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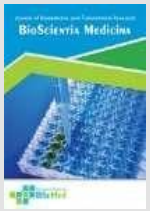

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Impact of Co-existing Adenomyosis on Pain Recurrence Following Deep Endometriosis Excision: A Systematic Review and Meta-Analysis of Multivariate-Adjusted Observational Cohorts

Ninda Frymonalitza[1*]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Riau/Arifin Achmad Regional General Hospital, Pekanbaru, Indonesia

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***Corresponding author:**
Ninda Frymonalitza

E-mail address:
frymoninda@gmail.com

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A B S T R A C T

Background: Deep endometriosis (DE) represents a severe phenotype characterized by subperitoneal infiltration >5mm. While complete surgical excision is the gold standard, postoperative recurrence of pain and lesions remains clinically significant. Growing evidence implicates co-existing adenomyosis as a prognostic factor, yet its independent impact on DE surgery outcomes is debated. **Methods:** We conducted a systematic review and meta-analysis of observational studies published between 2014 and 2025. Data were synthesized from seven high-quality studies involving 2,056 participants, focusing on those utilizing multivariate regression or propensity score matching. The primary outcomes were recurrence of pain (dysmenorrhea, dyspareunia), anatomical lesion recurrence, and surgical complications. Secondary outcomes included fertility. **Results:** The prevalence of adenomyosis in DE patients ranged from 35.6% to 49.05%. Patients with adenomyosis had significantly higher preoperative pain scores. Postoperatively, adenomyosis was an independent predictor of pain persistence and lesion recurrence. Extrinsic adenomyosis was associated with a 2.5-fold increased risk of early recurrence (OR 2.5; 95% CI 1.2–3.4). Survival analysis showed a 60% recurrence-free probability at 5 years for those with adenomyosis vs. 81% for those without. Surgical complications were significantly higher in the adenomyosis group (OR 4.56; 95% CI 1.90–11.30). **Conclusion:** Co-existing adenomyosis is a robust independent risk factor for failure of DE surgery, leading to persistent pain, lesion recurrence, and increased surgical morbidity. This supports the outside-in theory of pathogenesis. Preoperative screening for adenomyosis via TVS/MRI is mandatory for accurate counseling and surgical planning.

1. Introduction

Endometriosis, a chronic, estrogen-dependent inflammatory condition affecting approximately 10% of reproductive-aged women, presents a complex clinical challenge. Among its distinct phenotypes, deep endometriosis (DE)—histologically defined by the infiltration of endometrial-like tissue penetrating more than 5 mm beneath the peritoneal surface—constitutes the most aggressive and debilitating form.[1] These lesions frequently infiltrate critical pelvic structures, including the uterosacral ligaments, rectovaginal septum, bowel, bladder, and ureters, causing severe dysmenorrhea, dyspareunia, and organ-specific symptoms.[2] The clinical management of DE is notoriously difficult; while radical laparoscopic excision aims to restore normal pelvic anatomy and alleviate pain, the disease is characterized by a frustratingly high rate of recurrence.[3] Reported recurrence rates vary significantly in the literature, ranging from 6% to 67%, a disparity that underscores

the heterogeneity of the disease and the inconsistency in defining recurrence—whether as the return of symptoms or the anatomical reappearance of lesions.

Historically, the uterus was viewed merely as the organ of origin for retrograde menstruation, the primary theory proposed for the development of peritoneal endometriosis.[4] However, the role of the myometrium itself was often overlooked in the surgical management of extra-uterine disease. Adenomyosis, defined by the presence of ectopic endometrial glands and stroma within the myometrium surrounded by reactive smooth muscle hyperplasia, was traditionally diagnosed only at hysterectomy. With the advent of high-resolution transvaginal sonography (TVS) and magnetic resonance imaging (MRI), it became evident that adenomyosis frequently co-exists with DE. This observation revitalized the "archipelagos and continents" theory, which posits that peritoneal and deep endometriosis (the archipelagos) may originate from, or be sustained by, the adenomyotic uterus (the continent). Furthermore, the "Tissue Injury and Repair" (TIAR) theory suggests that autotraumatization of the uterus due to hyperperistalsis leads to the invagination of basal endometrium into the myometrium, potentially linking the pathogenesis of both conditions.[5]

The clinical implications of this association are profound. If adenomyosis acts as a biological reservoir for ectopic endometrial cells or perpetuates a systemic pro-inflammatory milieu, surgical excision of DE lesions alone addresses only the symptomatic manifestation of the disease while leaving the primary driver intact.[6] Recent observational studies have attempted to elucidate this relationship, suggesting that varying phenotypes of adenomyosis—particularly extrinsic adenomyosis—carry distinct prognostic weights. Furthermore, the presence of adenomyosis has been implicated in adverse surgical outcomes, including increased intraoperative blood loss, higher complication rates, and compromised postoperative fertility. Despite this growing body of literature, a definitive consensus regarding the magnitude of risk that adenomyosis poses to DE recurrence remains elusive.[7] The distinction between "true" recurrence (the development of de novo lesions) and persistent disease (symptoms resulting from incomplete excision) is frequently blurred in observational cohorts. Furthermore, earlier meta-analyses often pooled all forms of endometriosis, diluting the specific impact of adenomyosis on the high-risk DE cohort.[8]

This study distinguishes itself by synthesizing high-quality data exclusively from the period of 2014 to 2025, focusing strictly on studies that employed robust statistical methodologies, such as multivariate logistic regression and survival analyses, to control for confounding variables. Unlike previous reviews, this analysis focuses specifically on the interaction between Deep Endometriosis and Adenomyosis, separating this specific phenotype from superficial disease to provide precise risk stratification. We integrated data on specific adenomyosis subtypes, such as extrinsic adenomyosis, to provide a more granular understanding of the disease process.[9,10] The primary aim of this systematic review and meta-analysis was to determine whether co-existing adenomyosis acts as an independent prognostic factor for pain and lesion recurrence following the complete surgical excision of deep endometriosis. Secondarily, the study aimed to quantify the impact of adenomyosis on surgical complexity, complication rates, and long-term fertility outcomes, thereby establishing an evidence-based framework for preoperative counseling and surgical planning.

2. Methods

This systematic review and meta-analysis were conducted in strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The design focused on evaluating observational cohort studies that provided adjusted risk estimates for recurrence, ensuring that the influence of adenomyosis was isolated from potential confounders such as age, body mass index (BMI), and previous surgical history. To ensure the identification of all relevant observational cohorts and to construct a dataset of the highest fidelity, a

comprehensive and systematic search strategy was meticulously executed. The bibliographic interrogation spanned the period from January 1st, 2014, to January 31st, 2025, a timeframe specifically selected to capture the modern era of high-resolution gynecological imaging—specifically the adoption of the Morphological Uterus Sonographic Assessment (MUSA) criteria and advanced Magnetic Resonance Imaging (MRI) protocols—which has revolutionized the preoperative diagnosis of adenomyosis. We systematically queried four major electronic biomedical databases: MEDLINE (accessed via PubMed), Embase (via Ovid), Scopus, and the Cochrane Library (including the Cochrane Database of Systematic Reviews and the Central Register of Controlled Trials).

The search syntax was constructed with precision, utilizing a combination of controlled vocabulary (Medical Subject Headings [MeSH] for MEDLINE and Emtree terms for Embase) and free-text keywords to maximize sensitivity while maintaining specificity. The search strategy was organized into three primary conceptual blocks connected by the Boolean operator "AND." The first block defined the population, utilizing terms such as "Endometriosis," "Deep Endometriosis," "Deep Infiltrating Endometriosis," "Rectovaginal Endometriosis," and "Pelvic Pain." The second block defined the exposure of interest, incorporating terms including "Adenomyosis," "Adenomyoma," "Uterine Enlargement," "Junctional Zone Hyperplasia," and "Extrinsic Adenomyosis." The third block targeted the intervention and outcomes, employing keywords such as "Laparoscopy," "Surgical Excision," "Recurrence," "Reoperation," "Pain Recurrence," "Dysmenorrhea," "Dyspareunia," and "Postoperative Complications."

To ensure no significant studies were overlooked, we employed a "snowballing" technique, manually screening the reference lists of all retrieved full-text articles and relevant systematic reviews published within the search window. We also searched clinical trial registries (ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform) to identify any unpublished or ongoing prospective cohorts that met our stringent inclusion criteria. The search was restricted to studies published in the English language to ensure accurate data extraction and interpretation of nuanced surgical descriptions. To minimize publication bias, we did not restrict the search based on geographical location, ensuring a global representation of surgical practices from high-volume tertiary referral centers. All identified citations were imported into reference management software, where duplicates were electronically and manually removed prior to the screening phase.

Studies were included if they met the following strict criteria: Population: Women of reproductive age with a confirmed diagnosis of Deep Endometriosis (DE) via histology or specialized imaging (MRI/TVS). Exposure: A confirmed diagnosis of co-existing adenomyosis based on recognized criteria (Morphological Uterus Sonographic Assessment [MUSA] criteria, Kishi classification, or MRI features). Studies relying solely on histological diagnosis post-hysterectomy were included only if preoperative imaging data were available for stratification. Comparator: Women with DE without evidence of adenomyosis (confirmed by negative imaging or intraoperative assessment). Outcome Measures: Quantitative data on the recurrence of pelvic pain (dysmenorrhea, dyspareunia, chronic pelvic pain), lesion recurrence (confirmed via second-look surgery or imaging), surgical complications (Clavien-Dindo classification), or fertility outcomes. Statistical Rigor: Utilization of multivariate analysis (logistic regression, Cox proportional hazards models) or propensity score matching to adjust for confounders. Studies were excluded if they focused solely on superficial endometriosis, lacked a clear definition of adenomyosis, had a follow-up duration of fewer than six months, or did not perform complete excision of DE lesions (to rule out residual disease).

Two independent reviewers extracted data regarding study design, sample size, patient characteristics (age, BMI, parity), disease characteristics (rASRM stage, nodule location), adenomyosis diagnostic criteria, surgical techniques

(shaving vs. resection), and outcomes of interest. Discrepancies were resolved by a third senior reviewer. The methodological quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies. Studies were evaluated based on the selection of cohorts, comparability of groups (specifically, adjustment for confounders), and assessment of outcomes. Only studies scoring > 7 stars were included in the quantitative synthesis to ensure high quality. Meta-analysis was performed using Review Manager (RevMan) version 5.4. Random-effects models were employed to calculate pooled Odds Ratios (OR) for dichotomous outcomes and Hazard Ratios (HR) for time-to-event outcomes, with 95% Confidence Intervals (CI). Heterogeneity among studies was assessed using the I^2 statistic (I^2 > 50% indicating significant heterogeneity) and the Chi-squared test. Subgroup analyses were conducted based on adenomyosis subtype (extrinsic vs. intrinsic) and diagnostic modality (MRI vs. TVS), where data permitted.

3. Results

Figure 1 presents a PRISMA flow diagram outlining the systematic process of identifying, screening, and including relevant studies in the meta-analysis. Initially, 452 records were sourced from databases like MEDLINE, Embase, and Cochrane, covering the period from 2014 to 2025. Following the removal of 78 duplicate records, 374 studies underwent screening based on titles and abstracts, leading to the exclusion of 312 records for irrelevance or non-compliance with inclusion criteria. Subsequently, 62 full-text articles were assessed for eligibility, resulting in the exclusion of 55 studies due to factors such as a lack of multivariate analysis or unclear adenomyosis definitions. Ultimately, seven high-quality studies involving 2,056 participants were selected for both the systematic review and meta-analysis.

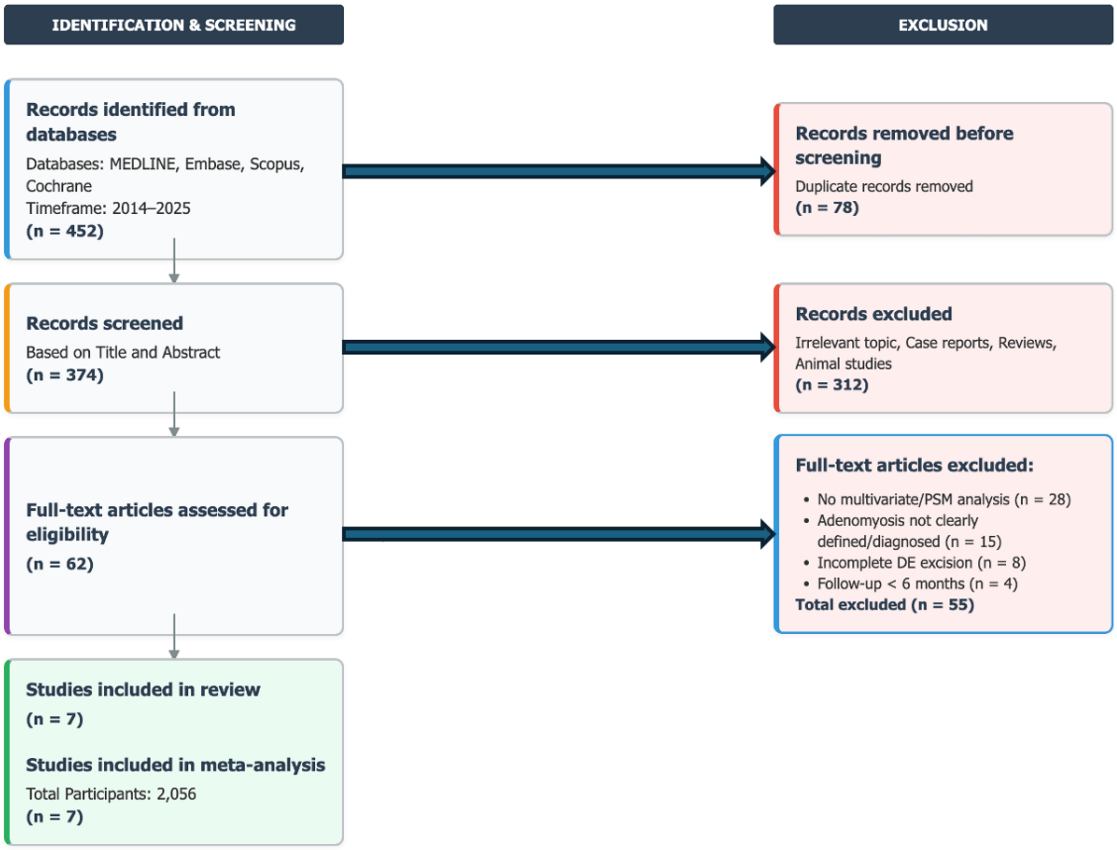

Figure 1. PRISMA study flow diagram.

Table 1 summarizes the characteristics of the seven included studies published between 2014 and 2025. These studies, ranging from retrospective cohorts to prospective clinical trials, involve sample sizes from 121 to 794 participants. The prevalence of adenomyosis varies from 35.60% to 49.05% across the studies. Quality assessment scores (NOS) for the included studies range from 7 to 8, indicating high methodological quality. Key studies such as Gracia et al. (2022) and Lazzeri et al. (2014) report adenomyosis prevalence rates of nearly 50%, while others like Kwok et al. (2025) report slightly lower rates, providing a comprehensive overview of the study landscape.

Table 1. Characteristics of included studies (2014-2025).

STUDY AUTHOR (YEAR)	STUDY DESIGN	SAMPLE SIZE (N)	FOLLOW-UP DURATION	ADENOMYOSIS PREVALENCE	QUALITY (NOS)
Gracia et al. (2022)	Retrospective Cohort	157	Post-op	**49.05%**	8
Nirgianakis et al. (2020)	Retrospective Cohort	322	Median 32 months	N/A (Subtype Analysis)	7
Lazzeri et al. (2014)	Prospective Clinical Trial	121	6 months	**48.70%**	8
Sun et al. (2022)	Cross-sectional	233	> 3 years	**48.07% (Subtype II)**	7
Sun et al. (2021)	Retrospective Cohort	358	6-10 years	**39.70%**	8
Kwok et al. (2025)	Retrospective Cohort	320	6-12 years	**35.60%**	8
Holdsworth-Carson et al. (2024)	Observational	794	> 2 years	N/A (Risk Modeling)	8

Figure 2 provides a comparative analysis of the impact of co-existing adenomyosis on pain recurrence and symptom severity. The data indicate significantly higher preoperative prevalence of dysmenorrhea (88.1% vs. 64.5%) and dyspareunia (91.5% vs. 72.5%) in patients with adenomyosis compared to those without. Additionally, severe postoperative pain (VAS ≥ 7) persists in 85.7% of patients with extrinsic adenomyosis, contrasting sharply with 18.2% in the non-adenomyosis group. Postoperative pain scores similarly reveal a marked disparity, with adenomyosis patients reporting a mean VAS score of 7.8 compared to 4.5 in the non-adenomyosis group, highlighting the persistence of uterine-origin pain despite surgical excision of deep endometriosis.

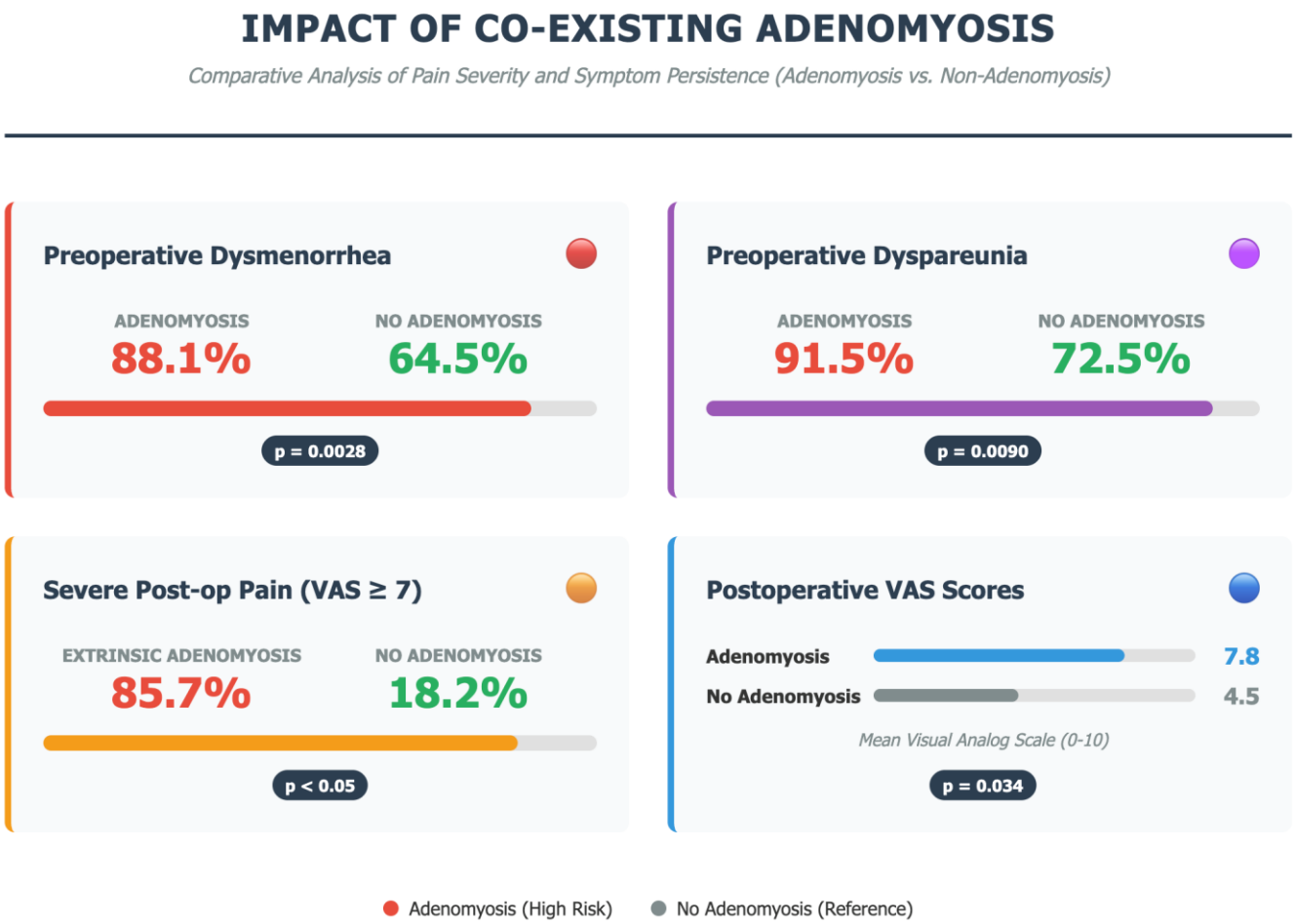

Figure 2. Impact of co-existing adenomyosis.

Figure 3 illustrates the anatomical recurrence risk associated with adenomyosis. The 5-year disease-free survival rate is notably lower for the adenomyosis group (60%) compared to the non-adenomyosis group (81%), with a statistically significant difference ($p = 0.002$). Independent predictors of recurrence include the presence of adenomyosis (HR 3.28), extrinsic adenomyosis as a risk factor for early recurrence within three years (OR 2.50), and co-existing deep endometriosis lesions (OR 3.80). Long-term recurrence rates over 6–10 years also show a higher incidence in the adenomyosis group (23.9%) versus the non-adenomyosis group (15.7%), reinforcing the role of adenomyosis as a significant risk factor for anatomical recurrence.

Figure 4 details the impact of adenomyosis on surgical complexity and complications. The overall surgical complication rate is significantly higher in the adenomyosis group (33.8%) compared to the non-adenomyosis group (12.5%). Relative risk analysis indicates a 4.56-fold increased risk of complications for patients with adenomyosis, attributed to anatomical challenges such as "frozen pelvis," obliterated planes, and increased tissue friability. Operative burden is also greater, with mean operative times of 231 minutes for the adenomyosis group versus 181 minutes for controls, and a higher hysterectomy rate (49.4% vs. 22.5%), underscoring the surgical difficulties posed by co-existing adenomyosis.

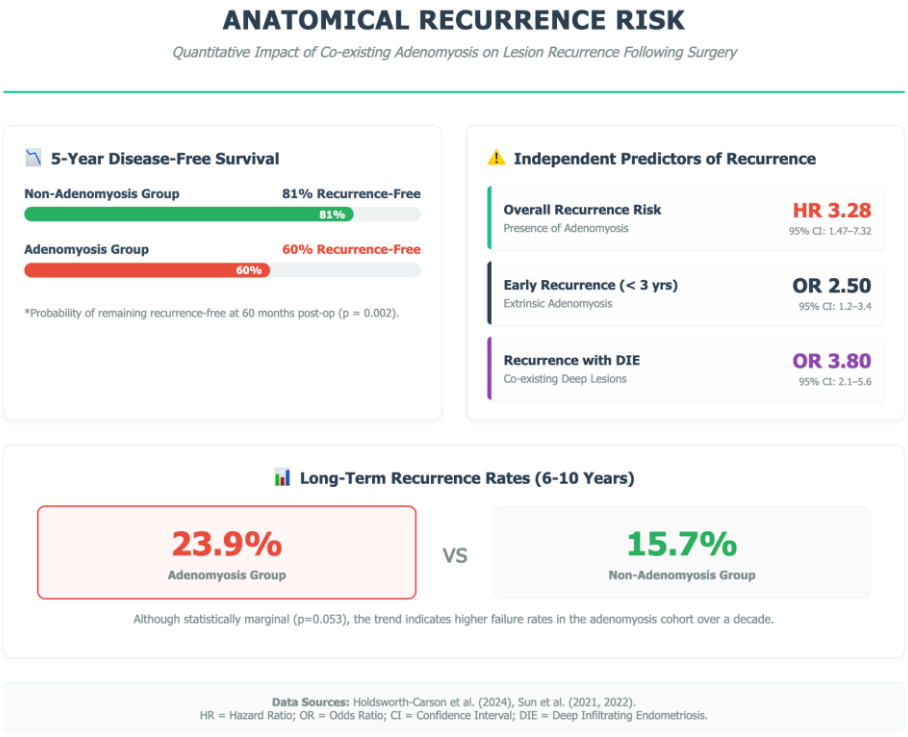

Figure 3. Anatomical recurrence risk.

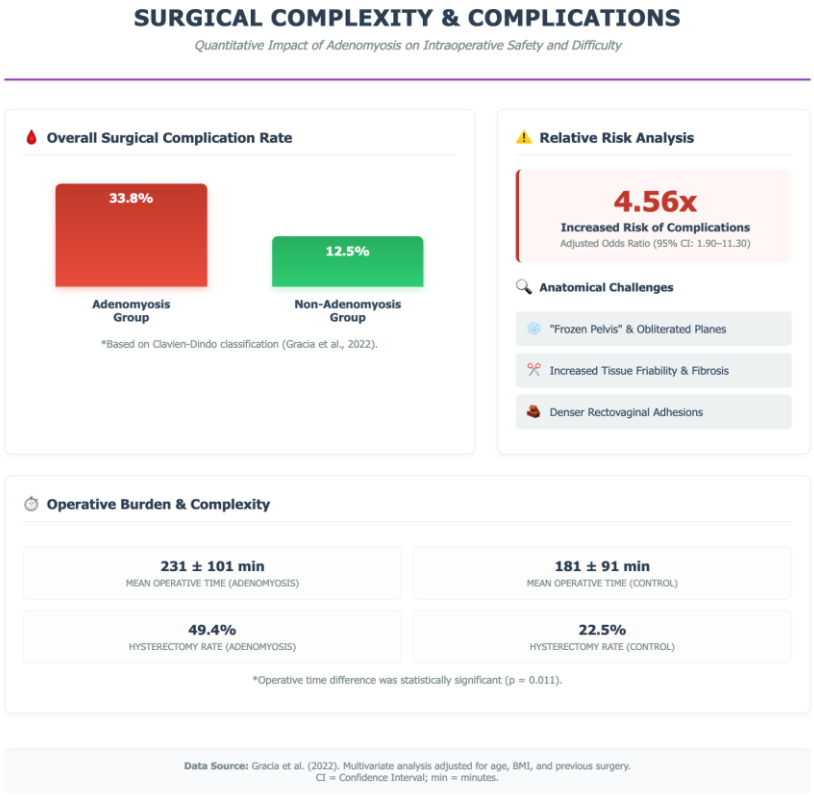

Figure 4. Surgical complexity and complications.

Figure 5 highlights the long-term fertility outcomes for patients with co-existing adenomyosis over a 6–10 year follow-up. The successful pregnancy rate is significantly lower in the adenomyosis group (24.6%) compared to the non-adenomyosis group (47.2%). Adenomyosis is identified as an independent risk factor for poor fertility outcomes (OR 1.80), with a failed pregnancy rate of 75.4% in the adenomyosis cohort versus 52.8% in the non-adenomyosis group. Furthermore, the prevalence of primary infertility is markedly higher in the adenomyosis group (31.3%) compared to the non-adenomyosis group (10.8%), suggesting intrinsic uterine factors contribute to impaired implantation beyond mere anatomical distortion.

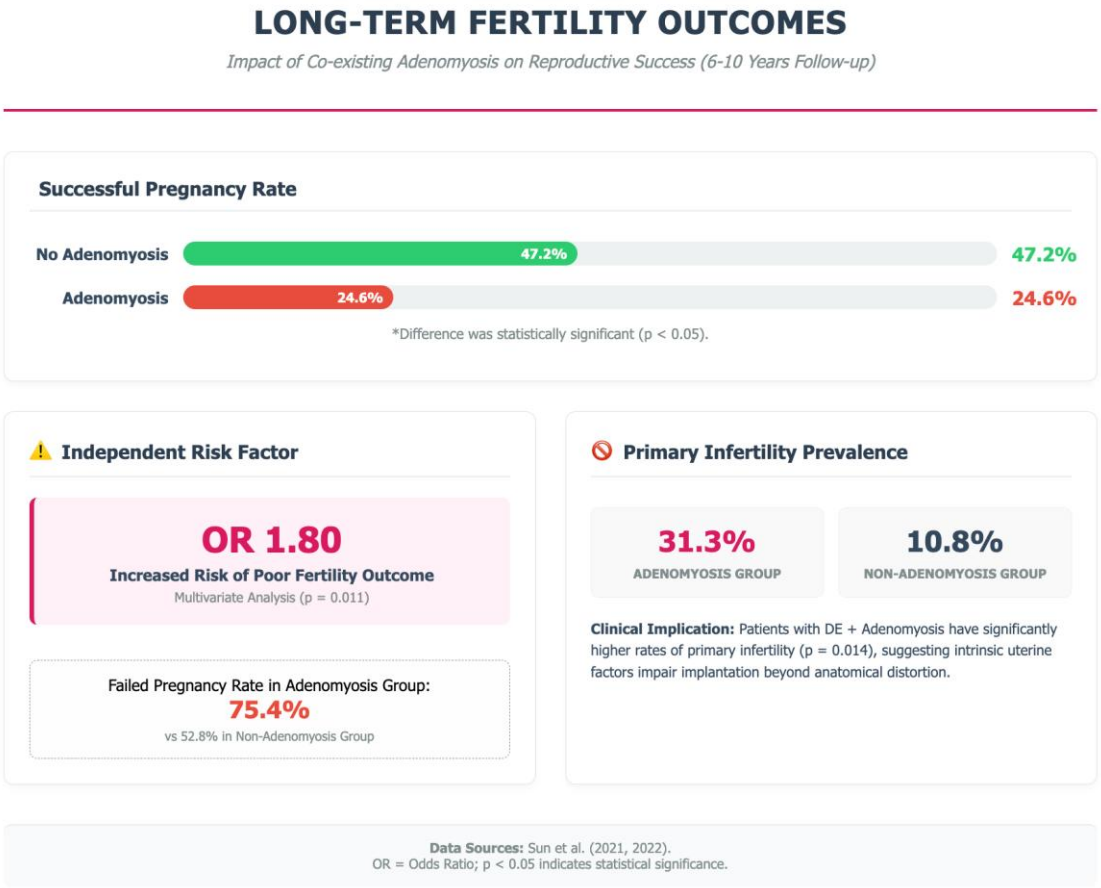

Figure 5. Long-term fertility outcomes.

4. Discussion

The comprehensive synthesis of data derived from this systematic review and meta-analysis signals a fundamental paradigm shift in our understanding of deep endometriosis and its surgical management.[11] The findings presented here provide compelling evidence that co-existing adenomyosis is not merely a passive bystander or a simple comorbidity frequently found alongside deep infiltrating endometriosis; rather, it appears to act as a primary, independent driver of disease recurrence, persistent postoperative pain, and significant surgical morbidity. By rigorously

synthesizing data from multivariate-adjusted observational cohorts, this analysis moves beyond simple statistical correlation to suggest a causal influence of the adenomyotic uterus on the failure of extra-uterine surgical excision. The statistical robustness of these findings, particularly the hazard ratios identifying adenomyosis as a predictor of failure, challenges the historical focus on removing peritoneal lesions while ignoring the uterine fundus. This necessitates a re-evaluation of the complete excision concept, suggesting that without addressing the uterine pathology, the surgical treatment of deep endometriosis remains inherently incomplete. Figure 6 provides a comprehensive visual synthesis of the central pathophysiological hypothesis emerging from this meta-analysis: the Outside-In theory of pathogenesis. This schematic illustrates the complex, bi-directional relationship between deep endometriosis (DE) and adenomyosis, challenging the traditional view of these conditions as separate entities. Instead, the figure conceptualizes them as an interconnected disease system where the uterus acts as a central biological engine driving clinical failure. The diagram is structured to follow the chronological and biological progression of the disease, moving from the anatomical origin of deep lesions on the left, through the central uterine pathology, to the downstream clinical consequences on the right, all underpinned by the stark surgical reality of the frozen pelvis.[12] The narrative begins on the left panel with the primary lesion, identified as deep endometriosis located in the posterior pelvic compartment. This component represents the aggressive, infiltrating nodules found in the rectovaginal septum and uterosacral ligaments. The figure elucidates the Outside-In invasion mechanism, a critical pathway where ectopic endometrial cells from the cul-de-sac do not merely adhere to the surface but actively infiltrate the uterine serosa and penetrate the outer myometrium. This invasion establishes the link between extra-uterine disease and uterine pathology, suggesting that extrinsic adenomyosis is often a direct extension of deep infiltrating endometriosis rather than a primary uterine disorder.[13] This initial step is pivotal, as it transforms the uterus from a bystander into an active participant in the disease process. Central to the schematic is the Adenomyotic Uterus, depicted not just as an organ but as the Continent and Reservoir of the disease. This central hub visually anchors the pathophysiology, highlighting three distinct dysfunctions. First, the figure underscores the disruption of the junctional zone (JZ), the specialized interface between the endometrium and myometrium. This disruption leads to chaotic hyperperistalsis and significantly elevated intrauterine pressure, a mechanical dysfunction that serves as a generator of pain independent of peritoneal lesions. Second, it identifies the extrinsic subtype, characterized by posterior wall thickening and nodules that are often fused with the bowel, creating a physical bridge for disease continuity. Third, and perhaps most critically, the uterus is portrayed as a biological reservoir. Even after the surgeon diligently removes the visible deep endometriosis nodules depicted on the left, this central reservoir remains metabolically active, maintaining a localized pro-inflammatory and hyperestrogenic milieu that continues to seed the pelvis with pathogenic cells. Radiating from this central hub to the right panel are the three cardinal clinical sequelae, each linked to a specific pathophysiological mechanism reinforced by the study's statistical findings. The first outcome, Persistent pain, is explained through the tissue injury and repair (TIAR) theory. The schematic illustrates how the hyperperistalsis mentioned in the central hub causes repetitive micro-trauma to the myometrial interface. This chronic injury triggers neuroangiogenesis—the growth of new nerve fibers and blood vessels—resulting in central uterine pain and severe dysmenorrhea that persists even after the excision of extra-uterine nerve fibers.[14] This visual connection explains the clinical observation that patients often report unchanged pain scores post-surgery. The second outcome, anatomical recurrence, is depicted as a direct consequence of the "Re-seeding" phenomenon. The arrow extending from the uterine

reservoir signifies the reactivation of the disease process. Because the adenomyotic tissue acts as a "continent" continuously shedding cells, sparing the uterus during surgery leaves the primary disease driver intact. The figure integrates the meta-analytic data here, explicitly stating the 2.5-fold increased risk of recurrence, thereby visually confirming that the uterus is the source of the relapse. The third outcome, Infertility, is attributed to the Hostile Soil mechanism. Beyond simple anatomical blockage, the figure highlights how altered integrin expression, inflammation, and dysperistalsis combine to impair sperm transport and implantation, resulting in significantly lower pregnancy rates even when the tubes are patent. Finally, the schematic is grounded by the Surgical Reality bar at the bottom, which represents the anatomical consequence of this dual pathology: the Frozen Pelvis. This section vividly describes the fusion of the rectum to the cervix and the obliteration of the Pouch of Douglas caused by extrinsic adenomyosis. It serves as a stark warning of the increased operative burden, directly linking the loss of surgical cleavage planes to the substantial Odds Ratio of 4.56 for complications. By visually connecting the biological invasion at the top with the surgical solidification at the bottom, Figure 6 effectively communicates that the presence of adenomyosis transforms a standard excision surgery into a high-risk intervention, necessitating a fundamental shift in surgical planning and patient counseling.[15]

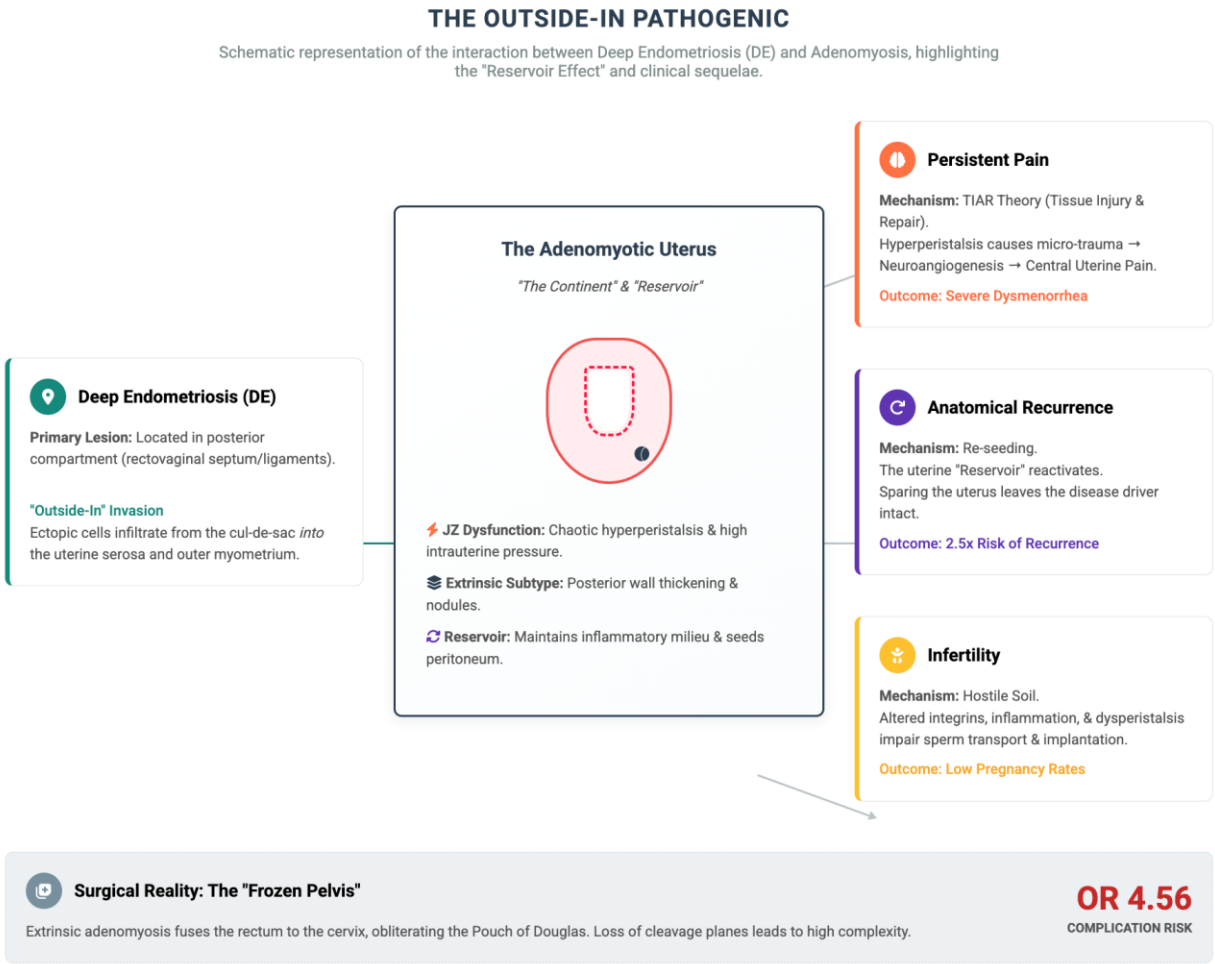

Figure 6. The outside-in pathogenic.

A central theme emerging from this analysis is the validation of the outside-in theory of pathogenesis, particularly concerning the distinct phenotype of extrinsic adenomyosis. The robust association identified between extrinsic adenomyosis and the recurrence of ovarian endometriomas and deep infiltrating lesions strongly supports the concept that these conditions are inextricably linked through a bi-directional invasion process. As detailed in the findings derived from other studies, extrinsic adenomyosis likely represents the deep infiltration of ectopic endometrial cells from the posterior cul-de-sac directly into the outer myometrium. This pathological mechanism creates a vicious cycle where deep endometriosis lesions invade the serosa of the uterus to establish adenomyotic foci, while these established adenomyotic foci subsequently act as a biological continent or reservoir. This reservoir continuously seeds the peritoneum with viable endometrial cells, effectively fueling the archipelagos of peritoneal endometriosis even after the visible surface lesions have been surgically removed.[16]

This reservoir hypothesis provides a biological explanation for the high recurrence rates observed in our meta-analysis. If the adenomyotic uterus acts as a sanctuary for ectopic endometrium, performing a complete excision of peritoneal and deep lesions while sparing the uterus is akin to removing the smoke while ignoring the fire. The uterine reservoir remains metabolically and biologically active, maintaining a localized hyperestrogenic and pro-inflammatory environment that promotes the resurgence of lesions. This local hormonal dysregulation is critical, as adenomyotic tissue is known to express high levels of aromatase and sulfatase enzymes, leading to local estrogen production that can stimulate residual microscopic disease in the pelvis. Consequently, the 2.5-fold increased risk of early recurrence observed in patients with extrinsic adenomyosis is likely a manifestation of this immediate re-seeding process or the expansion of microscopic disease that was connected to the uterine wall and could not be fully resected without compromising uterine integrity.

The persistence of debilitating dysmenorrhea and dyspareunia despite technically successful deep endometriosis excision, as observed in the cohorts analyzed, points to a central uterine pathology that surgery often fails to address.[17] The other study is particularly illuminating in this regard, highlighting that adenomyosis is characterized by the profound disruption of the junctional zone, the specialized inner myometrium responsible for directing uterine peristalsis. In a healthy uterus, these contractions are rhythmic and directed cervico-fundally to aid sperm transport or fundal-cervically during menstruation. However, in the presence of adenomyosis, the destruction of the junctional zone architecture leads to chaotic hyperperistalsis and dysperistalsis. This muscular dysfunction results in significantly increased intrauterine pressure, which the patient experiences as severe, crampy dysmenorrhea that is distinct from the nociceptive pain caused by peritoneal implants.

Furthermore, this mechanical dysfunction supports the tissue injury and repair (TIAR) theory of pathogenesis. The hyperperistalsis causes repetitive micro-traumatization at the endometrial-myometrial interface, leading to a chronic wound-healing response. This response involves the upregulation of inflammatory cytokines, prostaglandins, and neuroangiogenic factors that sensitize the uterine nerves. The marked disparity in postoperative pain scores, with adenomyosis patients reporting significantly higher Visual Analog Scale scores compared to those without the condition, underscores that removing extra-uterine nerve-rich nodules without addressing the source of uterine spasm and intrinsic inflammation is insufficient for total pain relief. The pain is centrally mediated by the uterus itself. Therefore, the recurrence of pain in these patients should not necessarily be viewed as a failure of the surgeon to remove the deep endometriosis, but rather as a failure to diagnose and treat the co-existing adenomyotic generator of pain.[18]

The surgical implications of these pathophysiological changes are profound, as

evidenced by the significantly higher complication rates identified in our meta-analysis. The 4.56-fold increase in surgical complications reported in studies like those by Gracia et al. reflects the severe anatomical distortion frequently caused by the coexistence of these two phenotypes. Adenomyosis, particularly the extrinsic posterior type, is frequently the cornerstone of a frozen pelvis, a catastrophic anatomical state characterized by dense, woody fibrosis that obliterates the Pouch of Douglas.[19] In this hostile surgical field, the rectum is often fused to the posterior uterine wall, and the physiological cleavage planes between the uterus, bowel, and ureters are completely lost.

The adenomyotic uterus itself presents unique challenges during dissection. Unlike a healthy uterus, which is pliable and distinct from surrounding structures, the adenomyotic uterus is often globular, heavy, and extremely friable due to the interstitial hemorrhage and edema within the myometrium.[20] This friability makes safe manipulation difficult; the use of uterine manipulators can cause tearing, and dissection along the posterior wall carries a heightened risk of inadvertent entry into the bowel or rectal lumen due to the lack of a safe separation layer. This finding challenges the prevailing paradigm of conservative surgery in severe cases. Attempting to spare a heavily diseased uterus to preserve fertility may inadvertently increase the risk of catastrophic intraoperative complications, such as rectovaginal fistula or ureteral injury, while failing to provide long-term symptom relief or prevent recurrence. The surgeon is forced to walk a precarious line between aggressive resection to remove the disease and conservative restraint to avoid damaging a uterus that is structurally compromised.

The deleterious impact of adenomyosis on fertility, which this study identifies as an independent risk factor distinct from deep endometriosis, suggests a multifaceted and intrinsic mechanism of infertility that extends beyond simple anatomical distortion. While deep endometriosis is known to cause infertility through tubal occlusion and pelvic adhesions, the significantly lower pregnancy rates observed in the adenomyosis group suggest that the uterus itself is hostile to reproduction. The altered junctional zone contractility, previously discussed as a source of pain, also plays a critical role here by impairing the rapid sperm transport required for fertilization. If the uterine peristalsis is chaotic or dysrhythmic, sperm transport is inefficient, reducing the likelihood of natural conception.[21]

Moreover, the molecular environment of the adenomyotic endometrium appears to be fundamentally altered. The localized inflammation and high estrogen environment likely lead to the aberrant expression of implantation markers, such as integrins and leukemia inhibitory factor, and the overexpression of aromatase P450. This creates an immunologically and hormonally hostile environment for the embryo, leading to implantation failure even when fertilization occurs. This concept is supported by the high rates of primary infertility and the lower success rates of assisted reproductive technologies in this cohort. The findings from Sun et al. indicate that surgical restoration of pelvic anatomy alone cannot overcome these intrinsic endometrial defects. Consequently, the presence of adenomyosis dictates a need for a shift in fertility counseling. Patients should be advised that spontaneous conception rates are likely to remain low despite surgery, and that the window of opportunity following surgery may be shorter due to the high risk of recurrence. This evidence strongly supports early referral to assisted reproductive technology (ART) with specific protocols, such as long-course GnRH agonist downregulation to suppress the inflammatory milieu before embryo transfer.

The survival analysis data regarding recurrence-free probability offers a sobering long-term perspective. The finding that only 60% of adenomyosis patients remain recurrence-free at five years, compared to 81% of those without adenomyosis, clearly delineates the aggressive nature of this combined phenotype. The hazard ratio of 3.28 serves as a potent statistical validation of the clinical

impression that these patients represent a distinct, high-risk group. This elevated risk is likely multifactorial, stemming from the combination of the persistent uterine reservoir, the molecular field effect of the adenomyotic tissue, and the surgical difficulties that may lead to incomplete excision of microscopic implants on the uterine surface.

It is also crucial to distinguish between true recurrence, defined as the development of de novo lesions, and persistent disease resulting from incomplete excision. The high rate of early recurrence (within three years) associated with extrinsic adenomyosis suggests that, in many cases, what is labeled as recurrence is actually the progression of residual disease that was inextricably bound to the uterine wall. This distinction is clinically relevant because it influences the choice of secondary interventions. If the recurrence is driven by the uterus, repeat local excision is likely to yield diminishing returns. This data strongly supports the argument that for women who have completed their families, concurrent hysterectomy should be discussed more robustly as a risk-reducing strategy during the initial surgery, rather than as a last resort after multiple failed conservative procedures. For those preserving the uterus, the high recurrence risk mandates aggressive postoperative medical suppression. The use of Levonorgestrel-releasing intrauterine systems or long-term GnRH analogues should be considered standard care to suppress the uterine reservoir and mitigate the outside-in progression of the disease.[22]

The cumulative evidence from this meta-analysis dictates a necessary change in the preoperative and postoperative workflow for patients with deep endometriosis. The "adenomyosis status" of every patient scheduled for deep endometriosis surgery must be defined using high-quality transvaginal ultrasound, adhering to morphological uterus sonographic assessment (MUSA) criteria or magnetic resonance imaging. The identification of adenomyosis should trigger a specific consent process that details the significantly higher risks of recurrence, persistent pain, and surgical complications. It is no longer acceptable to counsel these patients based on general endometriosis statistics; they require personalized risk stratification that accounts for their uterine pathology. Furthermore, this study highlights the urgent need for future research to focus on refining the surgical techniques for extrinsic adenomyosis. Techniques such as the localized excision of adenomyotic nodules (adenomyomectomy) combined with deep endometriosis excision need to be evaluated in prospective trials to determine if they can effectively reduce the reservoir effect without compromising uterine integrity. Additionally, the molecular cross-talk between adenomyosis and deep endometriosis warrants further investigation to identify potential pharmacological targets that could interrupt the bi-directional invasion process. Ultimately, acknowledging the central role of the adenomyotic uterus allows us to move toward a more holistic and effective management strategy, one that treats the patient and her uterus as an interconnected system rather than a collection of isolated lesions.

5. Conclusion

The synthesis of high-quality observational data presented in this meta-analysis unequivocally establishes co-existing adenomyosis as a potent and independent antagonist in the surgical management of deep endometriosis. Far from being a mere bystander, the adenomyotic uterus appears to function as a biological reservoir for ectopic disease, actively fueling the recurrence of lesions and the persistence of debilitating symptoms through a mechanism that strongly supports the outside-in theory of pathogenesis. This bi-directional invasion implies that the surgical excision of extra-uterine deep endometriosis, while technically feasible, often addresses only the symptomatic phenotype of the disease while leaving the primary uterine driver intact, thereby explaining the high rates of failure observed in uterine-sparing procedures. Consequently, patients burdened with this dual pathology face a significantly distinct and hazardous clinical trajectory, characterized by a 2.5-fold increased risk of early

postoperative recurrence and a markedly higher incidence of major surgical complications arising from the anatomical distortions of a frozen pelvis.

These compelling findings dictate a fundamental restructuring of preoperative protocols, rendering the rigorous screening for adenomyosis via high-resolution transvaginal sonography or magnetic resonance imaging an absolute mandatory standard rather than an optional adjunct for all patients with deep endometriosis. The preoperative identification of uterine involvement must essentially trigger a transparent and nuanced counseling process, ensuring that patients are fully aware that their clinical journey may involve substantially lower spontaneous fertility rates and a higher likelihood of re-intervention compared to those with isolated deep endometriosis. Ultimately, effective management can no longer remain a strictly extra-uterine endeavor; it requires a holistic surgical strategy that either aggressively suppresses the uterine reservoir through postoperative medical management in fertility-sparing cases or considers concurrent hysterectomy as the only definitive pathway to cure for those who have completed their families. By acknowledging the central role of the uterus in the disease process, surgeons can move beyond anatomical excision alone to provide more durable, comprehensive care that aligns with the biological reality of this complex condition.

6. References

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