic) history of endometriosis [126]. Other observation included a link between endometriosis and the use of sanitary napkins (pads) (63/87; 72%) and tampon use, findings that were similar to a study conducted by Kamalifard et al. [276].

## 12. CONCLUSION

Based on the results from our studies, only large and comprehensive studies can confirm the assertion that tissue dissemination–by direct or diffusion process as a result of some surgical procedures–could induce the development of endometriosis. Excessive or improperly performed obstetric and gynecological surgical interventions (i.e., abortions, HSG, and other gynecological interventions) could also cause tissue dissemination. Our study contributed to the literature by providing new perspectives

and approaches to managing obstetric and gynecological cases, including information on the potential etiological aspects of the implantation theory of endometriosis. The studies also ascertained that combined hysterolaparoscopy treatment was an efficient and reliable procedure; it enhanced women's well-being and QoL and significantly improved reproductive performance. The study also demonstrates a correlation between the site of endometriosis and association with pain-related and other symptoms.

The integration of a modified EHP-36 questionnaire could provide service providers with a broader scope for accessing women in outpatient clinics, with an early suspicion of endometriosis as the background disease behind the patient's symptoms, thereby reducing the frequency of delayed diagnosis.

In conclusion, our study highlighted that radical combined hysteroscopy–laparoscopy or laparoscopic surgery significantly improved fertility performance and, moreover, improved the QoL and general well-being of patients. Our study also showed that the procedure was safe in the hands of an expert endoscopy surgeon. The postoperative outcomes highlighted the significant improvements achieved in relieving some of the socioeconomic burden of individuals or society in general as a result of endometriosis.

## 13. 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, Rúcz 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)

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**17. ANNEX**

No. 1 Annex 1: Checklist for Postsurgical retrospective study II-III

A: General information

At what age symptoms appeared: …

Menarche… years old, Last menstruation…

Cycle regular: yes / no

Cycle length: days.

Duration of menstruation:

Pregnancy number… Abortion number… / Date……

Number / date / method of birth

……

B. Present complaints:

DysMenorrhea:

DysChesia:

DysPareunia:

Obstipation:

Puffiness:

Diarrhea:

Pencil-like stools:

HaematoChezia:

DysUria:

a Present complaints / onset (pain) (<1 year,> 1 year, <3,> 3 years, <5 years,> 5 years, <10 years,> 10 years) When did the pain begin in your life?
b Location and types of pain: Convulsive, dull, Sharp, (lower abdomen and waist, abdomen and back, other pain, does it radiate to the rectum or bladder?)
c History of abdominal surgery (day and date)
d Other diseases…

Infertility complaints.

a Duration: (> 1 year, <3 years,> 3 years, <5 years,> 5 years, <10 years,> 10 years)
b Reason: (Female / male, both, unknown?)
c Have you had this IVF / AIH before? (yes / no), effectiveness...
d Postoperative IVF / AIH? (yes / no), successful / unsuccessful
e Other conditions (hyperprolactinaemia, myoma, galactorrhea, insulin resist, hypo-hyperthyroidism, polypus endomy, uterine anomaly (septum), ovarian cyst, PID, Synechia or Asherman syndrome, other lesions, etc.)

C: Status (endometriosis):

a Endometrioma (left or right or both sides) Single-compartment or multicompartment
b peritoneal (as a surgical finding)
c adenomyosis
d deeply infiltrating, if so, where…

Endometrium Stadium: 1) I.std., 2) II.std., 3) III.std., 4). IV.std.

D: Establishing a diagnosis of endometriosis

a Routine ultrasound examination
b Laparoscopy
c During laparotomy
d Anamnestic?

E: Surgical interventions:

a CHT: tuba permeability after peritubary adhesion or spontaneous
b sychneciolyis hysteroscopica (yes / no)
c Septum eradication (yes / no)
d Salpingectomy
e cystectomy (right / left)
f EEPL, EEDL, AEOL, Laser (excision of endometriosis Douglasi et peritonealis, ablation of endometriosis ovarii laparoscopy)
g adhaesiolysis intraabdominalis

F: Events after the intervention:

a Has pregnancy occurred (yes / no)
b How to conceive (spontaneous / AIH / IVF-ET)
c The course of pregnancy (childbirth / abortion) ...
d Time between surgery and pregnancy (months)
e After pregnancy, did the patient leave for another institution? (Yes No)
f Patient did not return to the institution after surgery (LTFU = lost to follow-up)
g Are you planning to become pregnant after having an endometriosis surgery? (Yes No)
h Is the patient receiving medication after surgery (Visanne, GnRH analogue, other?) Yes / No
i i.Has your complaints decreased during the postoperative examination (yes / no) 1Hh, 6Mont, 1 year from now
j Has there been a relapse (<1 year,> 1 year,> 3 years,> 5 years)
k Nature of your complaints (lower abdominal pain, dysmenorrhea, dyspareunia, other pain, rectal, bladder bleeding or other complaints)
l Sites of endometriosis:

| Sites and stages | I. | II. | III. | IV. |
|---|---|---|---|---|
| Ovary | | | | |
| Deep infiltrating/ retrovaginal septum involvement | | | | |
| Peritoneal involvement | | | | |

| | | | | |
|---|---|---|---|---|
| Adenomyosis | | | | |
| Bladder, intestine, and other localizations | | | | |

No. 2 Annex 2 – Modified EHP- 36 (Modified Endometriosis Health Profile-36) Questionnaire:

QUESTIONNAIRE "A"
Log number… 2017
Introduction: Complaints caused by endometriosis, including constant abdominal and abdominal pain, menstrual complaints, and discomfort related to marriage, have been a relative setback in the doctors work for decades. Infertility as a condition or disease has existed since the beginning of humanity. With the development of medicine, new possibilities have opened up, such as IVF-ET, AIH, conservative drug treatments, and newer surgical techniques (laparoscopy), with the help of which significant results is achievable. We try to find out unique facts, the recognition of which, and with proper attention, we can get better results in solving such problems in the future. We ask for your help while providing information on any questions we handle discreetly and anonymously.
A. General information
B. Your age:
First month bleeding..…
How old did you start…
Did your complaint occur with your first regular menstrual bleeding? Yes No
If yes?

| Menstruation characteristics | Yes | No | Other options |
|---|---|---|---|
| Do your periods last more than 5 days? | | | |
| Do your periods last more than 5 days? | | | |
| Is your menstrual cycle generally shorter than 26 days? | | | |
| Is your menstrual cycle generally longer than 31 days? | | | |
| Do you ever experience irregular bleeding during your cycle (i.e. mid-cycle spotting)? | | | |
| Do you ever miss periods or have long breaks between periods? | | | |
| Does stress make your menstrual cycle length more irregular? | | | |
| Is your period dark in colour with a heavy flow and includes many small clots? | | | |
| Do you use sanitory pad? | | | |
| Do you use sanitory napkins? | | | |
| Do you experience a downward, dragging sensation in your abdominal region | | | |
| Do experience strong pelvic cramping with sharp pains and/or nausea during your period? | | | |
| Do you frequently experience sharp, stabbing period pain that feels worse when you apply pressure and/or warmth to it, but feels better if you lie or sit still? | | | |
| Do you frequently experience diarrhoea or loose stools at the onset of your period? | | | |
| Do you frequently faint or vomit at the onset of your period? | | | |
| Do all of your symptoms improve if you are relaxed and not under stress? | | | |
| Are you trying to conceive or have experienced difficulty conceiving? | | | |
| Have you undergone IVF treatment after the on set of symptoms | | | |

| | | | |
|---|---|---|---|
| Have you lost weight recently or are you underweight? | | | |
| Do you feel exhausted, pale and fatigued after your period? | | | |
| Do you frequently experience lower back pain following your period? | | | |
| Do you experience breast tenderness and/or swelling before your period? | | | |
| Do you have Lower abdominal burning pain? | | | |
| Do you experience premenstrual mood swings e.g. frustration, anger,irritability? | | | |
| Do you feel flat, depressed and/or weepy before your periods? | | | |
| Do you feel cold, tired and/or become pale before your period? | | | |
| Do you experience fluid retention and/or abdominal bloating before your period? | | | |
| Are you prone to premenstrual migraines or tension headaches? | | | |
| Do you experience changes in your stool e.g. diarrhoea, constipation or other digestive changes?dysmenorrhea | | | |
| Dyspareunia | | | |
| Have you been medically diagnosed with endometriosis? | | | |
| Have you been medically diagnosed with uterine fibroids? | | | |
| Have you been medically diagnosed with ovarian cysts? | | | |
| Have you been medically diagnosed with pelvic adhesions or masses? | | | |
| Have you been medically diagnosed with polycystic ovarian syndrome (PCOS)? | | | |
| Pain relief is achived only after medication | | | |
| Pain reliefs spontaneously | | | |

| | | | |
|---|---|---|---|
| After you had an abortion? | | | |
| After you had spontaneous deliver? | | | |
| After you had cesarean section operation(s)? | | | |
| After any abdominal surgery? | | | |
| After severe pelvic inflammatory diseases | | | |
| Few years after the first menstruation | | | |
| After serious stress and grieve situation | | | |

Endometriosis related symptoms

| Characteristics | Yes | No |
|---|---|---|
| Stabbing | | |
| Pressing | | |
| Tender | | |
| Crushing | | |
| Pricking | | |
| Gastrointestinal discomfort | | |
| Rectal bleeding | | |
| Urinary problems | | |
| Painful defecation | | |

Emotional and other related implications (Scale: measuring from 1-10 pending on severity)

| | Igen | Nem | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Exhausting | | | | | | | | | | | |
| Sickening | | | | | | | | | | | |
| Unbearable | | | | | | | | | | | |
| Miserable | | | | | | | | | | | |
| Torturing | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Depressing | | | | | | | | | | | |
| Affect your work negatively | | | | | | | | | | | |
| Affect your learning negatively | | | | | | | | | | | |

Strength of pain in endometriosis

The Numeric Rating Scale (NRS–11) is an 11–point scale for patient self-reporting of pain

| Pain rating | Pain level |
|---|---|
| 0 | No pain |
| 1-3 | Mild Pain (nagging, annoying, interfering little with ADLs |
| 4-6 | Moderate Pain (interferes significantly with ADLs) |
| 7-10 | Severe Pain (disabling; unable to perform ADLs) |

Other information: (Before symptoms)

1.What foods do you prefer (Sugar, fatty, spicy, pasta, baked goods, dairy, meat, fish, fruit, vegetables, eggs, Etc.) their may be more than one answer.
2.Do you often consume pleasure drugs (Cigarettes, alcohol, coffee, narcotics or illicit drugs, other). How often? On a daily / multiple daily / weekly / monthly basis?
3.Have you taken any medications (contraceptives, thyroid disease, hormones, epilepsy, sedatives, hypertension, diabetes, gastrointestinal disorders, urinary tract diseases, Etc.) How often? On a daily / multiple daily / weekly / monthly basis?
4.Did you have an endometriosis problem in your family (yes / no), and how is it related. Have you been treated for endometriosis before (yes / no) by what method (medicine, surgery, both)
The questionnaire helps us gather information to detect their complaints, especially about their pain and infertility. The results comparing the responses obtained, may provide information on the epidemiology, symptoms, and location of endometriosis.

Questionnaire „B”

Characteristics of pain and other symptoms of Endometriosis

| Characteristics-Dysmenorrhea | Yes | No | Other options |
|---|---|---|---|
| Very painful menstruation | | | |
| Lower abdominal pain | | | |
| Pain depends on the time in the monthly cycle | | | |
| Paralysing, handicapping pain that affects mobility, difficulty walking | | | |
| Pain that is unbearable, overwhelming, violent, intense | | | |
| Continuous pain with peaks or attacks of more intense pain | | | |
| Pain on one side, pain stronger on one side | | | |
| Ovarian pain | | | |

| | | | |
|---|---|---|---|
| The pain lasts longer than menstrual pain, and continues after the bleeding has stopped | | | |
| The pain increases in intensity over time | | | |
| Pain starts a few days before menstruation begins | | | |
| Pain throughout the monthly cycle, present all the time | | | |
| Pain spreads towards the back | | | |
| Pain before, during and after menstruation | | | |
| Stabbing pain | | | |
| Prickly pain, like being pricked or having an injection | | | |
| Lower abdominal burning pain | | | |
| The pain prevents sleep or wake up at night | | | |
| Pain interferes with work or daily life | | | |
| Pain spreads to the legs and hips | | | |
| Different types of pain at the same time, several different pain symptoms | | | |
| Dyspareunia | | | |
| Deep internal pain felt during sexual intercourse | | | |
| Pain in certain positions during sexual intercourse | | | |
| Distracting pain that prevents or interrupts sexual intercourse | | | |
| Burning feeling during or after sexual intercourse | | | |
| Bowels Symptoms | | | |
| Pain when passing a stool, painful bowel movements | | | |
| Bloating, bloated abdomen | | | |
| Diarrhoea during menstruation | | | |
| Spasms, cramp, pain in the bowel before having a bowel movement | | | |
| Constipation during menstruation | | | |
| Nausea, vomiting | | | |
| Anal pain | | | |
| Diarrhoea alternating with constipation | | | |
| Bloody stools | | | |
| painful urinary tract symptoms | | | |
| Feeling the need to urinate often, only small quantities at a time | | | |
| Pain with urge to urinate, pain when holding back | | | |
| Painful pressure on the bladder | | | |
| Pain or burning when urinating | | | |
| Difficult to start urination | | | |
| Bloody urine | | | |
| Other pathological manifestations | | | |

| | | | |
|---|---|---|---|
| Becoming increasingly tired, extreme exhaustion | | | |
| Dizziness, fainting | | | |
| Sciatica during menstruation | | | |
| Pain spreads toward breast or shoulder, right chest pain | | | |
| Depression | | | |
| Pneumothorax | | | |
| Inability to concieve | | | |

Candidates are screened with a questionnaire to obtain information about their pain and infertility problems in comparism to the epidemological, symptomological and localizational diversity of the disease?

## 18. ABBREVIATION

| | |
|---|---|
| ART: | Artificial reproductive technique |
| ASRM: | American Society of Reproductive Medicine |
| BSOE: | Bilateral superficial ovarian endometriosis |
| BDOE: | Bilateral ovarian endometrioma |
| CA-125: | Cancer antigen 25 |
| CA-19-9: | Cancer antigen 19-9 |
| CD16: | Cluster of differentiation molecule 16 |
| CHLS: | Combined hysterolaparoscopic surgery |
| CPP: | Chronic pelvic pain |
| CT: | Computed tomography |
| CVD: | Chronic vaginal discharge |
| CDKN2BAS: | Cyclin-dependent kinase inhibitor 2B anti sense |
| 3-D: | Three-dimensional |
| EEDL: | Electrocoagulation excision of deep endometriosis lesion |
| EEPL: | Electrocoagulation excision peritoneal endometriosis lesion |
| ERK: | Extracellular signal-related kinase |
| ESHRE: | European Society for Human Reproduction and Embryology |
| EURO QoL (EQ-5D): | Euro-form Quality of Life |
| GnSAF: | Gonadotropin surge-attenuating factor |
| General WB: | General well-being |
| GWAS: | Genome-wide association studies |
| HSG: | Hysterosalpingography |
| HYCOSY: | Hysterosalpingo-contrast sonography |
| ICAM-1: | Inter cellular adhesion molecule 1 |
| IL-1β: | Interleukin 1β |
| IBS: | Irritable bowel syndrome |
| IL-6: | Interleukin 6 |
| IVF/ICSI: | in vitro fertilization and intracytoplasmic sperm injection |
| IVF-ET: | in vitro fertilization-embryo transfer |
| L LAP: | Lower abdominal pain |
| LH: | Luteinizing hormone |
| LUS: | Lower uterine segment |
| MAP: | Mitogen-activated protein kinase |
| MFR: | Monthly fecundity rate |
| mEHP-36: | Modified Endometriosis Health Profile (EHP-36) |
| MRI: | Magnetic resonance imaging |
| NKp46: | Natural killer cell receptor |
| NKs: | Natural killer cells |
| NRS-11: | Numeric rating scale |
| NSAIDs: | Non-steroidal anti-inflammatory drugs |
| OCPs: | Organochlorine pesticides |

| | |
|---|---|
| OoP: | Out-of-pocket payment |
| PCOS: | Polycystic ovarian syndrome |
| PFD: | Pelvic floor dysfunction |
| PID: | Pelvic inflammatory disease |
| PCBs: | Polychlorinated biphenyls |
| Hormonal-IUCD: | Hormonal intrauterine contraceptive device |
| PMBD: | Postmenstrual bleeding disorder |
| QoL: | Quality of life |
| rAFS: | Revised American Fertility Society |
| ROS: | Reactive oxygen species |
| RVS: | Rectovaginal septum |
| TCDD: | 2,3,7,8-tetrachlorodibenzo-p-dioxin |
| TGF-β: | Transforming growth factor β |
| TNFR2: | Tumor necrosis factor receptor 2 |
| uNKs: | Uterine natural killer cells |
| VAS: | Visual analogue scale |
| VEGF: | Vascular endothelial growth factor |

## Submission of the doctoral dissertation and declaration of the originality of the dissertation

The undersigned,
Name: Dr. Atombosoba Adokiye Ekine
Maiden name:
Mother's maiden name: Fyne Samuel Opukiri
Place and time of birth: Nigeria, Krakrama, 1961.10.24

on this day submitted my doctoral dissertation entitled:

to the

"PR-18". Effect of endometriosis on quality of life Programme

of the Doctoral School of Health Sciences, Faculty of Health Sciences, University of Pécs.

Names of the supervisor(s):

At the same time, I declare that
- I have not submitted my doctoral dissertation to any other Doctoral School (neither in this country nor abroad),
- my application for degree earning has not been rejected in the past two years,
- in the past two years I have not had unsuccessful doctoral procedures,
- my doctoral degree has not been withdrawn in the past five years,
- my dissertation is independent work, I have not presented others' intellectual work as mine, the references are definite and full, on preparation of the dissertation I have not used false or falsified data.

Furthermore, I declare that I contribute to the request of DOI identification of my doctoral dissertation.

Dated: 2024.11.20.

signed by Candidate

Supervisor

Co-supervisor