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Investigation of the relationship between symptoms, BMI, and endometriotic lesions according to the #ENZIAN classification

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Nach der Zusammenführung der erhobenen Daten in einen einheitlichen Datensatz wurden die in dieser Arbeit angegebenen statistischen Auswertungen nach entsprechender Anleitung durch Herrn PD Dr. med Elvin Piriyev von mir selbst ausgeführt.
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Meinen Eltern und meiner Schwester

Table of Contents

Abbreviations

AFS American Fertility society
BMI Body Mass Index
CPP Chronic pelvic pain
DIE Deep infiltrating Endometriosis
DNA Deoxyribonucleic acid
EFI Endometriosis fertility index
IBS Irritable Bowel Syndrome
IL Interleukin
IVF In-vitro fertilization
JZ Junctional zone
MUSA Morphological Ultrasound Sonographic Assessment
NSAIDs Non-Steroidal Anti-Inflammatory drugs
rAFS revised American Fertility society
rASRM revised American Society of reproductive Medicine
SAT Subcutaneous adipose tissue
TNF Tumor necrosis factor
USL Uterosacral ligaments
VAT Visceral adipose tissue
VEGF vascular endothelial growth factor
WAT White adipose tissue
WHO World Health Organization

1. Abstract

Endometriosis is a prevalent gynecological condition defined by the growth of endometrium-like tissue at ectopic sites outside the uterine cavity. It predominantly affects women of reproductive age and, alongside adenomyosis, is associated with major symptoms including various forms of pain, such as dysmenorrhea, dyspareunia, dysuria, and dyschezia, as well as infertility, all of which can severely impair quality of life. Despite its high prevalence, diagnosis is often delayed. To assess disease extent, several classification systems have been proposed. The recently introduced #ENZIAN score (2021) combines the revised American Society for Reproductive Medicine (rASRM) system with the ENZIAN classification, providing a comprehensive assessment of peritoneal, ovarian, and deep infiltrating lesions, as well as adenomyosis and tubo-ovarian adhesions.

This cumulative thesis aims to bridge the gap between clinical presentation and intraoperative classification by employing the #ENZIAN system to systematically analyze associations between symptom profiles, lesion distribution, and body mass index (BMI) in endometriosis. Two retrospective studies were conducted: the first, based on 233 preoperative questionnaires, showed that while overall symptom severity did not differ across #ENZIAN-defined groups, specific symptoms such as dyschezia and dyspareunia were associated with distinct lesion localizations. The second, comprising 219 patients, revealed that BMI was associated with clinical outcomes but not with lesion distribution; normal-weight women reported higher pelvic pain intensity, while obese women had higher rates of infertility.

Taken together, these findings indicate that while symptoms, potentially modulated by BMI, may aid in the identification of endometriosis, they do not reliably reflect its anatomical extent. Overall, this thesis underscores the value of integrating the #ENZIAN classification with metabolic and clinical parameters to refine diagnosis and guide personalized, multimodal treatment strategies beyond surgery and hormonal therapy.

Zusammenfassung

Endometriose ist eine der häufigsten benignen gynäkologischen Erkrankungen, die durch das Vorkommen von endometriumähnlichem Gewebe außerhalb der Gebärmutterhöhle gekennzeichnet ist. Sie betrifft überwiegend Frauen im reproduktiven Alter und ist neben der Adenomyose mit Leitsymptomen wie Dysmenorrhoe, Dyspareunie, Dysurie, Dyschezie sowie Infertilität assoziiert, die die Lebensqualität erheblich beeinträchtigen können. Trotz ihrer hohen Prävalenz erfolgt die Diagnose häufig verzögert. Zur Erfassung des Erkrankungsausmaßes wurden verschiedene Klassifikationssysteme vorgeschlagen. Der 2021 eingeführte #ENZIAN-Score kombiniert das revidierte System der American Society for Reproductive Medicine (rASRM) mit der ENZIAN-Klassifikation und ermöglicht damit eine umfassende Beurteilung peritonealer, ovarieller und tief infiltrierender Läsionen sowie die Adenomyose und Adhäsionsprozesse im Adnexgebiet. Ziel dieser kumulativen Dissertation ist es, die Lücke zwischen klinischer Symptomatik und intraoperativer Klassifikation zu überbrücken, indem das #ENZIAN-System zur systematischen Analyse der Zusammenhänge zwischen Symptomprofilen, Läsionsverteilung und Body-Mass-Index (BMI) herangezogen wird. Hierzu wurden zwei retrospektive Studien durchgeführt: Die erste, basierend auf 233 präoperativen Fragebögen, zeigte, dass die Symptomlast nicht zwischen den nach #ENZIAN definierten Gruppen variierte, einzelne Symptome wie Dyschezie und Dyspareunie jedoch mit spezifischen Lokalisationen der Endometrioseherde assoziiert waren. Die zweite Studie mit 219 Patientinnen ergab, dass der BMI zwar nicht mit der Läsionsverteilung korrelierte, jedoch mit klinischen Parametern im Zusammenhang stand: Frauen mit Normalgewicht berichteten über höhere Intensität chronischer Beckenschmerzen, während bei adipösen Frauen eine erhöhte Infertilitätsrate beobachtet wurde.

Zusammenfassend legen die Ergebnisse nahe, dass die Symptomausprägung, welche möglicherweise durch den BMI moduliert wird, zur Identifikation der Endometriose beitragen könnte, jedoch nicht zuverlässig das anatomische Ausmaß der Erkrankung widerspiegelt. Die Ergebnisse dieser Arbeit verdeutlichen, dass eine Verknüpfung des #ENZIAN-Scores mit metabolischen und klinischen Parametern zur Weiterentwicklung der Diagnostik und zur Etablierung personalisierter, multimodaler Therapiestrategien jenseits chirurgischer und hormoneller Verfahren beitragen kann.

2. Introduction

2.1. Structure of the thesis

The present work is a cumulative dissertation submitted in fulfillment of the requirements for the degree of Doctor of Medicine (Dr. med.). The core of this thesis consists of two scientific peer-reviewed articles authored and published by the candidate as an equal first author. The publications included are:

1) "*Is there a relationship between symptoms and types of endometriosis according to #ENZIAN? A comparative study of preoperative questionnaires*", published in 2025 in *Archives of Gynecology and Obstetrics* (Q1) issued by Springer.

2) "*Does BMI Have an Impact on Endometriosis Symptoms and Endometriosis Types According to the #ENZIAN Classification?*", published in 2025 in the *Journal of Clinical Medicine* (Q1) issued by MDPI.

Prior to presenting the publications, the clinical context of endometriosis, the #ENZIAN classification and obesity are outlined. The discussion section critically examines the findings of the two studies and places them within the broader scientific context.

2.2. Definition of Endometriosis

Endometriosis is a benign gynecological condition characterized by the presence of tissue biologically analogous to the basal endometrium outside the uterine cavity, most commonly within the abdominal cavity, and in rare instances, at distant extra-pelvic sites.[1] The ectopic lesions typically consist of endometrial glands, stromal components, and smooth muscle cells, all of which are innervated trough neurogenesis and vascularized via lymphatic and blood vessels through angiogenesis. These cellular components express estrogen and progesterone receptors, rendering them responsive to hormonal therapies.[2] While endometriosis predominantly affects women of reproductive age, histological evidence confirms that it can also occur before menarche. In postmenopausal women, endometriosis is considered rare, accounting for fewer than 3% of diagnosed cases.[3]

2.3. History and developmental theories

One of the earliest morphological descriptions of endometriosis is attributed to Daniel Shroen of Jena in 1690, followed by Johann Crell's account of ovarian endometrioma in 1739.[4] In 1860/61, Karl von Rokitansky first described uterine intramural cysts as "adenoids".[5] Later, in 1896, Friedrich von Recklinghausen and Thomas Cullen independently reported adenomyomas and adenomyosis of the fallopian tubes, while rectovaginal endometriosis

was described by Johannes Pfannenstiel in 1899.[6] Until the 1920s, endometriosis was regarded as a benign hyperplastic condition and was described under several terms, including cystadenoma, cystic fibrosis, and adenomyoma. In 1927, John A. Sampson introduced the term *endometriosis* into medical terminology and proposed the theory of retrograde menstruation, which laid the foundation for a pathogenic understanding of the disease.[7] In the 1950s, biochemical and endocrine concepts such as the "pseudopregnancy" theory emerged.[8] From the 1970s onwards, immunological and molecular theories were developed and since 2000, research has increasingly focused on tissue arrays and gene expression profiling to better understand the pathogenesis of endometriosis.[3,9]

Adenomyosis

The first systematic description of adenomyosis was provided by Thomas Cullen at the turn of the 20th century, who identified the invading tissue as uterine mucosa and described its infiltration into the myometrium.[10] In 1925, Frankl introduced the term *adenomyosis uteri*. In 1932, Meyer further refined the morphological classification by defining *adenomyohyperplasia interna uteri* (now adenomyosis uteri), thereby expanding on earlier hormonal hypotheses.[3] The modern histopathological definition was established by Bird in 1972, characterizing adenomyosis as the benign presence of endometrial glands and stroma within the myometrium, typically accompanied by diffuse uterine enlargement and muscular hypertrophy.[3,11]

2.3.1. Developmental theories

Numerous theories have been put forward to explain the pathogenesis of endometriosis, yet none have been definitively validated so far. The most relevant concepts will be outlined in the following section. According to K. Schweppe, the various theories can be grouped into three main groups.[7] The first encompasses transplantation theories, including Sampson's theory of retrograde menstruation, mechanical implantation during surgical procedures and hematogenous or lymphatic dissemination of endometrial cells. The second category comprises in situ developmental theories, which suggest that endometriosis arises from residual embryonic cells or remnants of the genitourinary system. The third group is represented by Levander's induction theory from 1941, suggesting that exfoliated endometrial cells arrive in the peritoneal cavity and trigger the transformation of peritoneal epithelium into endometrial tissue.[7] Furthermore, genetics and epigenetics have emerged as areas of growing scientific interest and research.[12]

Retrograde menstruation theory (Sampson theory)

In 1927, Sampson proposed retrograde menstruation as the underlying mechanism for the development of peritoneal endometriosis. According to this theory, sloughed endometrial cells travel through the fallopian tubes into the peritoneal cavity, where they adhere to various anatomical structures and proliferate. The frequent localization of endometriotic lesions on the peritoneum of the ovarian fossa, the pouch of Douglas, the uterosacral ligaments and the bladder dome supports this hypothesis.[13] It is assumed that cell-rich menstrual fluid accumulates in these regions, facilitating implantation and proliferation.[14] Several lines of evidence corroborate this concept: Adolescent girls with congenital anomalies of the outflow tract demonstrate a markedly increased prevalence of endometriosis.[15] In a cohort study involving 279 patients with uterine malformations, 209 individuals (74.9%) were diagnosed with histologically confirmed endometriosis.[16] Furthermore, even minor disruptions to antegrade menstrual flow, such as those associated with a uterine septum, have been linked to an elevated risk of developing the condition.[17] Also, an increased volume of retrograde menstrual fluid commonly found in the pelvic cavities of women with endometriosis, compared to healthy individuals, may contribute to a higher risk of ectopic implantation of endometrial cells. However, retrograde menstruation is observed in 76% to 90% of women with patent fallopian tubes, yet not all of these individuals develop endometriosis.[18] This suggests other factors playing a role in the development of endometriosis.

On another note, the lymphovascular metastasis theory proposes that endometrial cells may disseminate to ectopic locations through lymphatic or hematogenous routes, thereby explaining the occurrence of endometriosis in distant extra pelvic sites.[19]

Coelomic Metaplasia theory

The theory of coelomic metaplasia, originally proposed by Iwanoff in 1898, suggests that endometriosis arises from extrauterine cells that undergo abnormal transdifferentiation into endometrial cells, potentially triggered by chronic inflammation or local irritation.[3] Specifically, it postulates that specialized cells within the mesothelial lining of the visceral and parietal peritoneum can transform into ectopic endometrial tissue under the influence of hormonal or immunological stimuli.[20] Coelomic metaplasia may also account for the presence of endometriosis in prepubertal individuals; however, as estrogen, a key driver of endometrial proliferation, is absent before puberty, the pathophysiology in such cases may differ from that in reproductive-age women.[18] Additionally, the detection of ectopic endometrial tissue in female fetuses has led to the hypothesis that endometriosis could result from defective embryogenesis. According to this embryonic rest theory, residual cells originating from

Müllerian ducts persist in ectopic locations and later develop into estrogen-responsive endometriotic lesions, such as those found at ovarian sites.[18,21]

Stem Cells theory

According to this theory, endometriosis may arise from stem cells, defined as undifferentiated cells with the capacity for self-renewal and the potential to differentiate into various specialized cell types.[22] Evidence for a resident stem cell population in the endometrium is supported by its regenerative capacity following menstruation, childbirth, or surgical curettage.[23] These stem cells are believed to reside within the basalis layer of the endometrium, which remains intact during the cyclical shedding of the functional layer and are thought to play a crucial role in endometrial regeneration.[19] Unlike fully differentiated endometrial cells, endometrial mesenchymal stem cells do not express estrogen receptors. In line with the retrograde menstruation theory, these stem cells may be shed through the fallopian tubes during menstruation, potentially contributing to the development of ectopic endometriotic implants. While stem cells themselves lack hormone receptor expression, the stem cell theory remains plausible, as their differentiated progeny can acquire estrogen and progesterone receptors once ectopically implanted, thus becoming responsive to hormonal stimulation.[24] Additionally, the stem cell theory supports the coelomic metaplasia hypothesis, which suggests that unidentified precursor cells within the mesothelium or residual Müllerian duct structures may differentiate into endometrial-like cells in response to specific stimuli.[19]

Hormones

Hormonal regulation, particularly through steroid hormones, is considered to play a central role in the pathogenesis of endometriosis, as the condition predominantly affects women of reproductive age and is uncommon in postmenopausal women not receiving hormonal therapy.[25] Ectopic lesions are thought to be regulated by ovarian steroids and may exhibit heightened estrogen sensitivity. Moreover, increased local estrogen production within endometriotic tissue, resulting from the aromatization of androgens and impaired conversion to less active forms, may further promote lesion growth and disease progression.[18]

Tissue Injury and repair theory

This theory proposed by Leyendecker et al. offers a uterine-based explanation for the development of endometriosis and adenomyosis by identifying the junctional zone (JZ) between endometrium and myometrium as the origin of the disease.[26] Uterine hyperperistalsis causes microtrauma within the JZ, triggering the release of proinflammatory mediators and upregulation of aromatase expression. The resulting local estrogen production promotes cellular proliferation and angiogenesis, thereby driving structural changes of the

JZ, which can be sonographically visualized as a hypoechoic band (the “halo phenomenon”).[27] Oxytocin-mediated myometrial hyperperistalsis further perpetuates the cycle of auto-traumatization. It is hypothesized that stem cells become activated during this process and, as part of tissue remodeling, may either migrate via retrograde menstruation to establish endometriotic lesions or infiltrate the myometrium, leading to adenomyosis.[12,28]

Immune dysfunction and inflammation

Recent research increasingly classifies endometriosis as a chronic inflammatory disorder, characterized by a dysregulated immune environment within the peritoneal cavity.[29] This dysregulated immune milieu may lead to an impaired clearance of menstrual debris and thereby facilitating the adhesion, survival, and proliferation of ectopic endometrial cells.[18] Endometriotic lesions are infiltrated by various immune cell populations, predominantly M2 macrophages, and are associated with elevated levels of pro-inflammatory cytokines, contributing to local inflammation.[30] Immune cells associated with lesions, originating from both eutopic endometrium and the peritoneal environment, have further been implicated in promoting angiogenesis, neurogenesis, and the development of chronic pelvic pain.[18,31] Furthermore, chronic activation of immunological pathways may contribute to the development of autoimmune diseases, which are frequently observed in women with endometriosis. However, a causal relationship has not yet been definitively established.[12]

Epigenetics and genetics

A genetic predisposition to the development of endometriosis is supported by familial clustering, increased risk among first-degree relatives and twin studies.[32] Endometriosis is believed to follow a polygenic mode of inheritance, with several loci, particularly those near genes involved in steroid hormone signaling and immune regulation, associated with increased disease risk.[18] However, a direct mechanistic link between these genetic variants and the pathophysiology of endometriosis remains unclear. Consequently, epigenetic mechanisms, which alter gene expression without changing the DNA sequence such as DNA methylation and histone modifiers, are increasingly considered key to understanding the complex interaction between genetic susceptibility, hormonal activity, and environmental factors in the development of endometriosis.[33]

Currently, a growing body of evidence indicates that a combination of all the above-mentioned theories ((epi-)genetic, hormonal, immunological) as well as environmental and life-style factors in addition to metabolic remodeling also seem to be involved in the pathogenesis of this complex disorder.[34]

2.4. Epidemiology and symptoms

Endometriosis remains a highly relevant topic in contemporary gynecology and is considered one of the most common conditions affecting women of reproductive age. Reliable data on the incidence of endometriosis is missing and reported prevalence rates vary considerably across studies. The highest prevalence rates of endometriosis have been reported in women aged 35 to 44 and 40 to 45 years.[35] In contrast, adolescents were underrepresented: one study reported that 0.05% of all patients with endometriosis were between 10 and 15 years of age, and 1.93% were aged 15 to 20 years.[36] Women diagnosed in the postmenopausal period accounted for 2.55% of all cases.[37] Among patients with chronic pelvic pain, prevalence rates range from 48% to 87%[38], whereas in patients with infertility, rates between 35% and 50% have been reported.[7,39]

Endometriosis is a disease with a variable clinical presentation. Approximately two-thirds of women with endometriosis experience symptoms before the age of 20 years.[40] Despite early symptom onset, contemporary literature indicates that the interval from symptom onset to definitive diagnosis often spans 4 and 11 years.[41] The primary clinical manifestation of endometriosis is pelvic pain, initially menstrual (dysmenorrhea), but may progress to encompass nonmenstrual and chronic pelvic pain (CPP), often accompanied by musculoskeletal complaints such as back and joint pain.[41] The most frequently reported symptoms are commonly referred to as the "4 Ds" of endometriosis. Among dysmenorrhea they include dyspareunia (pain during sexual intercourse), dyschezia (painful defecation), and dysuria (painful urination).[42] However, the symptomatology of endometriosis extends beyond these core complaints. Adolescents may lack the classical symptoms and instead often experience general pelvic pain, low energy, and abdominal discomfort.[43] More broadly, patients frequently report lower abdominal pain accompanied by a wide range of gastrointestinal symptoms, including diarrhea, constipation, flatulence, intestinal spasms, tenesmus, intestinal bleeding, bloating, stomach pain, and nausea.[44] Additionally, various bleeding disorders, such as hypermenorrhea and menorrhagia, may be present.[45] Infertility is a frequent and important complication of endometriosis with up to 50 % of infertile women being diagnosed with this condition.[46] Furthermore, in cases of deep infiltrating endometriosis (DIE) affecting the bowel or bladder, cyclical bleeding in the stool (hematochezia) or urine (catamenial hematuria) may occur.[47]

To gain a deeper understanding of the multifaceted clinical presentation of endometriosis, we investigated whether a relationship exists between symptomatology and disease types classified by the #ENZIAN system. Although this investigation enhances our understanding, additional research is needed to confirm and expand upon these findings.

2.4.1. Pain perception

Pain in endometriosis varies according to lesion location. Peritoneal lesions elicit somatic pain, which is typically sharp and well-localized due to the high density of sensory nerve fibers in the parietal peritoneum.[48] In contrast, visceral involvement (e.g., uterus, bladder, bowel) induces dull, cramping pain that is often poorly localized due to overlapping visceral nerve pathways.[49] Additionally, in cases of severe pain, activation of autonomic ganglia may trigger vegetative responses such as nausea, vomiting, syncope, and cyclical menstruation-associated diarrhea.[12] Pelvic pain associated with endometriosis is initially experienced in a cyclical pattern, reflecting classical nociceptive processing. However, with monthly recurrence, alterations in central pain modulation may occur, thereby increasing the risk of developing chronic pain syndromes. [50] Moreover, it is assumed that the inflammatory environment caused by endometriotic lesions contributes to a chronic state of neurogenic inflammation.[51] Taken together, these insights highlight that the origin of chronic pelvic pain in endometriosis is multifactorial, involving nociceptive, neuropathic, and nociplastic components.[38]

2.5. Forms of endometriosis

Both endometriosis and adenomyosis are heterogeneous conditions that present in various forms.[52] Endometriosis can be further categorized into three subtypes according to histopathological features and anatomical location: superficial endometriosis, deep infiltrating endometriosis, and ovarian endometriotic cysts, commonly referred to as endometriomas or "chocolate cysts".[53]

2.5.1. Superficial peritoneal endometriosis

Peritoneal endometriosis, also known as superficial endometriosis, is characterized by functional ectopic endometrium-like tissue extending up to 5 mm beneath the peritoneal pelvic surface and/or the serosa of pelvic organs.[54] During laparoscopy, lesion appearance varies in shape, distribution, and color; these features have been extensively studied to determine whether they reflect disease progression within the lesions.[55] Key morphological types of lesions include:[54,55,56]

- Black or black-blue lesions: The classic appearance of endometriotic lesions is a small black or dark bluish implant, often surrounded by a fibrotic rim that produces a retracted morphology. The dark coloration results from hemosiderin accumulation within macrophages following repeated hemorrhagic events and such lesions are generally considered histologically inactive.

- Red lesions: Many endometriotic implants appear as red or reddish-brown lesions, often presenting as erythematous spots or petechial structures. These lesions are considered active due to their high vascularization, with their bright coloration reflecting increased blood flow. Angiogenic factors such as vascular endothelial growth factor (VEGF) are commonly expressed.
- White fibrotic scars: Some endometriotic lesions present as white, yellow-white, or greyish scarred plaques or fibrotic patches, which may be flat or slightly indurated. These appearances reflect the progressive replacement of vital endometriotic tissue by fibrosis, ultimately leading to scar formation.
- Clear Vesicles: This atypical form presents as small, clear or translucent vesicles on the peritoneal surface and is thought to represent early-stage implants with minimal hemorrhagic activity.

2.5.2. Deep infiltrating endometriosis

Deep infiltrating endometriosis represents the most severe form of endometriosis and is defined as endometrial tissue infiltrating the peritoneum to a depth greater than 5 mm.[57] Based on pelvic anatomy, deep infiltrating endometriosis is classified into three regions: the anterior cul-de-sac, the posterior cul-de-sac, and the pelvic side wall.[58] The anterior cul-de-sac includes endometriosis involving the bladder and vesicovaginal space. Endometriosis affecting the rectovaginal septum and, potentially, the rectum is categorized within the posterior cul-de-sac. Lesions involving the pelvic walls, including ureteral endometriosis, are classified as pelvic side wall disease.[58] Due to its invasive nature and involvement of essential pelvic organs, DIE poses significant treatment challenges. Although hormonal therapies may provide symptom relief, they are often insufficient for extensive disease, particularly when organ obstruction occurs, necessitating surgical intervention.[59] Furthermore, anatomical changes resulting from the disease's invasive progression, extensive adhesions, and the accompanying inflammatory response make surgical management particularly complex.[60] Comprehensive preoperative education of the patient regarding potential complications is therefore essential.[61]

Although DIE is frequently associated with organ-specific symptoms, such as dyschezia, constipation, or hematochezia in bowel involvement, and dysuria and hematuria in bladder involvement, these correlations are not consistent across all patients.[62] In a recent study, we investigated the relationship between symptom patterns and the anatomical localization of endometriosis types including DIE according to #ENZIAN, which will be further addressed in the discussion section.

2.5.3. Ovarian endometriosis

Ovarian endometriosis most commonly manifests as a cystic lesion referred to as an endometrioma. Histologically, an endometrioma is characterized by a cystic cavity lined with ectopic endometrial epithelium and stroma, which accumulates hemosiderin-laden fluid due to recurrent cyclical hemorrhage.[63] They are found in approximately 17–44% of patients with endometriosis and account for around 35% of all benign ovarian cysts.[64,65] Increasing evidence suggests that ovarian endometriomas may adversely affect ovarian reserve, both due to the presence of the cyst itself and as a result of surgical excision.[66] Furthermore, emerging data indicate an association between ovarian endometriosis and an elevated risk of ovarian cancer, with malignant transformation reported in up to 1% of endometrioma cases.[67]

2.5.4. Adenomyosis

Adenomyosis is a specific form of endometriosis confined to the uterus. While adenomyosis shares many features with endometriosis and they frequently coexist, they are considered distinct conditions despite similarities in definition, symptoms, and molecular alterations.[68] Adenomyosis can be categorized as diffuse when endometrial tissue is dispersed throughout the myometrium, or focal when circumscribed nodular aggregates of endometrial glands and stroma are surrounded by normal myometrium.[69] Adenomyomas are a subgroup of focal adenomyosis characterized by nodules surrounded by hypertrophic myometrium.[70] Sonographic evaluation of adenomyosis is performed using the Morphological Uterine Sonographic Assessment (MUSA) criteria.[71]

Cutaneous or abdominal wall endometriosis is a rare and distinct form of the disease that may develop secondary to surgical procedures, such as caesarean sections, gynecological laparoscopies, or endometriosis-related surgeries, or, less commonly, as a primary manifestation, such as umbilical endometriosis.[72] Clinical presentation may include cyclical abdominal pain, localized swelling, or a palpable nodule, often accompanied by typical endometriosis-related symptoms. Curative treatment requires complete local surgical excision.[73]

2.6. Classification

Over the years, various classification systems have been developed to assess the extent and severity of endometriosis.[74] As early as 1973, Acosta et al. proposed a classification system for endometriosis in infertile women, categorizing the disease into mild, moderate, and severe stages. Furthermore, the reproductive outcome was listed as reported pregnancy

rates after surgical or medical therapy.[75] In 1979, the American Fertility Society (AFS) introduced the first standardized system aimed at evaluating the precise location of endometriotic lesions involving the peritoneum, ovaries, tubes, and cul-de-sac. The resulting cumulative score determined the disease stage, ranging from I (mild) to IV (extensive).[76] This system was subsequently revised in 1985 to further assess the functional status of the reproductive organs. The revised classification system categorized endometriosis into four stages (minimal to severe) based on point ranges (1–5, 6–15, 16–40, >40). Tubal endometriosis was excluded, and endometriotic lesions were differentiated into superficial and deep. Deep ovarian lesions >3 cm scored 20 points, dense adhesions or tubal blockages 16 points, and complete cul-de-sac obliteration alone scored 40 points, indicating severe disease.[77]

2.6.1. American Society for Reproductive Medicine

The revised American Society for Reproductive Medicine (rASRM) classification system (Figure 1), introduced in 1996 following a review commissioned by the American Society for Reproductive Medicine (formerly the American Fertility Society), remains the most widely adopted method for the standardized assessment of endometriosis severity.[78] This system quantifies endometriotic lesions and adhesions by assigning scores. Lesions on the peritoneum and ovaries are evaluated based on their size and depth (superficial or deep), while adhesions involving the ovaries and Fallopian tubes are graded by their extent (partial or complete) and consistency (filmy or dense). Additional points are assigned for the partial or complete obliteration of the posterior cul-de-sac. The total score, obtained by summing the points across these categories, stratifies the disease into four stages: Stage I (minimal, 1–5 points), Stage II (mild, 6–15 points), Stage III (moderate, 16–40 points), and Stage IV (severe, >40 points).[79] While primarily anatomical in scope, the classification is valued for its clarity and ease of use in both clinical and patient education contexts.[80] However, the disadvantages include the lack of correlation of endometriotic lesions and pain as well as fertility. To predict pregnancy outcomes in patients with surgically confirmed endometriosis, the group of authors around Adamson compiled a clinical tool called Endometriosis fertility index (EFI).[81] This score is based on the combination of demographic (historical) and surgical factors. Historical factors include the patient's age, duration of infertility, and history of prior pregnancy, whereas surgical factors encompass the functional assessment of the reproductive organs (least function score) and the extent of endometriotic lesions as defined by the revised American Fertility Society (rAFS) classification. The EFI ranges from 0 to 10, with higher scores indicating a more favorable prognosis for achieving spontaneous pregnancy. A score of 0 corresponds to the poorest fertility prognosis, while a score of 10 reflects the most favorable outcome.[82]

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name _____ Date _____

Stage I (Minimal) - 1-5
Stage II (Mild) - 6-15
Stage III (Moderate) - 16-40
Stage IV (Severe) - >40
Total _____

Laparoscopy _____ Laparotomy _____ Photography _____
Recommended Treatment _____
_____
Prognosis _____

PERITONEUM	**ENDOMETRIOSIS**	<1cm	1-3cm	>3cm
	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20

	POSTERIOR CULDESAC OBLITERATION	Partial	Complete
		4	40

OVARY	**ADHESIONS**	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

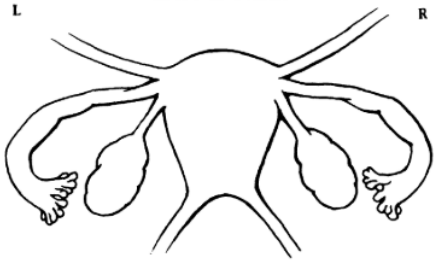
*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

Denote appearance of superficial implant types as red [(R), red, red-pink, flamelike, vesicular blobs, clear vesicles], white [(W), opacifications, peritoneal defects, yellow-brown], or black [(B) black, hemosiderin deposits, blue]. Denote percent of total described as R___%, W___% and B___%. Total should equal 100%.

Additional Endometriosis: _____

Associated Pathology: _____

To Be Used with Normal Tubes and Ovaries



To Be Used with Abnormal Tubes and/or Ovaries

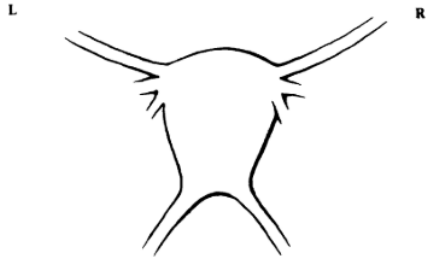


Figure 1: The revised American Society for Reproductive Medicine classification. Reproduced from the American Society of Reproductive medicine.[83]

2.6.2. #ENZIAN

Another major limitation of the rASRM classification is its failure to account for deep infiltrating endometriosis.[77] To address this limitation, the ENZIAN score was developed and initially published in 2003 and 2005 by a group of German-speaking authors.[84] Similar to the rASRM system, the ENZIAN score provides a standardized, morphology-based classification derived from intraoperative findings and aims to offer a detailed characterization of deep endometriosis, including involvement of the vagina, uterosacral ligaments (USL), bladder, ureter, bowel, uterus (adenomyosis), and extragenital locations.[85] This system considers the extent of infiltration, defined as DIE when lesions exceed a depth of 5 mm, as well as the specific anatomical location and the organs affected. The classification is organized around the concept of dividing the pelvic region into three compartments, each representing anatomically defined areas, allowing for a comprehensive and reproducible assessment of the severity and spatial distribution of the disease.[86] In the ENZIAN classification, compartment A represents (recto)vaginal involvement, B refers to the pelvic walls and the uterosacral ligaments, and C denotes rectal involvement. In addition, the category F (F standing for “far”) includes extragenital lesions, with FA representing uterine involvement (adenomyosis), FB the bladder, FU the ureters, FI the bowel (excluding the rectum), and FO other locations. To illustrate the extent of infiltration, compartments A, B, and C are further graded using numbers 1 to 3: grade 1 indicates lesions smaller than 1 cm, grade 2 refers to lesions between 1 and 3 cm, and grade 3 represents lesions larger than 3 cm.[87] However, peritoneal and ovarian involvement, as well as peritoneal adhesions within the pelvis, are not considered in this classification.[88] The 2021 revised #ENZIAN score (Figure 2) integrates the compartment-based ENZIAN system as well as the previously described rASRM classification of tubo-ovarian adhesions with optional tubal patency test and peritoneal involvement to provide a more comprehensive assessment.[89] In the #ENZIAN classification, compartments are denoted by capital letters in a specific sequence: P, O, T, A, B, C, and F. The extent of involvement is indicated by numbers (0–3) written directly after each letter, with "0" representing no involvement. Each compartment is separated by a comma. For paired organs such as the ovaries or fallopian tubes, both the left and right sides are noted, separated by a slash (e.g., O1/0), even if only one side is affected.[88] This classification is widely recognized as a reliable and practical tool for assessing deep endometriosis across various diagnostic modalities, including transvaginal sonography (#ENZIAN (u)), magnetic resonance imaging (#ENZIAN (m)), and surgical evaluation (#ENZIAN (s)). As the #ENZIAN classification is relatively recent, there is not yet as extensive a body of research available as there is for the rASRM classification.[90] This thesis focuses primarily on the more recent #ENZIAN classification.

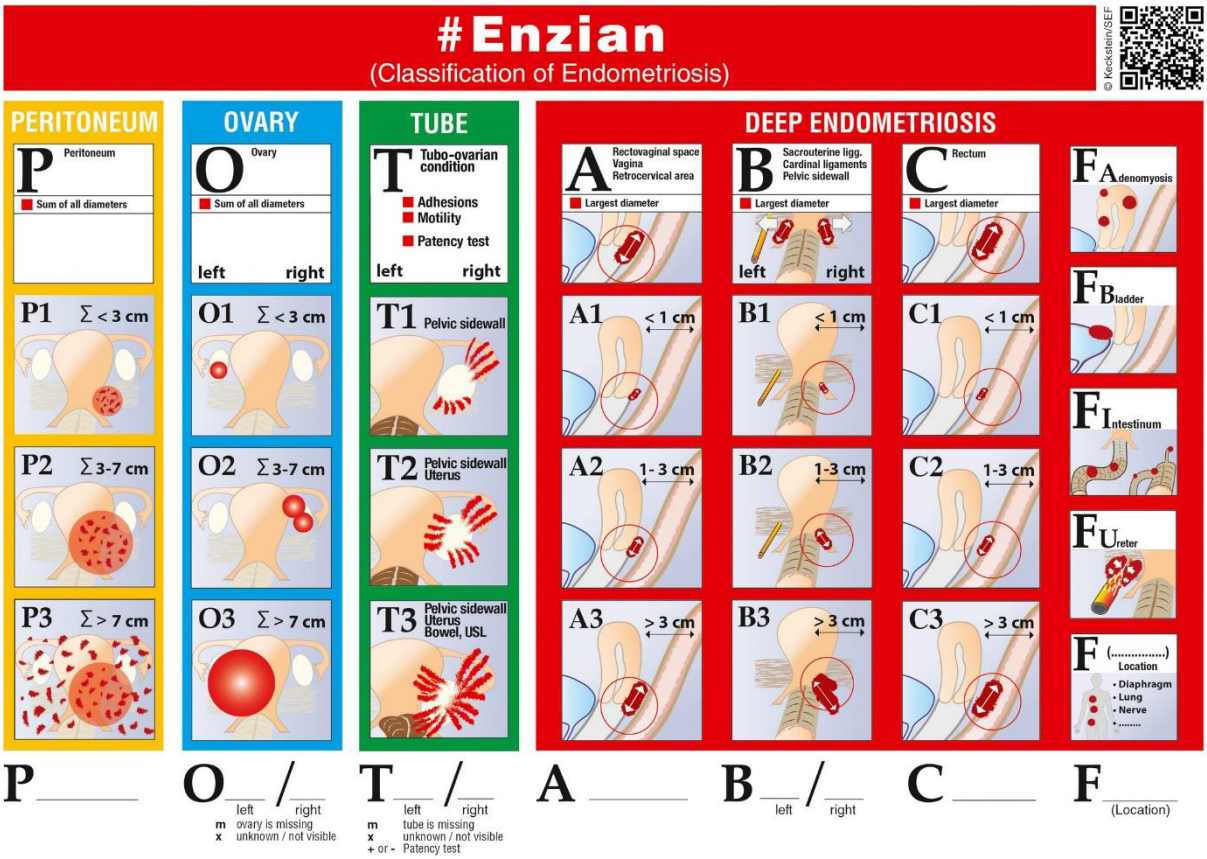


Figure 2: The #ENZIAN classification. Reproduced from Stiftung Endometriose Forschung [89]

2.7. Obesity – Definition

Obesity is a chronic, multifactorial health burden that has rapidly spread worldwide, reaching pandemic proportions. Officially classified as a disease in 2013, obesity is also a major risk factor for systemic conditions, including diabetes, cardiovascular disease, cancer, osteoarthritis, as well as markedly impaired female reproductive and hormonal health.[91] The World Health Organization (WHO) estimates that approximately one billion individuals are overweight and 300 million are obese.[92] Definitions of obesity may vary, but the WHO's criterion, based on the body mass index (BMI), is the most widely applied. BMI is calculated as the ratio of body weight in kilograms to the square of height in meters. A BMI exceeding 30 kg/m² qualifies an individual as obese. Furthermore, obesity is stratified into three grades: Grade I (BMI 30.0–34.9 kg/m²), Grade II (BMI 35.0–39.9 kg/m²), and Grade III (obesity permagna; BMI ≥ 40 kg/m²).[93]

2.8. Adipose Tissue as an endocrine organ

Adipose tissue develops between the 14th and 24th week of gestation and expands through increases in both cell number (hyperplasia) and cell size (hypertrophy) during fetal development, childhood, and adolescence.[94] Thereafter, the number of adipocytes stabilizes with maintained weight. As a highly dynamic and plastic organ, adipose tissue can expand via hyperplasia, which is considered metabolically favorable and less inflammatory, whereas

hypertrophy is associated with increased inflammation and greater metabolic risk.[95] The body harbors three distinct adipose depots. The largest is subcutaneous adipose tissue (SAT), which is generally associated with lower metabolic morbidity. In contrast, visceral adipose tissue (VAT), located primarily in the mesentery and omentum, is more metabolically active, highly vascularized, densely innervated and enriched with inflammatory and immune cells, thus increasing metabolic risk.[96] Lastly, ectopic lipid accumulation in organs such as the liver and skeletal muscle is non-adaptive and closely associated with metabolic dysfunction, with hepatic fat being particularly detrimental to metabolic health.[95]

Adipocytes derive from a common mesenchymal stem cell precursor and differentiate into distinct subtypes, including white, brown, beige, and pink adipocytes. White adipose tissue (WAT) is designed for fat storage and serves as an endocrine organ by secreting over 50 different hormones including bioactive peptides, known as adipokines, which exert autocrine, paracrine and endocrine effects both locally and systemically. In obesity, the secretion of proinflammatory adipokines such as TNF-α, IL-6 is elevated, leading to a chronic state of low-grade inflammation.[97] Furthermore, elevated TNF-α and IL-6 suppress the production of the beneficial adipokine adiponectin, which exhibits anti-inflammatory, anti-angiogenic, and insulin-sensitizing properties, leading to its inverse correlation with obesity.[98]

2.9. Aim and Objectives of this Thesis

Over the course of developing a classification nomenclature for endometriosis, various systems have been proposed and implemented in clinical practice.[77] The #ENZIAN classification, however, is the only system that encompasses all forms of endometriosis. Although the #ENZIAN classification is increasingly accepted in clinical use for categorizing endometriosis, it has not yet been widely adopted in scientific research. To address this gap, this thesis aims to investigate the associations between clinical symptoms and the type and extent of endometriotic lesions as classified by the #ENZIAN system. Furthermore, it examines the impact of BMI on both the symptomatology and the localization of endometriosis, equally defined by the #ENZIAN system.

The Endometriosis Center of excellence at the academic hospital Cologne Weyertal uses the #ENZIAN system for all patients presenting with suspected endometriosis for either hormonal or surgical treatment. A retrospective analysis of data collected through a standardized preoperative questionnaire (Table 1: Preoperative Questionnaire), complemented by intraoperative findings, constitutes the foundation of the two publications, presenting the main body of the thesis, as described below.

2.9.1. Paper 1

Symptom severity spans a broad spectrum, ranging from asymptomatic individuals to those suffering from serve and chronic pelvic pain.[33] The objective in Paper 1 is to investigate the symptom profiles of different types of endometriosis classified by #ENZIAN. A review of the existing literature reveals that most studies focus exclusively on the deep infiltrating form of endometriosis[62,99], whereas the impact of peritoneal lesions and ovarian endometriomas has largely been neglected. To date, no study has investigated the correlation between symptoms and the severity of the disease as classified by the #ENZIAN system.

For this reason, this paper addresses the question of whether a general association between symptomatology and the anatomical localization of endometriosis, as defined by the #ENZIAN classification, can be identified. A particular focus is placed on digestive symptoms. Furthermore, this study aims to determine whether the presence of a lesion in a specific #ENZIAN compartment is significantly associated with distinct clinical symptoms.

We stratified the patients into three groups based on the types and localization of the endometriosis: group one including only patients with peritoneal lesions, adnexal adhesions and adenomyosis. Group two comprises the sites included from group one and was extended by DIE excluding the digestive system. Whereas group three covers DIE of the digestive systems as well as other localizations.

2.9.2. Paper 2

In research, the link between BMI and endometriosis remains controversial. While some studies have shown no significant relationship or merely a weak trend between low BMI and endometriosis, others have established a significant negative correlation.[100,101] A growing body of evidence suggests that adipose tissue is a highly metabolically active organ that modulates processes central to the development of endometriosis.[102] To further investigate this link, this paper aims to evaluate the impact of BMI on endometriosis by assessing its relationship with endometriosis symptoms and its association with different types of endometriosis as classified by the #ENZIAN score. Here, patients were stratified into four BMI groups according to WHO criteria.

3. Publications

3.1. Paper 1

Is There a Relationship Between Symptoms and Types of Endometriosis according to #ENZIAN? A Comparative Study of Preoperative Questionnaires.

Journal: Archives of Gynecology and Obstetrics (Q1) issued by Springer

Archives of Gynecology and Obstetrics
https://doi.org/10.1007/s00404-025-08072-w

RESEARCH

Is there a relationship between symptoms and types of endometriosis according to #ENZIAN? A comparative study of preoperative questionnaires

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Abstract

Objective The primary objective was to evaluate the relationship between these three groups and digestive symptoms. The secondary objective was to evaluate all symptoms in all groups.

Study design It was a retrospective comparative analysis of preoperative questionnaires. Three groups of patients were compared: Group 1 Patients with only peritoneal endometriosis ± adnexal adhesions and adenomyosis (P ± T and FA), Group 2 Patients with DIE, excluding the digestive system, and/or cystic ± peritoneal and adnexal adhesions and adenomyosis (O, A, B ± P, T, and FA), Group 3 Patients with DIE of the digestive system (C, FI) ± other localizations.

Results This retrospective study of 233 preoperative questionnaires explored symptom profiles across #ENZIAN-classified endometriosis types. No overall symptom differences were found, but severe dyschezia (VAS ≥ 5) correlated with bowel involvement (C compartment), dyspareunia corelated with adenomyosis (FA compartment), and chronic pelvic pain was lower in bowel DIE (Group 3) than in peritoneal/ovarian groups. Symptom questionnaires may guide surgical referral despite imaging limitations.

Conclusion While these imaging modalities can help identify DIE and endometriomas, they are less effective in detecting superficial peritoneal lesions, which can also cause significant symptoms. For this reason, even though symptom questionnaires are not definitive diagnostic tools, they may serve as an important starting point for further investigation and referral for surgical evaluation.

Keywords Endometriosis · Symptoms · #ENZIAN · Digestive symptoms · Questionnaires

What does this study adds to the clinical work

Symptom questionnaires can aid early identification of endometriosis but are not sufficient for definitive diagnosis. Combining symptom profiles with advanced imaging and surgical evaluation offers a more accurate and holistic approach.

Introduction

Endometriosis is one of the most common benign gynecological diseases, characterized by the presence of endometrium-like tissue and/or stroma outside the uterus, usually associated with an inflammatory process. The pathogenesis of endometriosis remains largely unknown [1, 2]. The epidemiology of endometriosis is poorly understood [3]. However, according to available data, up to 10% of women of reproductive age may have endometriosis. Asymptomatic women might have a prevalence of 2–11%. The prevalence of endometriosis among infertile women is 25–50% [4]. In women with pelvic pain, the prevalence of endometriosis can be as high as 21%. Among symptomatic adolescents, the prevalence of endometriosis ranges from 49% in those with chronic pelvic pain to 75% in those with pain unresponsive to medical treatment [5].

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Endometriosis presents with diverse manifestations, ranging from superficial peritoneal and serosal lesions to ovarian endometriotic cysts (endometriomas) and nodules deeper than 5 mm (deep endometriosis), frequently accompanied by scarring (fibrosis) and adhesions [6]. The diagnosis of endometriosis can only be definitively confirmed through surgical visualization and histological examination, typically via laparoscopy. However, endometriomas and deep endometriosis may also be identified using imaging modalities such as ultrasonography or MRI [7].

Accurate classification of endometriosis is essential for understanding disease severity, identifying lesion locations, and evaluating clinicopathological outcomes. The #ENZIAN classification is among the most widely accepted systems, offering a comprehensive assessment of peritoneal, ovarian, and deep endometriosis across different compartments, as well as tubo-ovarian adhesions based on surgical observations [8, 9]. Additionally, the #ENZIAN classification can be applied using imaging modalities such as ultrasound and MRI [9]. In contrast to the revised American Society for Reproductive Medicine (rASRM) classification [4], which primarily addresses adhesions and endometriomas but lacks precision in describing the location and extent of deep endometriosis, the #ENZIAN system enables a more detailed evaluation of all endometriotic lesions. This facilitates effective communication among surgeons, diagnostic specialists, and reproductive health professionals.

Up to 70% of women with endometriosis are symptomatic [10, 11]. The primary clinical symptom of endometriosis is dysmenorrhea [10]. The most common symptoms are often referred to as the "4 Ds" of endometriosis (dysmenorrhea, dyspareunia, dysuria, dyschezia) [11]. However, symptoms are not limited to the "4 Ds". The development of chronic pelvic pain (CPP), digestive symptoms including nausea, vomiting, diarrhea, obstipation, and bloating, as well as urinary symptoms such as pollakiuria and cystitis, can also occur [12–15]. Furthermore, in cases of DIE in the bowel or bladder, catamenial blood in stool or urine may occur [16, 17].

To the best of our knowledge, no studies have explored the correlation between the symptoms and endometriosis type based on #ENZIAN classification. The primary objective was to evaluate the relationship between these three groups and digestive symptoms. The secondary objective was to evaluate all symptoms in all groups.

Method and materials

This study was a retrospective analysis of preoperative questionnaires. Patients admitted to the endometriosis consultation at the academic hospital Weyertal endometriosis center of excellence are given a standardized questionnaire (Fig. 1). Patients complete the questionnaire themselves, providing a subjective assessment of their symptoms. The questionnaire must be filled out before entering the examination room. We evaluated the questionnaires from the year 2021 and included a total of 513 questionnaires after excluding duplicate entries. The patients were then divided into 2 groups: those who chose hormonal treatment and those who opted for surgery. This study only included patients who underwent surgery. The inclusion criteria were as follows: (1) a fully completed preoperative questionnaire, (2) endometriosis as the main diagnosis, (3) histological confirmation of endometriosis. A total of 233 questionnaires were included and analyzed (Fig. 2).

Intraoperative classification of endometriosis was performed according to the #ENZIAN classification. The #ENZIAN provided a useful illustration of the type and localization of endometriosis lesions. It includes the peritoneum (P), the ovary (O), adhesions involving the tubo-ovarian unit (T), and deep infiltrated endometriosis (DIE) using three compartments: A—vagina, rectovaginal space; B—uterosacral ligaments/cardinal ligaments/pelvic sidewall; and C—rectum. It also includes so-called F (other locations), which includes the adenomyosis (FA), the urinary bladder (FB), the ureters (FU), and other parts of the intestines (sigmoid colon, small bowel; FI) [9]. The numbers 1, 2, and 3 in compartments P, O, T, A, B, and C represent the extent of endometriosis. Patients were categorized into three groups based on the type and localization of their endometriosis:

- Group 1: Patients with only peritoneal endometriosis ± adnexal adhesions and adenomyosis (P ± T and FA)
- Group 2: Patients with DIE, excluding the digestive system, and/or cystic ± peritoneal and adnexal adhesions and adenomyosis (O, A, B ± P, T, and FA)
- Group 3: Patients with DIE of the digestive system (C, FI) ± other localizations.

Statistical analyses were performed using a Chi-Square calculator for a 5×5 (or smaller) contingency table with a significance level of < 0.05, along with descriptive statistics, confidence intervals for the mean, and One-Way ANOVA including Tukey HSD for comparing the means of three groups. The data are presented as the mean and standard deviation.

Results

A total of 233 patients were enrolled in this study, categorized into three groups: Group 1 (n = 152), consisting of patients with P, T, and FA compartments; Group 2 (n = 57), consisting of patients with DIE without bowel involvement; and Group 3 (n = 24), consisting of patients with

Fig. 1 Questionnaire

Symptoms		
Pain during menstruation (dysmenorrhea)	yes/no ≥5/<5	
Onset of pain during menstruation since the first menstrual period (I° dysmenorrhea)	yes/no	
Abdominal pain outside of menstrual bleeding	yes/no ≥5/<5	
Chronic abdominal Pain	yes/no	
Pain days per month	≥5/<5	
Monthly need for analgesia in days		
Radiating Pain (back/hips/ legs)	yes/no	
Pain during sexual intercourse (dyspareunia)	yes/no	
Intercourse feasible	feasible/ unfeasible	
Discontinuation of Intercourse	yes/no	
Pain during defecation during menstruation (dyschezia)	yes/no ≥5/<5	
Interruption of defecation due to pain	yes/no	
Bleeding during defecation (haematochezia)	yes/no	
Pain during micturition during menstruation (dysuria)	yes/no ≥5/<5	
Bleeding during micturition (haematuria)	yes/no	
Bleeding disorder	yes/no	
Nausea/ vomiting during menstruation	yes/no	
Diarrhoea/ obstipation/ bloating during menstruation	yes/no	
Age at first manifestation of symptoms <20, 20-30, 30-40, >40 Years		
Unfulfilled desire to have children	yes/no	
Pregnancy in medical records (births/Abortions/interruptions)	yes/no	
Familial endometriosis	yes/no	
Pain during defecation during menstruation (dyschezia)		

bowel endometriosis. There were no significant differences between the groups regarding age or BMI (Table 1).

Endometriosis was classified according to the #ENZIAN, and significant differences in compartment involvement were observed across the groups (Table 2). Group 1 had a significantly higher prevalence of the P1 compartment (86.2%) compared to Groups 2 (38.6%) and 3 (45.8%) ($p=0.00001$). Group 2 had a higher prevalence of the O compartment compared to Group 3, but the difference was not statistically significant ($p=0.4750$). Notably, Groups 2 and 3 had a higher prevalence of the T compartment, with 57.9% of Group 2 and 58.3% of Group 3 compared to just 7.1% in Group 1 ($p=0.00001$). Group 3 also showed a significant increase in involvement of the A and B compartments compared to Group 2. Severe (A3, B3) lesions were also more frequently observed in Group 3, particularly in the B compartment ($p=0.0043$). The incidence of adenomyosis (FA) was notably lower in Group 3 (70.8%) compared to Groups 1 (89.5%) and 2 (85.9%) ($p=0.0433$).

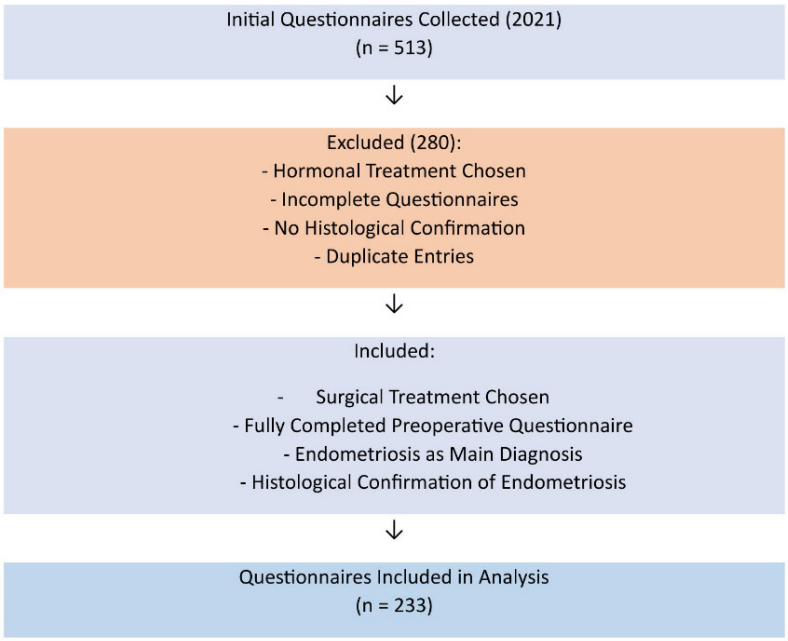

Fig. 2 Study population selection process

Dysmenorrhea was the most prevalent symptom, with 97.4% of patients in Group 1, 94.3% in Group 2, and 100% in Group 3 reporting it. The proportion of patients with a visual analog scale (VAS) ≥ 5 for dysmenorrhea did not differ significantly between groups. For dyspareunia, 75% of Group 1, 66.7% of Group 2, and 54.2% of Group 3 patients reported the symptom. A VAS score ≥ 5 for dyspareunia was observed in 23.7, 19.3, and 25% of the patients in Groups 1, 2, and 3, respectively ($p = 0.7667$). Dyschezia, which was more commonly reported in Group 3 (75%), followed by Group 2 (66.7%), and Group 1 (59.8%), showed a significant increase in the proportion of patients with severe dyschezia (VAS ≥ 5) in Group 3 compared to Groups 1 and 2 ($p = 0.0001$). Gastrointestinal symptoms, such as nausea/vomiting, were reported in similar proportions across all groups (Group 1 = 53.3%, Group 2 = 57.9%, Group 3 = 54.2%; $p = 0.8370$), while diarrhea, obstipation, and bloating were common in all groups (Group 1 = 92.1%, Group 2 = 91.2%, Group 3 = 91.7%; $p = 0.9783$). CPP was reported by 88.2% of Group 1, 89.5% of Group 2, and 66.7% of Group 3 ($p = 0.0126$), with a significantly lower incidence of CPP in Group 3. The mean number of days patients required analgesia per month was 5.75 ± 4.67 for Group 1, 5.88 ± 4.44 for Group 2, and 5.18 ± 3.41 for Group 3, with no significant difference ($p = 0.7605$). Infertility was reported in 22.4% of Group 1, 26.3% of Group 2, and 29.2% of Group 3. Group 3 had a higher proportion of patients with infertility compared to the other groups, but this difference did not reach statistical significance ($p = 0.6908$).

Other symptoms such as dysuria, hematochezia, and hematuria were observed in all groups, but no significant differences were found ($p = 0.3298$ for dysuria, $p = 0.0883$ for hematochezia, and $p = 0.9948$ for hematuria). Abnormal uterine bleeding (AUB) rate was also comparable across the groups, with no significant differences ($p = 0.9315$).

Discussion

The present study aimed to investigate the relationship between the symptoms of endometriosis and the type of disease as classified by the #ENZIAN system. Our findings provide novel insights into how different types of endometriosis manifest with varying symptom profiles, particularly with respect to gastrointestinal symptoms. Endometriosis can often lead to a range of symptoms that can significantly impact a woman's quality of life. The hallmark symptoms of endometriosis include CPP, dysmenorrhea, dyspareunia, and infertility [18]. Pelvic pain is often described as the most consistent and debilitating symptom, affecting up to 90% of women with the condition [19]. However, the intensity and presentation of pain can vary significantly between individuals, complicating the diagnostic process.

Table 1 Demographic and clinical characteristics of patients in groups 1, 2, and 3

N of patients	Group 1 152	Group 2 57	Group 3 24	p value
Age mean ± SD	32.84 ± 7.52	35.12 ± 7.64	33,71 ± 4.46	0.1421
BMI mean ± SD kg/m^2	24,72 ± 5.59	24,77 ± 5.68	25,78 ± 6.61	0.9903
Dysmenorrhea	148 (97.4%)	54 (94.3%)	24 (100%)	0.6382
≥ 5 VAS	140 (92.1%)	50 (87.7%)	21 (87.5%)	0.5419
< 5 VAS	8 (5.3%)	4 (7%)	3 (12.5%)	0.3976
Dyspareunia	114 (75%)	38 (66.7%)	13 (54.2%)	0.0828
≥ 5 VAS	36 (23.7%)	11 (19.3%)	6 (25%)	0.7667
< 5 VAS	78 (51.3%)	27 (47.4%)	7 (29.2%)	0.1294
Dyschezia	91 (59.8%)	38 (66.7%)	18 (75%)	0.2933
≥ 5 VAS	25 (16.4%)	12 (21.1%)	13 (54.2%)	0.0001*
< 5 VAS	66 (43.4%)	26 (45.6%)	5 (20.8%)	0.0887
Dysuria	68 (44.7%)	19 (33.3%)	10 (41.7%)	0.3298
≥ 5 VAS	8 (5.3%)	6 (10.5%)	2 (8.3%)	0.3895
< 5 VAS	60 (39.5%)	13 (22.8%)	8 (33.3%)	0.0780
Hematochezia	30 (19.7%)	7 (12.3%)	8 (33.3%)	0.0883
Hematuria	26 (17.1%)	10 (17.5%)	4 (16.7%)	0.9948
CPP	134 (88.2%)	51 (89.5%)	16 (66.7%)	0.0126*
≥ 5 VAS	91 (59.8%)	29 (50.9%)	12 (50%)	0.3971
< 5 VAS	43(28.3%)	22 (38.6%)	4 (16.7%)	0.1185
Monthly need for analgesia (days) mean ± SD	5.75 ± 4.67	5.88 ± 4.44	5.18 ± 3.41	0.7605
Nausea/vomiting	81 (53.3%)	33 (57.9%)	13(54.2%)	0.8370
Diarrhea/obstipation/bloating	140 (92.1%)	52 (91.2%)	22 (91.7%)	0.9783
AUB	105 (69.1%)	38 (66.7%)	16 (66.7%)	0.9315
Infertility	34 (22.4%)	15 (26.3%)	7 (29.2%)	0.6908

* P value with significance level 0.05

In our study all three groups displayed similar overall symptom profiles, with dysmenorrhea being the most prevalent symptom across all groups, while majority of the patients reported severe dysmenorrhea (VAS ≥ 5). CPP was another prominent symptom observed across all groups. However, Group 3 exhibited a significantly lower prevalence of CPP compared to Groups 1 and 2. This unexpected finding might be explained by the fact that DIE involving the bowel (Group 3) may not always manifest with the same intensity of pelvic pain as seen in more superficial peritoneal or ovarian endometriosis. This observation is consistent with studies suggesting that patients with bowel endometriosis may experience different pain profiles, sometimes less acute but potentially more persistent in nature, particularly when gastrointestinal symptoms dominate [20] and it is possible that the severity of pain in Group 3 patients could be masked by the pronounced dyschezia, leading to a lower reported prevalence of CPP. Our finding of a lower chronic pelvic pain (CPP) prevalence in patients with bowel endometriosis (Group 3) compared to other forms of endometriosis suggests differences in pain mechanisms, with important clinical implications. Deep bowel lesions often provoke more localized pain (e.g., dyschezia) rather than diffuse pelvic pain due to distinct visceral innervation and referred pain patterns [21]. Such lesions may also induce visceral hypersensitivity by upregulating neural pathways, leading to IBS-like gastrointestinal pain perception instead of widespread pelvic pain [22]. Clinically, women with bowel involvement may present with atypical pain distribution (primarily gastrointestinal or referred back pain) and lack classic CPP, so deep endometriosis should be considered even if CPP is absent. Consistent with our results, ENZIAN-based studies have found that lesion extent or location does not reliably predict pain severity [23]. These observations underscore the complex pathophysiology of endometriosis pain and warrant further research into how lesion location influences pain pathways. Future studies should employ pain mapping and assess central sensitization to clarify why some patients with deep lesions develop CPP while others do not, guiding more personalized pain management.

In terms of infertility, no significant differences were found across the three groups. Our findings align with previous studies that show infertility may not always correlate

Table 2 #ENZIAN classification of patients in groups 1, 2, and 3

#ENZIAN	Group 1 (152 P)	Group 2 (57 P)	Group 3 (24 P)	p value
P (total)	152 (100%)	45 (78.9%)	17 (70.8%)	0.00001*
1	131 (86.2%)	22 (38.6%)	11 (45.8%)	0.00001*
2	16 (10.5%)	13 (22.8%)	5 (20.8%)	0.0535
3	5(3.3%)	10 (17.5%)	1 (4.2%)	0.0011*
O (total)		19 (33.3%)	10 (41.7%)	0.4750
bilateral		5 (8.8%)	4 (16.7%)	0.3018
unilateral		14 (24.6%)	6 (25%)	1.0000
1*		13 (11.4%)*	6 (12.5%)*	0.8430
2*		8 (7%)*	4 (8.3%)*	0.7702
3*		3 (2.6%)*	3 (6.25%)*	0.2654
T (Total)	11 (7.1%)	33 (57.9%)	14 (58.3%)	0.00001*
bilateral	3 (1.9%)	13 (22.8%)	5 (20.8%)	0.00001*
unilateral	8 (5.2%)	20 (35.1%)	9 (37.5%)	0.00001*
1*	12 (3.9%)*	13 (11.4%)*	4 (8.3%)*	0.0157*
2*	1 (0.3%)*	12 (10.5%)*	1 (2.1%)*	0.00001*
3*	1 (0.3%)*	21 (18.4%)*	14 (29.2%)*	0.00001*
A (total)		19 (33.3%)	19 (79.1%)	0.0001*
1		8 (14%)	2 (8.3%)	0.4762
2		11 (19.3%)	7 (29.2%)	0.3293
3			10 (41.7%)	0.00001*
B (total)		34 (59.6%)	22 (91.7%)	0.0043*
bilateral		13 (22.8%)	9 (37.5%)	0.1746
unilateral		21 (36.8%)	13 (54.2%)	0.1491
1*		23 (20.2%)*	8 (16.7%)*	0.6041
2*		22 (19.3%)*	14 (29.2%)*	0,1677
3*		1 (0.9%)*	9 (18.7%)*	0.00001*
C (total)			24 (100%)	
1			7 (29.2%)	
2			4 (16.7%)	
3			3 (12.5%)	
x			10 (41.7%)	
FA	136 (89.5%)	49 (85.9%)	17 (70.8%)	0.0433*
FB		1 (1.7%)	1 (4.2%)	0.5074
FI			3 (12.5%)	0.0237
FU			2 (8.3%)	0.0852
F diaphragm		1 (1.7%)	1 (4.2%)	0.5074
F umbilicus		2 (3.5%)	1 (4.2%)	1.0000

*The sub analysis of bilateral compartments (O, T, B) was carried out under taking into account the number of organs (double number of patients), 304, 114 and 48 in the group 1, group 2 and group 3 respectively

directly with the type or location of endometriotic lesions [4].

Vercellini et al. investigated pain syndrome, including dyspareunia, in 1000 patients. They compared 2 groups, patients with absent/mild dyspareunia and with moderate/severe dyspareunia. The data showed the significantly higher prevalence of absent/mild dyspareunia regardless of the endometriosis stage according to the AFS classification [24]. Montanari et al. identified a statistically significant association between involvement of the ENZIAN compartment B and the presence of dyspareunia [25]. In our analysis, we compared the prevalence of dyspareunia according to #ENZIAN. The rate of mild dyspareunia (VAS < 5) was higher in all three groups. There was no statistically significant difference in dyspareunia across all groups, regardless of the severity of dyspareunia and involved compartments

according to #ENZIAN (Table 1). Furthermore, if comparing groups 1 and 3, dyspareunia occurred significantly higher (p = 0.0343) in patients with the P compartment. In contrast to Montanari et al., no difference was found between groups with and without B compartment (groups 1 and 2). Notably, the incidence of adenomyosis was also the same in groups 1 and 2 and significantly lower in Group 3 (Table 2). Therefore, we can make 2 conclusions. First, the role of adenomyosis in dyspareunia may be more significant than that of deep-infiltrating endometriosis. Second, we should not underestimate the role of peritoneal endometriosis in dyspareunia.

Previous studies indicated that gastrointestinal symptoms such as dyschezia and nausea are more common in patients with bowel endometriosis (#ENZIAN C and FI) [16, 24]. In contrast, in our analysis, there was no statistically significant difference in terms of dyschezia when considering it as a symptom in general and not its severity. However, considering severe dyschezia (VAS ≥ 5), the rate was significantly higher (p = 0.0001) in Group 3. The significantly higher incidence of severe dyschezia in Group 3 highlights the impact of bowel endometriosis on gastrointestinal function and quality of life.

Gastrointestinal symptoms, including diarrhea, obstipation, bloating, and nausea, were frequently reported across all groups, reflecting the widespread nature of gastrointestinal involvement in endometriosis. The prevalence of such symptoms was notably high in all three groups, without statistically significant difference across the groups (Table 1). This doesn´t align with existing literature that suggests a direct correlation between the severity of gastrointestinal symptoms and the extent of deep infiltrating endometriosis, particularly involving the bowel (C and FI compartments) [16]. There was no significant difference in hematochezia when comparing all groups (p = 0.0883) or group 3 with group 1 (p = 0.1324), but there was a significant difference when comparing group 3 with group 2 (p = 0.0259). On the one hand, this finding supports previously published data on the association between the C compartment and blood in the stool in patients with DIE. On the other hand, interestingly, we found no difference between patients with C compartments and only P compartments.

While the prevalence of dysuria was high in all groups, hematuria occurs much less. It is to be highlighted, that only 2 patients had bladder endometriosis (FB compartment). No significant differences were observed between groups for dysuria and hematuria, p = 0,3298 and 0,9948, respectively.

Conclusion

The use of validated symptom questionnaires has been suggested to aid in the early identification of women at high risk for endometriosis [26]. This focuses on the key symptoms of endometriosis and assess their impact on a woman's daily functioning. The thorough anamnesis of the symptoms can indicate the presence of the disease endometriosis and ensuring timely intervention. However, the extent of the disease does not always correlate with symptom severity, further highlighting the limitations of symptom-based diagnosis [6].

The present study highlights the relationship between symptoms and the type of endometriosis classified by the #ENZIAN system. All three groups displayed similar overall symptom profiles. A correlation was found only between severe dyschezia (VAS ≥ 5) and the C compartment, in the prevalence of CPP (Group 1 and Group 2 exhibited higher prevalence of CPP compared to Group 3), as well as between dyspareunia and adenomyosis (FA compartment). Therefore, additional diagnostic tools are necessary. In recent years, advances in non-invasive imaging techniques, such as transvaginal ultrasound and magnetic resonance imaging, have provided valuable adjuncts to the diagnostic process [27, 28]. While these imaging modalities can help identify DIE and endometriomas, they are less effective in detecting superficial peritoneal lesions, which can also cause significant symptoms. For this reason, even though symptom questionnaires are not definitive diagnostic tools, they may serve as an important starting point for further investigation and referral for surgical evaluation. This limitation of imaging tools underscores the importance of considering a comprehensive symptom profile in conjunction with imaging and laparoscopic findings for a more accurate diagnosis.

Limitations and bias

While the study provides valuable insights into the symptomatology of endometriosis classified by the #ENZIAN system, there are several limitations to consider. The retrospective nature of the study and reliance on preoperative questionnaires mean that the data are subject to recall bias, and the severity of symptoms might have been underreported or overreported by patients. However, we believe that even a prospective study would likely yield similar results. This is because, despite the retrospective nature, we used prospectively collected data, as it is our routine practice to systematically document all surgical findings using the #ENZIAN classification.

Author contributions EP and CM manuscript writing, data management, data analysis. SS and TR critical review and administration.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval According to 15§ of the professional code of the North Rhine Medical Association, neither advice nor an ethics vote is necessary for a retrospective study.

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3.2. Paper 2

Does BMI Have an Impact on Endometriosis Symptoms and Endometriosis Types According to the #ENZIAN Classification?

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Article

Does BMI Have an Impact on Endometriosis Symptoms and Endometriosis Types According to the #ENZIAN Classification?

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Abstract: Background/Objectives: The relationship between body mass index (BMI) and endometriosis symptoms or lesion types remains unclear. This study investigates the association between BMI and symptom severity as well as the anatomical distribution of endometriosis using the #ENZIAN classification. **Methods**: A retrospective analysis was conducted on 219 patients with histologically confirmed endometriosis who underwent laparoscopic surgery at a tertiary endometriosis center in 2021. Preoperative symptom data were collected using standardized questionnaires. Patients were grouped by BMI categories based on WHO criteria. Endometriosis was classified intraoperatively using the #ENZIAN system. Statistical analyses included chi-square tests and one-way ANOVA. **Results**: Patients with low/normal BMI (<25 kg/m^2, n = 150) reported significantly higher intensity of chronic pelvic pain (CPP) compared to those with overweight/obesity (≥25 kg/m^2, n = 69; $p = 0.0026$). When stratified into four BMI groups, dyspareunia was significantly less frequent in obese patients ($p = 0.0306$), and high-intensity CPP was less common in both underweight and obese categories compared to normal-weight patients ($p = 0.0069$). Infertility rates increased significantly with higher BMI ($p = 0.00001$). No significant differences in the distribution of endometriosis lesions across #ENZIAN compartments were observed in relation to BMI. **Conclusions**: Our findings indicate that BMI does not significantly influence the anatomical distribution of endometriosis lesions as defined by the #ENZIAN classification, but it does correlate with some symptom intensity and infertility. These results suggest that while BMI may not predict disease localization, it plays a role in shaping the clinical phenotype of endometriosis.

Keywords: endometriosis; BMI; #ENZIAN classification; symptoms; chronic pelvic pain; infertility

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1. Introduction

Endometriosis is one of the most common benign gynecological conditions, characterized by the ectopic implantation of endometrial tissue outside the uterus, typically accompanied by chronic inflammation. Despite extensive research, the pathogenesis of endometriosis remains largely unclear [1,2]. Its epidemiology is also not fully understood [3]; however, current data suggest that up to 10% of women of reproductive age may be affected [4].

The disease manifests with a wide range of symptoms, most commonly including dysmenorrhea, dyspareunia, dysuria, and dyschezia [5]. However, the symptom spectrum

extends beyond these. Chronic pelvic pain (CPP), gastrointestinal complaints such as nausea, vomiting, diarrhea, constipation, and bloating, as well as urinary symptoms like increased frequency and cystitis, may also be present [6–9]. In cases of deep infiltrating endometriosis involving the bowel or bladder, catamenial bleeding may occur in stool or urine [10,11]. Moreover, endometriosis is a well-established cause of infertility [4].

Accurate classification of endometriosis is essential for evaluating disease severity, identifying lesion location, and guiding clinical management. The #ENZIAN classification system is widely accepted and provides a detailed assessment of peritoneal, ovarian, and deep endometriosis across various anatomical compartments, as well as tubo-ovarian adhesions, based on surgical findings [12]. Compared to the revised American Society for Reproductive Medicine (rASRM) classification—which primarily focuses on peritoneal endometriosis, adhesions, and endometriomas [13]—the #ENZIAN system offers a more comprehensive description, particularly for deep infiltrating endometriosis.

The relationship between body mass index (BMI) and endometriosis remains controversial. While some studies report no significant association—or only a marginal trend—between low BMI and the presence of endometriosis at diagnosis, others have demonstrated a significant negative correlation [14]. Epidemiologic studies also examining BMI and endometriosis have generally indicated an inverse correlation between the two (i.e., higher BMI is associated with a lower risk of endometriosis) [15]. In particular, endometriosis appears to be more prevalent among lean or underweight women and less common in women who are overweight or obese relative to those of normal BMI [15,16]. For example, a meta-analysis reported approximately a 33% decrease in endometriosis risk for every 5 kg/m^2 increase in BMI and noted that obese women had significantly lower odds of endometriosis compared to normal-weight controls. This evidence collectively suggests a negative association between adiposity and endometriosis prevalence across the spectrum of BMI categories [15].

A growing body of evidence suggests that body composition may influence endometriosis pathophysiology and presentation. Adipose tissue is not merely an inert energy store but a highly active endocrine organ: it produces adipokines (e.g., leptin, adiponectin, resistin) and inflammatory cytokines that regulate immune responses, angiogenesis, and metabolism [17]. These mediators modulate estrogen signaling (via aromatization in fat) and inflammation, processes central to endometriotic lesion growth. Notably, women with endometriosis often have lower BMI and altered fat distribution (more peripheral subcutaneous fat) compared to unaffected women [18]. Obesity creates a pro-inflammatory milieu, while leanness is associated with shifts in immune cell polarization (e.g., M2 macrophages) [18]. Since chronic inflammation and estrogen dependence are hallmarks of endometriosis, differences in adiposity could plausibly affect lesion characteristics and symptoms [17,18]. This provides a biological and clinical rationale to examine whether BMI correlates with symptom severity or endometriosis subtype (e.g., deep infiltrating lesions) under the #ENZIAN classification. In other reproductive disorders (e.g., PCOS, infertility) adiposity is known to influence hormonal and immune factors; similar links may exist in endometriosis.

The aim of the present study was to evaluate the impact of BMI on endometriosis. The primary objective was to assess the relationship between BMI and endometriosis symptoms. The secondary objective was to examine the association between BMI and different types of endometriosis as classified by the #ENZIAN score.

2. Materials and Methods

This retrospective study analyzed endometriosis cases treated at Academic Hospital Weyertal, a Level III Endometriosis Center of Excellence. All patients presenting to

the endometriosis consultation at our center are routinely asked to complete a standardized, self-administered questionnaire, which includes a subjective assessment of symptoms. Key pain symptoms were rated individually on a 0–10 visual analog scale (VAS), where 0 = no pain and 10 = worst imaginable pain. The questionnaire explicitly asked about dysmenorrhea (menstrual pain), deep dyspareunia (painful intercourse), non-cyclic chronic pelvic pain, dyschezia (pain with bowel movements), dysuria (urinary pain) and other endometriosis-related symptoms We chose the VAS/NRS format because it is the most commonly used and validated method for endometriosis pain measurement [19]. Numerical values (0–10) were recorded for analysis. Demographic and gynecological data were also collected. BMI was calculated from measured height and weight at the preoperative visit.

We reviewed medical records from patients treated in 2021. Only those who underwent laparoscopic excision of endometriosis were considered for inclusion. The inclusion criteria were as follows: (1) a fully completed preoperative questionnaire, (2) endometriosis as the main diagnosis, (3) histological confirmation of endometriosis, and (4) complete BMI data. After excluding duplicate entries, a total of 219 patients were included in the final analysis. A diagnosis of endometriosis was confirmed only when endometrial-type glands and stroma were identified outside the uterus. In other words, lesions had to contain at least endometrial glands and/or stroma to meet diagnostic criteria. Cases without histological confirmation were excluded from the analysis. This ensured that only women with pathologically verified endometriosis were included.

Intraoperative classification of endometriosis was performed according to the #ENZIAN classification system [12]. This classification provides a detailed mapping of endometriosis lesions by site and depth. It includes the following components:

- P: Peritoneum
- O: Ovaries
- T: Adhesions of the tubo-ovarian unit
- Deep infiltrating endometriosis (DIE), which is further subdivided into:
    - A: Vagina and rectovaginal space
    - B: Uterosacral and cardinal ligaments, pelvic sidewall
    - C: Rectum
- F: Other locations, including adenomyosis (FA), urinary bladder (FB), ureters (FU), and bowel (FI) [12].

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2) and categorized according to World Health Organization (WHO) criteria [20]:

- BMI < 18.5: Underweight
- BMI 18.5–24.9: Normal weight
- BMI $\geq$ 25.0: Overweight
- BMI $\geq$ 30.0: Obesity

Three statistical analyses were conducted:

1. Patients were initially categorized into two groups: Group 1 included those with underweight or normal BMI (BMI < 25), and Group 2 included those who were overweight or obese (BMI $\geq$ 25).
2. For a more nuanced analysis, patients were further stratified into four subgroups:
    - Group 1: BMI < 18.5
    - Group 2: BMI 18.5–24.9
    - Group 3: BMI 25.0–29.9
    - Group 4: BMI $\geq$ 30.0

3. A reverse analysis was performed by dividing patients based on the type of endometriosis: those with DIE (compartments A, B, C) versus those with peritoneal or ovarian endometriosis without DIE (compartments P and O). A subanalysis also compared patients with rectal involvement (compartment C) to those without DIE. To further explore the interaction between BMI and endometriosis phenotype on symptom presentation, patients were additionally subdivided based on BMI into two subgroups: BMI < 25 kg/m^2 and BMI ≥ 25 kg/m^2. Symptom frequencies were compared across BMI subgroups within each phenotype group to identify potential BMI-related differences in clinical presentation.

To our knowledge, this is the first study investigating the relationship between BMI and both the symptom profile and classification of endometriosis using the #ENZIAN system.

Statistical analysis was performed using chi-square tests for contingency tables (up to 5 × 5), with a significance threshold of $p < 0.05$. Descriptive statistics were calculated, including means and standard deviations. One-way ANOVA with Tukey HSD post hoc analysis was used to compare means across groups. Results are presented as mean ± standard deviation (SD). Odds ratios (OR) and adjusted odds ratios (aOR) with 95% confidence intervals (CI) were calculated using logistic regression models to assess the association between BMI categories and the presence of specific endometriosis symptoms, adjusting for potential confounders including age.

3. Results

A total of 219 patients with histologically confirmed endometriosis were included in the analysis. Based on BMI, patients were categorized into two main groups: Group 1 (low/normal BMI, <25 kg/m^2; n = 150) and Group 2 (overweight/obese, ≥25 kg/m^2; n = 69). The mean BMI differed significantly between the groups (21.43 ± 2.11 vs. 30.03 ± 4.33 kg/m^2; $p = 0.0001$), while the mean age was comparable (33.51 ± 6.85 vs. 33.60 ± 7.42 years; $p = 0.9356$).

3.1. First Analysis (Tables 1 and 2)

The overall prevalence of symptoms such as dysmenorrhea, dyspareunia, dyschezia, and chronic pelvic pain (CPP) was high in both BMI groups. While the frequency of these symptoms did not differ significantly between groups, patients with low/normal BMI reported significantly higher CPP intensity ($p = 0.0026$ for VAS > 5; $p = 0.0141$ for VAS < 5), indicating a greater pain burden in this subgroup. Other symptoms, including abnormal uterine bleeding (AUB), nausea/vomiting, and gastrointestinal complaints, did not show statistically significant differences between the groups (Table 1).

Table 1. Comparison of symptoms between patients with low/normal BMI and those with overweight/obesity (First Analysis).

	Group 1	Group 2	*p*-Value
N of patients	150	69	
Age mean ± SD	33.51 ± 6.85	33.60 ± 7.42	0.9356
BMI mean ± SD kg/m^2	21.43 ± 2.11	30.03 ± 4.33	**0.0001**
Dysmenorrhea	147 (98%)	66 (95.6%)	0.3227
>5 VAS	137 (91.3%)	61 (88.4%)	0.4942
<5 VAS	10 (6.7%)	5 (7.2%)	0.8746

Table 1. *Cont.*

	Group 1	Group 2	*p*-Value
Dyspareunia	110 (73.3%)	44 (63.8%)	0.1500
>5 VAS	37 (24.7%)	18 (26.1%)	0.8218
<5 VAS	73 (48.7%)	26 (37.7%)	0.1291
Dyschezia	103 (68.7%)	38 (55.1%)	0.0509
>5 VAS	31 (20.7%)	10 (14.5%)	0.2765
<5 VAS	72 (48%)	28 (40.6%)	0.3057
Dysuria	68 (45.3%)	24 (34.8%)	0.1416
>5 VAS	12 (8%)	3 (4.3%)	0.3202
<5 VAS	56 (37.3%)	21 (30.4%)	0.3205
Hematochezia	29 (19.3%)	14 (20.3%)	0.8685
Hematuria	30 (20%)	8 (11.6%)	0.1270
CPP	135 (90%)	59 (85.5%)	0.3314
>5 VAS	85 (56.7%)	24 (34.8%)	**0.0026**
<5 VAS	50 (33.3%)	35 (50.7%)	**0.0141**
Monthly need for analgesia (days) mean ± SD	5.04± 5.51	5.92± 5.18	0.2453
Nausea/Vomiting	80 (53.3%)	45 (65.2%)	0.0988
Diarrhea/Obstipation/Bloating	138 (92%)	65 (94.2%)	0.5606
AUB	96 (64%)	53 (76.8%)	0.0589
Infertility	32 (21.3%)	21 (30.4%)	0.1440

CPP—chronic pelvic pain, VAS—visual analog scale, AUB—abnormal uterine bleeding.

Evaluation of endometriosis localization based on the #ENZIAN classification showed no significant differences between BMI groups regarding the involvement of compartments P, O, T, A, B, or C. The prevalence of adenomyosis (FA) was slightly higher in the overweight/obese group compared to the low/normal BMI group (91.3% vs. 84.7%); however, this difference was not statistically significant ($p = 0.1782$) (Table 2).

Table 2. Comparison of endometriosis lesions according to the #ENZIAN classification between patients with low/normal BMI and those with overweight/obesity (First Analysis).

#ENZIAN	Group 1 (150 P)	Group 2 (69 P)	*p*-Value
P	110 (73.3%)	53 (76.8%)	0.5836
O	21 (14%)	6 (8.7%)	0.2673
bilateral	6 (4%)	2 (2.9%)	0.6864
unilateral	15 (10%)	4 (5.8%)	0.3046
T	28 (18.7%)	13 (18.8%)	0.9755
bilateral	8 (5.3%)	5 (7.2%)	0.5778
unilateral	20 (13.3%)	8 (11.6%)	0.7203
A	26 (17.3%)	10 (14.5%)	0.5982
B	34 (22.7%)	17 (24.6%)	0.7485
bilateral	16 (10.7%)	6 (8.7%)	0.6521

Table 2. *Cont.*

#ENZIAN	Group 1 (150 P)	Group 2 (69 P)	*p*-Value
unilateral	18 (12%)	11 (15.9%)	0.4239
C	14 (9.3%)	7 (10.1%)	0.8497
FA	127 (84.7%)	63 (91.3%)	0.1782

3.2. Extended Analysis Across Four BMI Categories (Second Analysis, Tables 3 and 4)

When stratifying patients into four BMI categories (<18.5, 18.5–24.9, 25.0–29.9, and ≥30.0 kg/m^2), no significant differences were observed in age or general symptom prevalence. However, a statistically significant decrease in dyspareunia was noted in the obese group (46.2%, $p = 0.0306$), as well as a lower proportion of patients reporting high-intensity CPP in both the underweight and obese categories compared to the normal BMI group ($p = 0.0069$). Additionally, infertility showed a clear trend of increasing prevalence with rising BMI, reaching 38.5% in patients with BMI ≥ 30 kg/m^2 ($p = 0.00001$) (Table 3).

Table 3. Comparison of endometriosis-related symptoms in patients according to BMI categories (Second Analysis).

BMI kg/m^2	<18.5	18.5–24.9	25.0–29.9	≥30.0	*p*-Value
N of patients	12	138	43	26	
Age mean ± SD	33.58 ± 7.57	33.32 ± 7.27	32.67 ± 7.08	35.12 ± 7.84	0.5844
BMI mean ± SD kg/m^2	17.52 ± 0.94	21.77 ± 1.81	27.48 ± 1.40	34.26 ± 4.23	**0.0002**
Dysmenorrhea	12 (100%)	135 (97.8%)	41 (95.3%)	25 (96.2%)	0.6476
>5 VAS	9 (75%)	128 (92.7%)	38 (88.4%)	23 (88.5%)	0.2139
<5 VAS	3 (25%)	7 (5.1%)	3 (6.9%)	2 (7.7%)	0.0748
Dyspareunia	10 (83.3%)	100 (72.5%)	32 (74.4%)	12 (46.2%)	**0.0306**
>5 VAS	6 (50%)	31 (22.5%)	14 (32.6%)	4 (15.4%)	0.0705
<5 VAS	4 (33.3%)	73 (52.9%)	18 (41.9%)	8 (30.8%)	0.1100
Dyschezia	7 (58.3%)	96 (69.6%)	23 (53.5%)	15 (57.7%)	0.2086
>5 VAS	3 (25%)	28 (20.3%)	4 (9.3%)	6 (23.1%)	0.3386
<5 VAS	4 (33.3%)	68 (49.3%)	9 (20.9%)	9 (34.6%)	**0.0081**
Dysuria	4 (33.3%)	64 (46.4%)	15 (34.9%)	9 (34.6%)	0.4023
>5 VAS	0 (0%)	12 (8.7%)	2 (4.6%)	1 (3.8%)	0.7270
<5 VAS	4 (33.3%)	52 (37.7%)	13 (30.2%)	8 (30.8%)	0.7818
Hematochezia	1 (8.3%)	28 (20.3%)	8 (18.6%)	6 (20.1%)	0.7451
Hematuria	2 (16.7%)	28 (20.3%)	5 (11.6%)	3 (11.5%)	0.4881
CPP	10 (83.3%)	125 (90.6%)	37 (86%)	22 (84.6%)	0.6709
>5 VAS	4 (33.3%)	81 (58.7%)	14 (32.6%)	10 (38.5%)	**0.0069**
<5 VAS	6 (50%)	44 (31.9%)	23 (53.5%)	12 (46.2%)	**0.0478**
Monthly need for analgesia (days) mean ± SD	4.08 ± 3.38	5.12 ± 5.66	5.57 ± 4.42	6.52 ± 6.29	0.5293
Nausea/Vomiting	7 (58.3%)	73 (52.9%)	28 (65.1%)	17 (65.4%)	0.4140
Diarrhea/Obstipation/Bloating	11 (91.7%)	127 (92%)	41 (95.3%)	24 (92.3%)	0.9050
AUB	7 (58.3%)	89 (64.5%)	33 (76.7%)	20 (76.9%)	0.2885
Infertility	2 (16.7%)	30 (21.7%)	11 (25.6%)	10 (38.5%)	**0.00001**

CPP—chronic pelvic pain, VAS—visual analogue scale, AUB—abnormal uterine bleeding.

The logistic regression analysis revealed notable associations between BMI and specific endometriosis symptoms (infertility and CPP) (Table 4). Patients with obesity (BMI ≥ 30 kg/m^2) had more than twice the odds of infertility compared to non-obese patients, a trend approaching statistical significance after age adjustment (age-adjusted OR = 2.30; 95% CI: 0.97–5.47; $p = 0.060$). Furthermore, patients with low or normal BMI

(<25 kg/m^2) showed significantly higher odds of experiencing high-intensity chronic pelvic pain (CPP, VAS > 5) compared to overweight or obese patients (age-adjusted OR = 2.22; 95% CI: 1.17–4.28; p = 0.015), underscoring a meaningful link between lower BMI and severe pelvic pain.

Table 4. Logistic Regression Analysis for BMI and Endometriosis Symptoms.

Symptom	BMI Comparison	Odds Ratio (95% CI)	p-Value
Infertility	Obese (≥30 kg/m^2) vs. non-obese (<30 kg/m^2)	2.18 (0.92–5.15)	0.071
Infertility (age-adjusted)	Obese (≥30 kg/m^2) vs. non-obese (<30 kg/m^2)	2.30 (0.97–5.47)	0.060
High-intensity CPP (VAS > 5)	Low/Normal (<25 kg/m^2) vs. Overweight/Obese (≥25 kg/m^2)	2.45 (1.36–4.43)	0.006
High-intensity CPP (VAS > 5, age-adjusted)	Low/Normal (<25 kg/m^2) vs. Overweight/Obese (≥25 kg/m^2)	2.22 (1.17–4.28)	0.015

CPP—chronic pelvic pain.

Analysis of lesion distribution using the #ENZIAN classification across the four BMI categories again demonstrated no statistically significant differences in the involvement of pelvic compartments (P, O, T, A, B, C). Adenomyosis is universally present in underweight patients (100%); however, this difference was not statistically significant (p = 0.2139) (Table 5).

Table 5. Comparison of endometriosis lesion distribution according to the #ENZIAN classification based on BMI categories (Second Analysis).

Group	<18.5	18.5–24.9	25.0–29.9	≥30.0	p-Value
N of patients	12	138	43	26	
P	8 (66.7%)	102 (73.9%)	35 (81.4%)	18 (69.2%)	0.6009
O	1 (8.3%)	20 (14.5%)	2 (4.6%)	4 (15.4%)	0.3414
bilateral	0 (0%)	6 (4.3%)	1 (2.3%)	1 (3.8%)	0.8498
unilateral	1 (8.3%)	14 (10.1%)	1 (2.3%)	3 (11.5%)	0.4177
T	3 (25%)	25 (18.1%)	6 (13.9%)	7 (26.9%)	0.5446
bilateral	1 (8.3%)	7 (5.1%)	1 (2.3%)	4 (15.4%)	0.1405
unilateral	2 (16.7%)	8 (5.8%)	5 (11.6%)	3 (11.5%)	0.3546
A	2 (16.7%)	24 (17.4%)	6 (13.9%)	4 (15.4%)	0.9588
B	1 (8.3%)	33 (23.9%)	10 (23.3%)	7 (26.9%)	0.6314
bilateral	1 (8.3%)	15 (10.9%)	3 (6.9%)	3 (11.5%)	0.8837
unilateral	0 (0%)	18 (54.5%)	7 (16.3%)	4 (15.4%)	0.8605
C	0 (0%)	14 (10.1%)	3 (6.9%)	4 (15.4%)	0.7270
FA	12 (100%)	115 (83.3%)	41 (95.3%)	22 (84.6%)	0.2139

3.3. Reverse Analysis by Endometriosis Type

Patients were regrouped based on lesion characteristics into those with deep infiltrating endometriosis (DIE, n = 66), patients without DIE (n = 153), and those with compartment C involvement (n = 21). No significant differences were found in age or BMI between these

subgroups. The presence of DIE or compartment C involvement was not associated with higher or lower BMI (Table 6).

Table 6. Comparison of Age and BMI According to Endometriosis Type (Reverse Analysis).

Group	Patients Without DIE (P, O, T, FA)	Patients with DIE (A, B, C ± Others)	Patients with Compartment C Involvement
N	153	66	21
Age (mean ± SD)	32.97 ± 7.47	34.29 ± 6.72	33.05 ± 3.93
p-value of age		0.2179 *	0.9617 **
BMI (mean ± SD)	24.20 ± 5.00	23.93 ± 5.03	24.54 ± 5.74
p-value of BMI		0.7147 *	0.7745 **

* The *p*-value reflects the statistical comparison between Group 1 and Group 2. ** The *p*-value reflects the statistical comparison between Group 1 and Group 3.

When stratifying patients by lesion phenotype and BMI, we observed notable differences in symptom presentation (Table 7). Among patients with deep infiltrating endometriosis (DIE), those with a BMI $\geq$ 25 kg/m^2 reported significantly lower rates of dyschezia (45% vs. 84.8%, $p = 0.0056$) and no cases of dysuria ($p = 0.0047$). Additionally, chronic pelvic pain with VAS > 5 was less frequent in the higher BMI subgroup without DIE ($p = 0.0144$), suggesting BMI may influence symptom perception or manifestation.

Table 7. Comparison of Symptom Profiles by BMI in Patients With and Without Deep Infiltrating Endometriosis According to the #ENZIAN Classification.

	Patients Without DIE (P, O, T, FA)		Patients with DIE (A, B, C ± Others)		*p*-Value
BMI kg/m^2	**<25**	≥25	<25	≥25	
N of patients	104	49	46	20	
Age mean ± SD	32.72 ± 7.37	33.50 ± 7.75	34.34 ± 6.80	33.85 ± 6.72	0.5648
BMI mean ± SD kg/m^2	21.54 ± 2.12	29.98 ± 4.48	21.18 ± 2.11	30.17 ± 4.03	**0.0016**
Dysmenorrhea	102 (98.1%)	47 (95.9%)	45 (97.8%)	19 (95%)	0.7939
>5 VAS	94 (90.3%)	46 (93.8%)	43 (93.5%)	15 (75%)	0.0836
<5 VAS	8 (7.7%)	1 (2.1%)	2 (4.3%)	4 (20%)	0.0511
Dyspareunia	82 (78.8%)	33 (67.3%)	28 (60.9%)	11 (55%)	**0.0450**
>5 VAS	26 (25%)	14 (28.6%)	11 (23.9%)	4 (20%)	0.8905
<5 VAS	56 (53.8%)	19 (38.8%)	17 (36.9%)	7 (35%)	0.1088
Dyschezia	64 (61.5%)	29 (59.2%)	39 (84.8%)	9 (45%)	**0.0056**
>5 VAS	19 (18.3%)	8 (16.3%)	12 (26.1%)	2 (10%)	0.4172
<5 VAS	45 (43.3%)	21 (42.8%)	27 (58.7%)	7 (35%)	0.2157
Dysuria	48 (46.1%)	24 (48.9%)	20 (43.5%)	0	**0.0047**
>5 VAS	7 (6.7%)	3 (6.1%)	5 (10.9%)	0	0.7597
<5 VAS	41 (39.4%)	21 (42.8%)	15 (32.6%)	0	0.0174

Table 7. *Cont.*

	Patients Without DIE (P, O, T, FA)		Patients with DIE (A, B, C ± Others)		*p*-Value
Hematochezia	19 (18.3%)	12 (24.5%)	10 (21.7%)	2 (10%)	0.5397
Hematuria	20 (19.2%)	7 (14.3%)	10 (21.7%)	1 (5%)	0.3445
CPP	95 (91.3%)	43 (87.7%)	40 (86.9%)	16 (80%)	0.4944
>5 VAS	62 (59.6%)	16 (32.6%)	23 (50%)	8 (40%)	**0.0144**
<5 VAS	33 (31.7%)	27 (55.1%)	17 (36.9%)	8 (40%)	0.0514
Monthly need for analgesia (days) mean ± SD	5.03 ± 5.75	6.28 ± 5.40	5.27 ± 4.98	5.05 ± 4.59	0.5581
Nausea/ Vomiting	52 (50%)	33 (67.3%)	28 (60.8%)	12 (60%)	0.2056
Diarrhea/ Obstipation/ Bloating	93 (89.4%)	47 (98.9%)	45 (97.8%)	18 (90%)	0.2215
AUB	67 (64.4%)	39 (79.6%)	29 (63.1%)	14 (70%)	0.2410
Infertility	21 (20.2%)	14 (28.6%)	11 (23.9%)	7 (35%)	0.4411

CPP—chronic pelvic pain, VAS—visual analogue scale, AUB—abnormal uterine bleeding.

We performed a post hoc power analysis for the primary pain outcome (chronic pelvic pain with VAS > 5) comparing Group 1 vs. Group 2. Using $\alpha = 0.05$ and a target power of 80%, the analysis revealed an achieved power of 86.2%, indicating that our sample was sufficiently powered.

4. Discussion

Obesity and endometriosis are both common conditions characterized by systemic inflammation. The finding of an inverse association between these two conditions is intriguing but not yet fully understood [21,22]. Several studies have reported a relationship between BMI and endometriosis, suggesting a higher risk of endometriosis in patients with lower BMI [23]. Additionally, other research has indicated that DIE is more frequently associated with a low BMI [14]. These studies typically compared patients with endometriosis to control groups without the disease. In contrast, our analysis focused on evaluating the impact of BMI on symptom severity and lesion distribution according to the #ENZIAN classification in histologically confirmed cases of endometriosis. This retrospective analysis is, to our knowledge, the first to systematically evaluate the association between body mass index (BMI) and endometriosis phenotypes based on the anatomically detailed #ENZIAN classification system. Our results demonstrate that BMI does not significantly influence the anatomical distribution of endometriosis lesions across pelvic compartments (P, O, T, A, B, C, FA) or the prevalence of DIE in general. However, we observed notable differences in symptom intensity and infertility rates among BMI categories, highlighting a potential role of BMI in shaping the clinical presentation rather than the anatomical manifestation of the disease.

Specifically, we observed a significantly higher intensity of chronic pelvic pain (CPP) in patients with normal BMI compared to underweight and obese patients. This finding challenges assumptions that higher adiposity uniformly amplifies pain in endometriosis and may reflect differences in pain perception, reporting behaviors, or neuroinflammatory pathways between BMI groups [24,25]. Interestingly, the monthly need for analgesia was similar in the groups. However, many factors influence analgesic use, including individual pain tolerance, coping strategies, access to care, and personal preferences or concerns about

medication. For example, some patients with high pain levels may avoid taking more painkillers due to fear of side effects or dependence, while others with moderate pain might take regular medication as a precaution. Indeed, prior research in chronic pain populations has shown that higher analgesic consumption does not necessarily equate to higher pain intensity—and in some cases, an inverse relationship is observed [26]. This underscores that analgesic usage is an imperfect proxy for pain severity. After adjusting for age, patients with a BMI < 25 kg/m^2 had 2.22 times higher odds of experiencing high-intensity chronic pelvic pain compared to those with a BMI $\geq$ 25 kg/m^2 (unadjusted OR = 2.45, 95% CI: 1.36–4.43; age-adjusted OR = 2.22, 95% CI: 1.17–4.28), highlighting a significant association between lower BMI and severe CPP (Table 4). Interestingly, dyspareunia was significantly less prevalent in obese women, suggesting that increased BMI may be associated with altered pelvic biomechanics or variations in sexual activity; however, psychological and hormonal factors might also contribute [27]. Furthermore, infertility showed a marked increase with rising BMI, with the highest prevalence in the obese group (38.5%), which is consistent with the established literature linking obesity to subfertility due to both ovulatory dysfunction and endometrial receptivity alterations [28]. In our cohort, patients with obesity (BMI $\geq$ 30 kg/m^2) had more than twice the odds of infertility compared to non-obese patients (unadjusted OR = 2.18, 95% CI: 0.92–5.15; age-adjusted OR = 2.30, 95% CI: 0.97–5.47), suggesting a clinically relevant trend toward increased infertility risk among women with obesity (Table 4). Our analysis found no significant correlation between infertility and the #ENZIAN scores (Table 7).

Endometriosis pathophysiology is profoundly modulated by body fat–derived signals. Adipose tissue in obesity secretes pro-inflammatory cytokines and adipokines that amplify lesion inflammation and nociception. For example, peritoneal leptin—elevated in obese patients—correlates with disease stage and chronic pelvic pain [29]. By contrast, adiponectin (an anti-inflammatory, anti-angiogenic adipokine) is suppressed in endometriosis, so excess fat removes a protective brake on inflammation [22]. Obesity also enriches other proinflammatory adipokines (resistin, visfatin) in endometriotic lesions, driving local cytokine release [30]. These mediators sensitize pelvic nociceptors (via NGF, cytokines, etc.) and heighten pain signaling. In lean women, the immune milieu differs; low BMI is associated with an M2 macrophage–skewed profile that promotes angiogenesis and ectopic lesion survival [22]. This may paradoxically enhance nerve ingrowth into lesions and explain why lean patients often report worse pain despite less adiposity.

Endocrine effects also diverge by BMI. High adiposity raises aromatase activity and systemic estrogens, and obesity-induced insulin resistance elevates IGF-1 and adrenal androgens, which support ectopic cell survival while perturbing the hypothalamic–pituitary–ovarian axis [22]. Obesity thus often causes anovulation and luteal dysfunction, reducing menstrual reflux yet impairing fertility [22]. In sum, an obese milieu drives chronic inflammation and hormonal dysregulation that preserve lesions but compromise ovulation and endometrial receptivity, whereas low-BMI women with endometriosis experience an immune/endocrine state favoring lesion innervation and sensitization of pain pathways.

In this cohort, BMI modulated symptom profiles differently between patients with and without DIE (Table 6). Lean patients (BMI < 25) with DIE reported significantly more dyschezia, whereas overweight DIE patients (BMI $\geq$ 25) reported no dysuria. Chronic pelvic pain was also more severe in lower-BMI patients regardless of DIE status. These findings imply that lower adiposity amplifies pelvic pain and bowel symptoms, consistent with evidence linking low BMI to more extensive DIE [14]. Posterior DIE implants strongly correlate with dyschezia severity, suggesting that prevalent posterior lesions in lean women drive painful defecation [31]. Adipose-derived hormones and cytokines (e.g., leptin) promote systemic inflammation and angiogenesis in endometriosis. Obesity

may thus alter lesion activity or sensory thresholds [31]. Conversely, low BMI might intensify neurogenic hyperalgesia. Overall, the interplay of inflammatory, neurological, and hormonal/metabolic factors appears to shape these BMI-specific symptom patterns [31,32].

The prevalence of adenomyosis (FA) in our study was notably high across all BMI categories, in contrast to previous studies that reported a positive correlation between higher BMI and the presence of adenomyosis [33,34]. This discrepancy may be attributed to improved recognition of adenomyosis and advances in imaging techniques in recent years, which have likely enhanced detection rates compared to the period when the cited studies were conducted. These factors may help explain the uniformly high prevalence of adenomyosis observed across all groups in our analysis. Notably, no significant differences in lesion (P, O, T, A, B, C, FA) distribution were observed between BMI groups, even when patients were categorized according to DIE versus non-DIE phenotypes, or by rectal involvement (compartment C). These results are consistent with the findings of Chapron et al., who reported no significant difference in BMI between patients with deep infiltrating endometriosis (DIE) and those with superficial disease [35]. Our data, derived from a cohort with histologically confirmed disease and standardized #ENZIAN mapping, suggest that BMI may not be a strong determinant of lesion depth or localization.

5. Clinical Applications and Future Directions

Our findings suggest that BMI-related factors could have practical implications in endometriosis management. For instance, stratifying patients by BMI may help tailor therapy: obese women (with higher inflammation and estrogen levels) might benefit from adjunct anti-inflammatory or metabolic interventions, whereas underweight women may require different pain management strategies. Surgeons could also consider BMI as part of preoperative counseling: both obesity and certain #ENZIAN lesion patterns (e.g., A3, B3, C1) are associated with higher complication rates, so knowing a patient's BMI in advance might refine risk assessment. In addition, if higher adiposity is linked to more extensive pelvic involvement, medical treatment (e.g., aromatase inhibitors, hormonal suppression) might be optimized by weight or fat distribution. Conversely, recognizing a lean phenotype (often seen in endometriosis) could prompt the evaluation of metabolic factors that might influence recurrence risk. Overall, incorporating BMI into clinical decision-making (alongside #ENZIAN staging) could improve personalized care for endometriosis patients.

Future research should build on these observations. In particular, we recommend:

- Metabolic and hormonal profiling. Future studies should collect data on insulin resistance, lipid profiles, and circulating adipokines (leptin, adiponectin, inflammatory cytokines) in endometriosis patients. Correlating these markers with BMI and #ENZIAN stage may uncover mechanistic links between adiposity and lesion behavior.
- Prospective validation. Large, prospective cohorts should confirm whether BMI predicts disease progression or treatment response. For example, tracking symptoms and #ENZIAN scores over time in patients with different BMIs could test causality. Randomized trials of weight-loss or metabolic treatments in high-BMI endometriosis patients may also be warranted.
- Integration with biomarker discovery. Combining #ENZIAN staging with systemic biomarkers (e.g., serum cytokines, microRNAs) could improve diagnostic models. For instance, a composite score incorporating BMI and inflammatory markers might enhance early detection or recurrence risk stratification.
- Multidisciplinary management. Given the links between metabolism and gynecologic health, interdisciplinary approaches (gynecology, endocrinology, nutrition) should be explored. Trials of lifestyle interventions (diet, exercise) on endometriosis outcomes by BMI subgroup could inform comprehensive care.

Together, these directions aim to integrate metabolic and anthropometric insights into endometriosis research and care. In summary, understanding how adiposity interfaces with endometriosis can refine symptom stratification and guide both surgical and medical decision-making, ultimately leading to more personalized treatment strategies.

6. Conclusions

In conclusion, our findings indicate that BMI does not significantly influence the anatomical distribution of endometriosis lesions as defined by the #ENZIAN classification, but it does correlate with some symptom intensity and infertility. These results suggest that while BMI may not predict disease localization, it plays a role in shaping the clinical phenotype of endometriosis. Future prospective studies incorporating hormonal, metabolic, and imaging data could further elucidate the mechanistic pathways linking adiposity and endometriosis expression.

7. Strengths and Limitations

One of the strengths of this study is the rigorous application of the #ENZIAN classification, which provides a more nuanced assessment of lesion topography than the traditional rASRM staging. Additionally, by stratifying BMI both dichotomously and across WHO-defined categories, we captured trends that might have been missed in simpler binary analyses. The use of standardized preoperative questionnaires allowed for a homogeneous analysis. Furthermore, histological confirmation strengthens diagnostic accuracy.

However, the study has limitations. First, its retrospective design may introduce selection and reporting biases. However, we believe that even a prospective study would likely yield similar results. This is because, despite the retrospective nature, we used prospectively collected data, as it is our routine practice to systematically document all surgical findings using the #ENZIAN classification. Second, BMI, while widely used, is an imperfect proxy for body composition and does not account for fat distribution, which may have differential effects on hormonal and inflammatory profiles. Parameters such as fasting glucose, insulin resistance markers, sex-steroid levels, and waist-to-hip ratio would help disentangle the contributions of endocrine and metabolic factors from BMI per se. However, these assessments are not part of our routine preoperative evaluation, and the retrospective design precluded their inclusion. Future prospective studies should incorporate comprehensive metabolic and body composition profiling to clarify these mechanistic pathways. Third, although the preoperative symptom questionnaire was standardized, pain perception is inherently subjective and influenced by psychosocial factors not captured in our analysis. Fourth, we did not systematically assess coexisting chronic pain conditions such as fibromyalgia, interstitial cystitis, or irritable bowel syndrome, which could have influenced pain perception independently of BMI. However, as this limitation applies equally to all BMI groups, the potential bias is likely non-differential. Finally, the sample sizes in certain BMI subgroups—particularly the underweight and obese categories—were small, limiting the statistical power for some comparisons and requiring cautious interpretation of subgroup analyses.

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4. Discussion

In the studies presented in this thesis, the #ENZIAN classification was employed as the reference framework to systematically examine the relationship between symptom profiles and the anatomical distribution of endometriotic lesions, as well as to investigate the influence of BMI on disease presentation. In the first study, based on 233 preoperative questionnaires, specific symptoms correlated with distinct lesion localizations, whereas overall symptom severity did not differ between #ENZIAN-defined groups. In the second study, comprising 219 cases, BMI was not associated with lesion distribution across #ENZIAN compartments but showed significant correlations with clinical outcomes. The following sections will integrate the findings of both papers into the current body of knowledge and discuss their limitations as well as their implications for diagnostic approaches and clinical perspectives.

4.1. Symptom-based diagnosis?

Although research on endometriosis has intensified in recent years, significant gaps remain concerning the relationship between patients' subjective symptomatology and the objectively determined extent of the disease.[103] As classified by the #ENZIAN system, endometriosis can involve many organs and structures within the abdominal cavity, each innervated by pain-processing afferent nerve fibers.[88] Our findings showed that all three groups had similar overall symptom profiles, with dysmenorrhea being the most prominent symptom and CPP also commonly reported across all groups. However, patients with rectal DIE (group 3) presented with a significantly lower prevalence of CPP compared to the other groups.[104] This finding contrasts with reports from other authors, who have described noncyclic CPP as being more common in DIE involving the bowel.[105,106] The pathophysiology of endometriosis-associated pelvic pain is multifactorial, involving both local inflammatory processes and sensitization of the nervous system. The latter can be further differentiated into peripheral sensitization, characterized by a lowered activation threshold, and increased excitability of nociceptive neurons. In addition, central sensitization is characterized by an enhanced excitability of central nociceptive neurons in response to both normal and subthreshold stimuli. Moreover, cross-sensitization refers to nociceptive input from affected tissues altering pain perception in neighboring healthy structures.[107,108] Based on cross-sensitization mechanisms, CPP would be expected to occur at least as frequently, if not more commonly, in patients with bowel endometriosis. In contrast, our findings revealed a lower prevalence. Interestingly, our data demonstrated that severe dyschezia was significantly more prevalent in group 3.[104] A plausible explanation is that the pronounced

manifestation of dyschezia may mask the presence of CPP in this subgroup, suggesting that bowel involvement is more likely to cause localized rather than diffuse pain patterns.
In our analysis, the prevalence of gastrointestinal symptoms such as diarrhea, bloating, constipation, and nausea was high across all three groups, warranting further discussion.[104] While several studies have reported an association between bowel involvement and gastrointestinal manifestations[105,99,44], other authors have even suggested a direct correlation between the extent of DIE, particularly in the C and FI compartments, and the severity of gastrointestinal symptoms.[109] In contrast, Maroun et al. observed an exceptionally high prevalence of gastrointestinal complaints (90%) among women with endometriosis, regardless of lesion localization, with bloating being the most frequently reported symptom. As bowel endometriosis was present in only 7.6% of cases, these findings suggest that gastrointestinal symptoms are largely independent of disease localization.[110] Garavaglia et al. conducted a study comparing digestive symptoms before and after laparoscopic colorectal resection for deep infiltrating endometriosis involving the rectum or rectosigmoid colon. They reported a significant postoperative reduction in general pain symptoms, including dysmenorrhea, dyspareunia, and non-menstrual pelvic pain. In contrast, gastrointestinal complaints such as nausea, vomiting, and diarrhea persisted. These findings further underscore the relative independence of digestive symptoms from intestinal involvement.[111] Consistent with our findings, another author has reported that gastrointestinal dysfunction and pain symptoms appear to occur irrespective of the anatomical extent and localization of endometriosis.[112] On another note, a hyperexcitable nervous system is considered one of the underlying mechanisms contributing to the occurrence of comorbid CPP syndromes, such as irritable bowel syndrome (IBS), which also presents with diffuse digestive symptoms and has been reported to occur with a five-fold higher prevalence in women with endometriosis compared to those without.[113,114]

To date, the extent to which endometriosis in specific anatomical localizations may represent the source of dyspareunia remains unclear. Vercellini et al. reported a strong association between involvement of pouch of Douglas and the presence of dyspareunia.[115] Similarly, Jimenez et al. linked dyspareunia to deep infiltrating nodules located in the retrocervical region.[116] Furthermore, several authors including Porpora, Fauconnier, and Montanari et al. demonstrated a higher prevalence of dyspareunia in cases with uterosacral ligament involvement.[117,105,99] In our studies, mild dyspareunia was frequently reported across all groups; however, no statistically significant differences in prevalence were identified in relation to the affected #ENZIAN compartments. Notably, when comparing groups 1 and 3, dyspareunia was more frequently reported in the group with peritoneal involvement (group 1), which also showed a higher prevalence of adenomyosis, implying that adenomyosis could

have a greater impact on dyspareunia than deep-infiltrating endometriosis. Moreover, the impact of peritoneal endometriosis should not be underestimated.[104]

Dysuria was frequently reported across all groups, although only two patients with bladder endometriosis (involvement of the FB compartment) were included in our study. This contrasts with the findings of Metzemaekers et al., who reported that dysuria has predictive value for bladder endometriosis.[62] Based on our data, dysuria appears to be attributable to a localization other than the bladder, namely peritoneal involvement. This association has likewise been reported by Hsu et al., who identified a link to superficial peritoneal lesions.[118]

In summary, while symptom assessment may aid in identifying endometriosis, symptom severity alone is not a reliable indicator of disease extent. Although symptom questionnaires are insufficient for definitive diagnosis, they provide a valuable basis for initiating further evaluation and surgical referral.

4.2. The paradox of BMI: Is obesity a protective factor in endometriosis?

The relationship between BMI and endometriosis remains controversial, with systemic chronic inflammation serving as a potential biological link between the two conditions.[119] While some authors report no associations between BMI and endometriosis, an increasing number of studies suggest an inverse relationship.[120,100,121] In particular, endometriosis appears to be more prevalent among lean or underweight women, whereas in obese women it is often diagnosed at a more advanced stage.[122] Moreover, other studies have shown that deep infiltrating endometriosis is more frequently associated with a low BMI.[101,123] Against this background, our analysis focused on assessing the influence of BMI on both symptom severity and lesion distribution according to the #ENZIAN classification. Our findings indicate that BMI is not significantly related to the anatomical distribution of endometriosis lesions or to the prevalence of DIE. However, we observed marked differences in symptom severity and infertility rates across BMI categories, suggesting that BMI may influence the clinical presentation rather than the anatomical distribution of the disease.[124] The following discussion examines the contrasting explanations for the ambiguous relationship between BMI and endometriosis.

Through the secretion of proinflammatory cytokines (IL-6, TNF-α, IL-1β), adipose tissue creates an inflammatory microenvironment.[97] Given the anatomical proximity of VAT to pelvic organs frequently affected by endometriosis, paracrine signaling of such adipokines released into the pelvic cavity may contribute to the establishment or advancement of endometriosis.[98]

Leptin, an adipokine with metabolic properties, regulates appetite in eutrophic individuals, but is also recognized as a proinflammatory and angiogenic factor.[125] Elevated leptin concentrations have been observed in the peritoneal fluid of women with endometriosis, regardless of disease stage; since leptin production is increased in obesity and promotes proinflammatory signaling, it has been proposed as a key mediator linking adipose tissue to endometriosis.[126] However, leptin levels in the peritoneal fluid were elevated irrespective of BMI, suggesting that local production within the peritoneal environment, by visceral adipocytes, immune cells, or endometriotic lesions themselves, may be more relevant than the systemic increase associated with obesity.[127]

Adiponectin, unlike most other adipokines, is reduced in obese individuals and possesses anti-inflammatory, anti-apoptotic, anti-fibrotic, and anti-angiogenic properties, thereby playing a distinct regulatory role in biological processes relevant to the pathogenesis of endometriosis.[128] Conversely, several studies have reported decreased serum and peritoneal fluid adiponectin concentrations in women with endometriosis, suggesting a potential protective role of this adipokine against the disease.[129,130] Furthermore, adiponectin exerts anti-inflammatory effects by shifting macrophage polarization from the M1 to the M2 phenotype, the latter predominating in endometriotic lesions. Leanness tends to promote M2 macrophages, while adiposity is more often associated with a predominance of M1 macrophages.[98,119] Thus, the link between adiponectin, BMI, and endometriosis highlights the paradoxical and still controversial nature of the inverse association between BMI and endometriosis.

Beyond these immunological mechanisms, endocrine pathways further illustrate the complex interplay between adiposity and endometriosis. On the one hand, aromatase activity in adipose tissue increases estrogen production, and since endometriosis is an estrogen-dependent disease, a positive correlation would be expected.[131] On the other hand, obesity-related insulin resistance elevates IGF-1 and adrenal androgens, thereby disrupting the hypothalamic–pituitary–ovarian axis and contributing to anovulation and luteal dysfunction, which contradicts the theory of retrograde menstruation.[98] Additional explanations associate low BMI in endometriosis with appetite suppression caused by chronic pain and with reduced food tolerance resulting from gastrointestinal side effects of analgesics, particularly non-steroidal anti-inflammatory drugs (NSAIDs).[132]

Building on these considerations, our analysis demonstrated that women with a normal BMI reported the greatest intensity of CPP, contradicting the prevailing assumption that adiposity uniformly exacerbates pain in endometriosis and instead suggesting BMI-dependent variations in pain perception or neuroinflammatory mechanisms.[133] Notably, the monthly

requirement for analgesics did not differ between groups. However, analgesic consumption cannot be considered a reliable proxy for pain severity, as pain perception and processing are inherently subjective and vary considerably between individuals.[38] The reduced prevalence of dyspareunia among obese women in our cohort contrasts with the findings of Shah et al., who reported an association between obesity and increased sexual pain.[91] This discrepancy further underscores the complex relationship between BMI and symptomatology. Modified pelvic biomechanics, changes in sexual activity, or hormonal and psychological factors associated which obesity are some possible explanations;[134] but to date, very little research has been done on this relationship.

Consistent with previous studies, our data revealed a positive correlation between BMI and infertility. An American study reported that obese women exhibit reduced fertility even when ovulatory function is preserved, indicating sub-fertility in eumenorrheic women.[135] Similarly, a Spanish retrospective study reported that female obesity negatively affects in-vitro fertilization (IVF) outcomes, with pregnancy and live birth rates progressively declining with each unit increase in BMI. However, embryo quality was not impaired, indicating obesity-related alterations in the uterine environment.[136] In support of this, a mouse model linked obesity-associated subfertility to impaired decidualization of endometrial stromal cells and suggested that defective autophagy may be the underlying mechanism.[137] Notably, our analysis found no significant connection between infertility and #ENZIAN scores, suggesting that in our cohort, fertility outcomes were not affected by lesion localization or extent as defined by the #ENZIAN system.[124]

Taken together, our findings suggest that BMI shapes the clinical presentation and fertility outcomes in women with endometriosis, but its influence seems to arise from complex immunological, endocrine, and behavioral mechanisms rather than from the anatomical extent or localization of the disease as defined by the #ENZIAN classification.

4.3. Limitations and perspectives

Despite the insightful findings of this thesis, some limitations must be considered when interpretating the results. The cohort of both studies was recruited from our institution, the largest endometriosis center in Germany, thereby ensuring broad representation of the clinical variability observed in affected women. Furthermore, using the #ENZIAN score as part of routine clinical practice ensured standardized and thorough documentation of lesion characteristics for all patients. Nevertheless, the retrospective, single-center design and the use of preoperative questionnaires in both studies may have introduced recall bias in symptom reporting. In addition, BMI was used as a general proxy for obesity, however, it does not sufficiently reflect adipose tissue composition. A more precise assessment would

include measures of adipose tissue distribution, particularly the amount of VAT. Looking beyond BMI alone, additional anthropometric parameters such as waist circumference, waist-to-hip ratio, and indicators of sarcopenic adiposity may provide a more comprehensive understanding of the relationship between body composition and endometriosis.[138] The single-center design may also restrict the extent to which our findings can be generalized to other populations and health care systems. Finally, without longitudinal follow-ups, the potential impact of BMI on symptom progression and fertility outcomes cannot be assessed. Future research should therefore take a prospective approach, with prospective designs, larger cohorts, control groups, and extended follow-up, to strengthen and extend upon these findings.

Perspectives in endometriosis

Future research should move beyond BMI as the only anthropometric measure and incorporate more detailed biological and clinical assessments alongside the #ENZIAN classification. Collecting hormonal and metabolic laboratory data (lipid profiles, markers of insulin resistance) together with inflammatory biomarkers such as cytokines and adipokines (including adiponectin and leptin) could provide deeper insights into the cellular and molecular pathways that connect body composition with endometriosis. In addition, prospective studies are required to assess the impact of lifestyle interventions, particularly dietary weight reduction, on disease activity and symptom burden. Beyond lifestyle modification, therapeutic approaches including bariatric surgery and pharmacological weight-loss agents should also be examined for their potential to improve reproductive outcomes and alleviating endometriosis-associated symptoms in women with obesity.[132]

From a clinical perspective, incorporating BMI into the preoperative assessment could refine risk stratification, given that higher BMI is associated with increased perioperative risk and complication rates. In such cases, initial hormonal therapy, including the consideration of aromatase inhibitors in combination with dienogest may represent a more appropriate therapeutic strategy prior to surgery.[39] Conversely, women with a lower BMI, who in our study exhibited more severe pain, may particularly benefit from referral to specialized multimodal pain centers. Furthermore, a more detailed assessment of psychosocial determinants of pain perception, together with the systematic evaluation of coexisting chronic pain conditions, is indicated. Finally, a life-course perspective may offer valuable insights. Determining BMI at the onset of symptoms in childhood or adolescence and tracking its trajectory over time could clarify the extent to which obesity contributes to the development of endometriosis.[139] Moreover, it remains to be elucidated whether women with endometriosis

display distinct eating attitudes compared with controls, and whether chronic pain promotes emotional eating that, through increased caloric intake, may further reinforce obesity.[140]

4.4. Conclusion

This cumulative thesis demonstrates that the #ENZIAN classification provides a valuable framework for systematically analyzing the relationship between symptom profiles, BMI, and lesion distribution in endometriosis. Across two large retrospective studies, our findings showed that lesion localization was not associated with overall symptom severity or BMI. However, clear correlations were observed between specific symptoms and anatomical compartments, as well as BMI-related differences in clinical presentation. These findings emphasize the importance of taking both patient-reported symptoms and metabolic factors into account when making diagnostic and treatment decisions. Overall, this work contributes to a broader understanding of endometriosis as a multifactorial condition at the intersection of gynecology, immunology, and endocrinology. Future research involving hormonal and metabolic profiling is required to fully understand the complex relationship between obesity and endometriosis. Looking ahead, management of endometriosis should expand beyond surgery and hormonal therapy to encompass multimodal pain approaches, targeted lifestyle interventions such as weight reduction, and integrative strategies that take into account both the biological and psychosocial aspects of the disease.

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6. Appendix

6.1. List of figures

6.2. List of tables

Table 1: Preoperative Questionnaire

Endometriosis Questionnaire EVK Weyertal

Patient name:

Date:

Symptoms and clinical examination	**Peritoneal Endometriosis**	**Physician´s Notes**
Vaginal Palpation		
Pain on palpation in pouch of Douglas	yes/no	
Pain on palpation on sacrouterine ligaments	Right: yes/no Left: yes/no	
Pain on palpation on bladder wall	yes/no	
Symptoms and clinical examination	**Deep infiltrating Endometriosis (DIE)**	
Speculum insertion: livid endometriosis	yes/no	
Vaginal palpation: scar/ nodule	yes/no	
Rectal palpation: scar/nodule	yes/no	
Sonography		
Bladder nodule	yes/no	
Rectovaginal septum nodule	yes/no	
Bowel nodule	yes/no	
Sliding Sign Test	positive/negative	
Hydronephrosis	Right: yes/no Left: yes/no	
Symptoms and clinical examination	**Adenomyosis uteri**	

Uterine tenderness on vaginal palpation	yes/no	
Sonography		
Uterine length (cm) 1) <5,5, >9 2) 5,5-6; 7,5-9 3) 6-7,5		
MUSA criteria: a) Globular b) Asymmetrical thickening c) Cysts d) Hyperechoic islands e) Fan-shaped shadowing f) Echogenic sub-endometrial lines and buds g) Translesional vascularity h) Irregular junctional zone i) Interrupted junctional zone		
Symptoms	**Peritoneal Endometriosis**	NRS >5: requiring pain medication NRS <5: no need for pain medication
Pain during menstruation (dysmenorrhea)	yes/no <5/>5	
Onset of pain during menstruation since the first menstrual period (I° dysmenorrhea)	yes/no	
Abdominal pain outside of menstrual bleeding	yes/no <5/>5	
Chronic abdominal Pain	yes/no	
Pain days per month	<5/>5	
Monthly need for analgesia in days		
Radiating Pain (back/hips/ legs)	yes/no	
Pain during sexual intercourse (dyspareunia)	yes/no	
Intercourse feasible	feasible/ unfeasible	

Discontinuation of Intercourse	yes/no	
Nausea/ vomiting during menstruation	yes/no	
Diarrhoea/ obstipation/ bloating during menstruation	yes/no	
Age at first manifestation of symptoms <20, 20-30, 30-40, >40 Years		
Age at recurrence of symptoms <20, 20-30, 30-40, >40 Years		
Improvement under hormonal therapy	yes/no IF yes: Substance:	
Previous operations due to endometriosis	yes/no	
Improvement after the operation	yes/no	
Unfulfilled desire to have children	yes/no	
No pregnancy up to the time of presentation	yes/no	
Pregnancy in medical records (births/Abortions/interruptions)	yes/no	
Familial endometriosis	yes/no	
Symptoms and clinical examination	**Deep infiltrating Endometriosis (DIE)**	
Pain during defecation during menstruation (dyschezia)	yes/no <5/>5	
Interruption of defecation due to pain	yes/no	
Bleeding during defecation (haematochezia)	yes/no	
Pain during micturition during menstruation (dysuria)	yes/no <5/>5	
Bleeding during micturition (haematuria)	yes/no	

Pain during sexual intercourse (dyspareunia)	yes/no <5/>5	
Intercourse feasible	feasible/ nonfeasible	
Discontinuation of Intercourse	yes/no	
Improvement under hormonal therapy	yes/no IF yes: Substance:	
Symptoms and clinical examination	**Adenomyosis uteri**	
Pain during menstruation (Dysmenorrhea)	yes/no <5/>5	
Onset of pain during menstruation since the first menstrual period (I° dysmenorrhea)	yes/no <5/>5	
Bleeding disorder	yes/no	
Intervention Uterus (abrasion, curettage, fibroid treatment, C-section)	yes/no	
Births	yes/no IF yes: number	

Signature:

7. Publications related to this thesis

Piriyev E, Mennicken C, Schiermeier S, Römer T. Is there a relationship between symptoms and types of endometriosis according to #ENZIAN? A comparative study of preoperative questionnaires. *Arch Gynecol Obstet* 2025; : 1–9.

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