International Journal of Advanced Multidisciplinary Research
ISSN: 3139-3918 (Print), ISSN: 2393-8870 (Online)
www.ijarm.com
(A Peer Reviewed, Referred, Indexed and Open Access Journal)
DOI: 10.22192/ijamr Volume 13, Issue 7-2026

Research Article

DOI: http://dx.doi.org/10.22192/ijamr.2026.13.07.003

Embryonic origin of Adenomyosis: A systematic review of molecular and clinical evidence

Origem embrionária da Adenomiose: Uma revisão sistemática das evidências moleculares e clínicas

Bianca Borges[1]
João Ronaldo Tavares[2]
[1] *UNEF. E-mail: biancabiomed9@gmail.com*
[2] *UNEF. E-mail: joao.neto@gruponobre.edu.br*

Keywords

Adenomyosis; Endometrial Receptivity; Embryo Implantation.

Abstract

Introduction: Adenomyosis is a gynecological condition associated with hormonal alterations that impair endometrial function and embryo implantation. **Objective:** To analyze how hormonal alterations influence endometrial receptivity and endometrial cell functionality in adenomyosis. **Methodology:** An exploratory-descriptive bibliographic study with a qualitative approach was conducted using PubMed and Virtual Health Library databases, including articles published between 2015 and 2025. **Results and Discussion:** The studies demonstrated that hyperestrogenism, progesterone resistance, inflammatory processes, and molecular alterations impair endometrial receptivity and contribute to disease progression, while hormonal therapies and treatments targeting specific molecular pathways show promising results. **Conclusion:** An integrated understanding of the hormonal, inflammatory, and cellular mechanisms is essential for the development of more effective and individualized diagnostic and therapeutic approaches.

Resumo

Introdução: A adenomiose é uma condição ginecológica associada a alterações hormonais que comprometem a funcionalidade endometrial e a implantação embrionária. **Objetivo:** Analisar como as alterações hormonais influenciam a receptividade endometrial e a funcionalidade das células endometriais na adenomiose. **Metodologia:** Estudo bibliográfico do tipo exploratório-descritivo, com abordagem qualitativa, realizado nas bases PubMed e Biblioteca Virtual em Saúde, incluindo artigos publicados entre 2015 e 2025. **Resultados e Discussão:** Os estudos evidenciaram que o hiperestrogenismo, a resistência à progesterona, os processos inflamatórios e as alterações moleculares comprometem a receptividade endometrial e favorecem a progressão da doença, enquanto terapias hormonais e direcionadas a vias moleculares específicas apresentam resultados promissores. **Conclusão:** A compreensão integrada dos mecanismos hormonais, inflamatórios e celulares é fundamental para o desenvolvimento de abordagens diagnósticas e terapêuticas mais eficazes e individualizadas.

Palavras-chave:

Adenomiose;
Receptividade Endometrial;
Implantação Embrionária.

Introduction

Adenomyosis is a complex gynecological condition characterized by the presence of endometrial tissue in the myometrium, resulting in structural and functional alterations of the uterus and significantly impacting female reproductive health. In recent decades, scientific advances have shown that this pathology is closely related to hormonal dysregulations, especially involving sex steroids such as estrogen and progesterone (Liu et al., 2018; Viganò et al., 2018). Furthermore, adenomyosis interacts with several fields of knowledge, including endocrinology, molecular biology, and reproductive medicine, being frequently associated with inflammatory and immunological processes, and even mechanisms similar to those observed in neoplastic diseases (Inoue et al., 2019; Peterson et al., 2023). Despite these advances, important gaps persist regarding the integrated understanding of pathophysiological mechanisms, especially concerning the relationship between hormonal alterations and endometrial dysfunctions, which reinforces the need for further scientific investigation on the topic.

Within this context, the relevance of investigating the hormonal alterations associated with adenomyosis and their impacts on endometrial functionality stands out, particularly regarding endometrial receptivity and the embryo implantation process. Studies demonstrate that the disease presents an estrogen-dependent profile associated with progesterone resistance, a condition that compromises the proper regulation of the menstrual cycle and favors uncontrolled cellular proliferation (Lee et al., 2015; Chodankar; Critchley, 2019). Simultaneously, alterations in the expression of hormonal receptors and the activation of molecular pathways, such as PI3K/AKT/mTOR, contribute to disease progression and the disorganization of the uterine microenvironment (Driva et al., 2022). These findings evidence that adenomyosis is not limited to a structural condition but involves a complex network of hormonal, cellular, and molecular interactions that justify in-depth investigation.

From a global perspective, it is estimated that adenomyosis affects a significant portion of women of reproductive age, although its exact prevalence is underestimated due to diagnostic difficulties and the variability of clinical and histological criteria (Vercellini et al., 2024; Rawlings et al., 2023). International studies indicate that hormonal alterations, such as local hyperestrogenism and progesterone resistance, are present in most cases and are associated with manifestations such as infertility, pelvic pain, and abnormal uterine bleeding (Zhang et al., 2021; Singh et al., 2018). Additionally, risk factors such

as a history of uterine surgeries, multiparity, and metabolic conditions have been frequently described in the literature (Nougaret et al., 2021; Wang et al., 2023). These data reinforce the global impact of the disease and highlight the need for more effective diagnostic and therapeutic strategies.

In Brazil, a trend similar to that described in international studies is observed, with a growing recognition of adenomyosis as a major cause of gynecological morbidity and infertility. Clinical data indicate a frequent association between the disease and symptoms such as severe dysmenorrhea, increased menstrual flow, and embryo implantation failures, directly reflecting the underlying hormonal imbalances (Valenzuela-Islas; Frías-Mendívil; Luis-Zárate, 2017). Furthermore, limitations in accessing advanced diagnostic methods and standardizing therapeutic protocols contribute to underdiagnosis and inadequate management of the condition. This scenario highlights inequalities in healthcare and reinforces the need for national scientific production that contributes to a better understanding of the disease in the Brazilian context.

Given this panorama, this study seeks to understand how hormonal alterations associated with adenomyosis influence the functionality of endometrial cells and uterine receptivity. To this end, the objective is to analyze the main hormonal, molecular, and inflammatory mechanisms involved in the pathophysiology of the disease, based on recent scientific evidence. Such investigation is justified by the scientific and clinical relevance of the topic, as the understanding of these processes may contribute to the development of more effective therapeutic strategies, the improvement of reproductive outcomes, and advancements in the personalized management of adenomyosis, filling existing gaps in the literature.

Methodology

This was an exploratory-descriptive bibliographic study with a qualitative approach, based on the analysis of scientific literature related to hormonal alterations in adenomyosis and their impacts on endometrial receptivity and the embryo implantation process.

Data collection was carried out through a bibliographic survey covering the period from 2015 to 2025, considering full-text scientific articles directly related to the theme. Included studies were systematic reviews, narrative reviews, experimental studies, and institutional guidelines published in Portuguese, English, and Spanish. Exclusion criteria included: duplicate articles, studies that did not directly address the proposed theme, incomplete publications, simple abstracts, letters to the editor, and materials unavailable in full text.

The search was conducted in the PubMed and Virtual Health Library (VHL) databases, widely recognized in the health field for the relevance and reliability of their indexed publications. Search strategies were developed based on the Health Sciences Descriptors (DeCS), using terms in Portuguese and English.

The methodological process followed systematized steps: initially, descriptors and search strategies were defined; next, studies were identified in the selected databases. Subsequently, the articles were organized into a table according to the database and established criteria. Duplicate studies were excluded, followed by screening through title and abstract reading. Potentially relevant articles were read in full, and those that fully met the inclusion criteria were selected.

In the initial search stage, 245 scientific articles were identified in the selected databases. Of these, 45 articles were found in PubMed, while 200 were identified in the VHL. After applying eligibility criteria and analyzing titles and abstracts, 162 studies were excluded due to duplication, lack of direct relation to the theme, unavailability of the full text, or inadequacy to the established methodological criteria.

During the screening stage for articles from PubMed, 24 studies were excluded (15 for not directly addressing the theme and 9 for methodological inadequacy or incompatibility with the study objectives). Thus, 21 articles remained for the final analysis from this database.

Regarding the VHL, 138 articles were excluded during the selection process (125 for lack of specific relation to the theme and 13 for not meeting the previously defined inclusion criteria). At the end of the screening, 62 articles remained eligible for the study.

Therefore, the final sample of this research consisted of 83 scientific articles, used in the construction of the theoretical foundation, analysis of results, and discussion of the present work.

For data analysis, five thematic axes were established based on the specific objectives of the study: (1) main hormonal alterations in adenomyosis; (2) influence of progesterone resistance on endometrial receptivity; (3) impact of hormonal imbalance on the inflammatory and vascularization processes of the endometrium; (4) effects of hormonal alterations on endometrial cell functionality during embryo implantation; and (5) therapeutic strategies aimed at improving endometrial receptivity. These axes guided the critical analysis of the selected articles, allowing the organization and interpretation of the data presented in the results section.

Results and Discussion

Main hormonal alterations observed in women with adenomyosis

Adenomyosis is a gynecological condition characterized by the infiltration of endometrial glands and stroma into the muscular layer of the uterus (the myometrium), resulting in significant structural and functional alterations. This pathological process is directly associated with hormonal imbalances, mainly involving female sex steroids like estrogen and progesterone.

Studies indicate that the disease has a clearly estrogen-dependent profile, with the excess of this hormone being one of the main drivers for its development and progression (Liu et al., 2018; Zhang et al., 2022). Furthermore, adenomyosis frequently coexists with other gynecological conditions related to hyperestrogenism, reinforcing its hormonal nature.

One of the primary mechanisms involved in the pathophysiology of adenomyosis is progesterone resistance, characterized by a reduced response of the endometrial tissue to this hormone. This condition is linked to a decrease in the expression of progesterone receptors, especially the PRA and PRB isoforms, compromising the proper regulation of the menstrual cycle (Lee et al., 2015; Chodankar & Critchley, 2019). Consequently, there is a loss of the antiproliferative effect of progesterone, allowing estrogen to exert a predominant action on the uterine tissue. This imbalance contributes to uncontrolled cell proliferation and the maintenance of an environment favorable to the disease's development.

Simultaneously, a significant increase in estrogen levels is observed, both systemically and locally, with the latter intensified by the increased activity of the aromatase enzyme. This enzyme converts androgens into estrogens, raising the local concentration of estradiol in the uterus (Zhang et al., 2024; Horton et al., 2019). β-estradiol, one of the most active forms of estrogen, plays a major role in inducing angiogenesis and cell proliferation, promoting the invasion of endometrial tissue into the myometrium (Liu et al., 2022). Moreover, its action on specific molecular pathways, such as the let-7a/Lin28B axis, promotes the growth of uterine smooth muscle cells (Zhang et al., 2021).

Another relevant aspect is the alteration in the expression of hormone receptors, including the reduction of estrogen receptor α (ERα) and progesterone receptor (PR), associated with increased expression of estrogen receptor β (ERβ). This differential modulation contributes to the predominance of estrogenic effects in the

uterine tissue (Singh et al., 2018). Furthermore, there is an overexpression of anti-apoptotic proteins, such as Bcl-2, which prolong cell survival in adenomyosis foci, reinforcing the proliferative character of the disease (Musa et al., 2012). These factors indicate a profound reorganization of the hormonal and cellular microenvironment.

Adenomyosis is also associated with inflammatory and immunological alterations, with an imbalance in cytokine production and an increased inflammatory response in both eutopic and ectopic endometrium (Park et al., 2016; Viganò et al., 2018). The dysregulated expression of mediators such as IL-33 and alterations in genes related to endometrial receptivity, such as HOXA10 and LIF, compromise reproductive function and embryo implantation (Zhang et al., 2021; Liu et al., 2023). This inflammatory scenario, combined with the altered hormonal environment, favors the progression of the disease and its clinical manifestations.

Clinical and reproductive factors also influence the development of adenomyosis, including a history of uterine surgeries, previous pregnancies, and metabolic conditions like obesity and hypertension (Nougaret et al., 2021; Wang et al., 2023). In addition, prolonged use of estrogen-only hormonal therapies may contribute to the onset of the disease (Szegedi et al., 2016). Changes in the menstrual cycle, such as irregularity, heavy bleeding, and dysmenorrhea, directly reflect the underlying hormonal imbalances (Valenzuela-Islas, Frías-Mendívil & Luis-Zárate, 2017).

From a therapeutic standpoint, approaches mainly target hormonal regulation, focusing on reducing estrogen levels and restoring progesterone action. The use of levonorgestrel-releasing intrauterine systems (LNG-IUS) has shown efficacy by promoting high local concentrations of progestin in the endometrium (Kim & Seong, 2013). Additionally, GnRH agonists act by suppressing the production of FSH and LH, consequently reducing estrogen synthesis (Zhou et al., 2016). These strategies highlight the importance of hormonal control in managing adenomyosis, reinforcing the central role of sex steroids in the pathophysiology of the disease.

Progesterone resistance influences endometrial receptivity in patients with adenomyosis

Progesterone resistance is considered one of the main pathophysiological hallmarks of adenomyosis, directly influencing endometrial receptivity and embryo implantation capacity. This condition results from a significant reduction in the response of the endometrial tissue to progesterone, impairing essential processes for reproductive function (Viganò et al., 2018; Zhang et al., 2021). Furthermore, the endometrium's inability to respond adequately to this hormone leads to structural and functional alterations, including impaired decidualization and increased chronic inflammatory processes (Vercellini et al., 2024; Rawlings et al., 2023). Thus, progesterone resistance constitutes a central element in adenomyosis-associated infertility.

Several molecular mechanisms are involved in the genesis of this hormonal resistance, notably genetic alterations such as KRAS gene mutations, which interfere with progesterone-mediated cellular communication, hindering its action in the endometrial tissue (Suda et al., 2025; Inoue et al., 2019). Additionally, the reduced expression of the PTEN gene promotes abnormal activation of the PI3K/AKT/mTOR pathway, contributing to the development of progesterone resistance (Driva et al., 2022). These molecular events reflect a dysregulated cellular environment in which hormonal signaling is deeply compromised.

Another relevant factor is the altered expression of hormone receptors, especially the progesterone receptor isoforms, such as PR-B. A decrease in this isoform is directly associated with increased progesterone resistance, impairing the cellular response to the hormone (Chodankar & Critchley, 2019). Furthermore, the hypermethylation of the progesterone receptor β also contributes to reduced hormonal sensitivity, worsening the clinical picture (Zhang et al., 2024). The low expression of these receptors in the endometrial epithelium compromises intracellular signaling

and negatively interferes with decidualization (Monsivais et al., 2019).

Progesterone resistance also directly impacts the regulation of enzymes vital for hormonal metabolism, such as 17β-hydroxysteroid dehydrogenase. The inhibition of this enzyme leads to increased ERβ expression and reduced ERα, promoting a relative hyperestrogenic environment and uncontrolled cell growth (Singh et al., 2018; Habiba et al., 2018). This hormonal imbalance contributes to endometrial hyperplasia and a loss of tissue functionality, further compromising endometrial receptivity and embryo implantation.

Alongside hormonal alterations, inflammatory processes play an important role in progesterone resistance. The activation of the NF-κB pathway reduces PR-B receptor expression, intensifying hormonal resistance (Park et al., 2016). Concurrently, increased cell proliferation, apoptosis, and inflammation are observed in the ectopic endometrium, evidencing an altered microenvironment (Lee et al., 2015). These factors, combined with the hormonal imbalance, contribute to impaired endometrial function and disease persistence.

Clinically, progesterone resistance is associated with manifestations such as abnormal uterine bleeding resulting from the hormonal imbalance and the endometrium's inability to respond appropriately to the menstrual cycle (Whitaker et al., 2017; Valenzuela-Islas, Frías-Mendívil & Luis-Zárate, 2017). Furthermore, the limited efficacy of progesterone-based treatments can be explained by the reduction of hormone receptors in adenomyotic lesions, which hinders therapeutic action (Tsui et al., 2014). Even interventions such as the use of levonorgestrel present variable effects, although they can reduce endometrial glandular activity (Kim & Seong, 2013).

Progesterone resistance directly impairs fundamental processes such as decidualization and endometrial receptivity, both essential for embryo implantation. Progesterone-regulated genes, including those of the homeobox family, show reduced expression in adenomyosis, affecting the preparation of the endometrium for pregnancy (Zhou et al., 2016; Vannuccini et al., 2018). Moreover, the failure to activate factors like FOXO1 impairs the control of cell growth and endometrial tissue organization (Peng et al., 2022). Consequently, progesterone resistance acts as a major determinant of the reproductive alterations observed in adenomyosis.

Hormonal imbalance associated with adenomyosis impacts the processes of vascularization and inflammation of the endometrium

The hormonal imbalance associated with adenomyosis exerts a direct impact on the vascularization and inflammation processes of the endometrium, with estrogen acting as a primary mediator of these alterations. This hormone drives the progression of chronic inflammation and stimulates the formation of new blood vessels through the activation of pathways such as the Slug-VEGF axis, promoting endometrial tissue growth (Vercellini et al., 2024; Zipponi; Cacciottola; Dolmans, 2024). In response to this scenario, pharmacological treatments aim to restore the balance between estrogen and progesterone to reduce chronic inflammation in the endometrial tissue (Suda et al., 2025). Thus, hormonal regulation becomes essential for controlling disease progression.

Adenomyosis exhibits characteristics resembling neoplastic processes, such as accelerated growth, angiogenesis, and tissue invasion capability. Studies show that genetic mutations can favor the development and progression of the disease, relating to cellular communication and growth processes (Chen et al., 2024; Inoue et al., 2019; Liu et al., 2018). Endometrial cells show a higher capacity for survival, migration, and adaptation, including through epithelial-mesenchymal transition, which contributes to their invasion into adjacent tissues (Peterson et al., 2023; Liu et al., 2020). These alterations indicate a highly dynamic and complex biological behavior.

Increased vascularization is one of the main findings in adenomyosis, observed both in histological analyses and imaging tests like color Doppler, which shows vessels crossing the lesion and dispersed in the myometrium (Sharma et al., 2020). Angiogenic factors such as VEGF and HIF-1α are significantly elevated in the ectopic endometrium, contributing to the formation of new blood vessels and disease progression (Driva et al., 2022). Additionally, proteins like Talin1 potentiate the effects of β-estradiol, intensifying angiogenesis and cell growth (Liu et al., 2022). These changes reflect a significant vascular reorganization in the uterus.

Chronic inflammation is another central component of adenomyosis, mediated by various molecular pathways, including the activation of the cGAS-STING and NF-κB pathways. Pro-inflammatory cytokines like IL-1β and TNF-α stimulate the production of COX-2, VEGF, and tissue factor, intensifying the inflammatory response and contributing to angiogenesis (Park et al., 2016; Zhang et al., 2024). There is also an increase in cytokines such as IFN-γ, IFN-α, and IL-1β, indicating an exacerbated inflammatory environment (Prašnikar et al., 2022). This continuous inflammatory state impairs endometrial function and favors disease progression.

The inflammatory process in adenomyosis shares similarities with the menstrual process, involving increased vascular permeability, tissue degradation, and the presence of defense cells (Critchley et al., 2020). However, in adenomyosis, this process occurs in an unregulated manner, leading to persistent endometrial changes. The presence of mediators like annexin A2 and aquaporins contributes to processes such as vessel formation, inflammation, and cell invasion (Zhang et al., 2013; Li et al., 2018). Furthermore, increased levels of enzymes like MMP-2 and MMP-9 promote extracellular matrix degradation, facilitating cellular invasion (Yi et al., 2015).

Functionally, the altered inflammatory and vascular environment compromises endometrial receptivity and embryo implantation. Cytokine dysregulation and impaired spiral artery remodeling hinder the blood flow necessary to sustain early pregnancy (Monsivais et al., 2019). Additionally, elevated oxidative stress, evidenced by alterations in enzymes like NOS, XO, SOD, and catalase, contributes to a hostile uterine environment (Zhang et al., 2023). The presence of macrophages and inflammatory mediators reinforces this adverse scenario (Zhou et al., 2016).

The hormonal imbalance, associated with inflammation and angiogenesis, results in a disorganized and hostile uterine environment. The continuous activation of inflammatory pathways, such as NF-κB, and the estrogenic stimulus contribute to excessive cell proliferation and the failure of tissue repair mechanisms (Horton et al., 2019; Juárez-Barber et al., 2022). This set of alterations favors the persistence of the disease and its clinical complications. Thus, adenomyosis stands out as a complex condition where hormonal, inflammatory, and vascular factors interact in an integrated way, dictating its evolution and reproductive impact.

Hormonal alterations affect the functionality of endometrial cells during the embryo implantation process

Hormonal alterations in adenomyosis profoundly affect the functionality of endometrial cells, especially during the embryo implantation process. It is observed that endometrial cells can attach to inappropriate sites, outside the physiological location, favoring disease progression (Vercellini et al., 2024). Epithelial-mesenchymal transformation contributes to this process, allowing greater cell mobility and tissue invasion capacity (Zipponi; Cacciottola; Dolmans, 2024). These alterations share similarities with neoplastic processes, indicating that tissues affected by adenomyosis exhibit biological behavior similar to that seen in cancer (Inoue et al., 2019). Furthermore, genes related to hormonal imbalance are directly involved in the disease's development (Liu et al., 2018).

In some cases, the progression of these alterations can evolve into malignant processes, with glandular tissue transformation and the development of endometrial cancer (Ohira et al., 2023; Wang et al., 2023). The YTHDF2 protein is associated with the emergence of endometrial adenocarcinoma, reinforcing the link between cellular alterations and malignancy (Zhang et al., 2021). Estrogen plays a central role by activating the PI3K/AKT/mTOR pathway, enhancing the migration and invasion capacity of endometrial cells (Driva et al., 2022). Cellular structural changes, such as nuclear disorganization and cytoplasmic accumulation, show compromised endometrial receptivity (Singh et al., 2018).

β-estradiol intensifies the proliferation of endometrial cells in both eutopic and ectopic tissues, promoting accelerated cell growth (Liu et al., 2022; Zhang et al., 2021). The endometrium, by its dynamic nature, undergoes modifications throughout the menstrual cycle under hormonal control, which are essential for gestational preparation (Camboni & Marbaix, 2021). Alterations in microRNAs, such as the reduction of miR-124-3p, increase the expression of Neuropilin 1, favoring cell migration and epithelial-stromal transition (Liu et al., 2020). Moreover, the thickness of the uterine junctional zone varies according to hormone levels, directly influencing receptivity (Nougaret et al., 2021).

Decidualization, a fundamental process for embryo implantation, relies on adequate hormonal signaling and involves cell growth, immune cell recruitment, and tissue transformation (Critchley et al., 2020). However, in adenomyosis, this preparation occurs in a disordered manner, impairing endometrial receptivity (Munro, 2019). Ovarian hormones influence the contractions of the junctional zone, which may interfere with endometrial changes throughout the menstrual cycle and compromise implantation (Tanos et al., 2020). Alterations in proteins like aquaporins also contribute to abnormal cellular behavior (Li et al., 2018).

Increased cell proliferation and reduced apoptosis are evidenced by markers such as Ki-67, indicating exacerbated cell growth in the eutopic endometrium (Chodankar & Critchley, 2019). Hormonal alterations compromise cell function and reduce embryonic receptivity capacity (Silva et al., 2021). Additionally, progesterone resistance affects the production of the 17β-hydroxysteroid dehydrogenase enzyme, leading to the accumulation of active estradiol and failure in tissue differentiation (Habiba et al., 2018). Gene regulation mediated by estrogen and progesterone depends on coregulators that modulate the expression of specific genes (Lee et al., 2015).

Several molecular and genetic factors directly influence embryo implantation. The reduced expression of genes such as HOXA10, HOXA11, LIF, and integrin β3 compromises the interaction between the embryo and the endometrium (Zhou et al., 2016). Alterations in lncRNAs, like ENST00000433673, affect processes of proliferation, apoptosis, and cell adhesion (Liu et al., 2018). Immunological factors such as LIF, HLA-G, and KIR2DL4 play an essential role in modulating the immune response and forming the blood vessels required for embryonic development (Zhang et al., 2020). The failure of epithelium-stroma communication also compromises implantation (Rawlings et al., 2023).

The uterine environment in adenomyosis becomes unfavorable due to immunological, inflammatory, and hormonal changes. The elevation of immune cells, such as uNK and macrophages, can negatively interfere with embryo implantation (Prašnikar et al., 2022). Furthermore, a reduction in proteins like SCRIB, FOXO1, and NR4A impairs endometrial preparation, making the proper formation of the implantation site difficult (Peng et al., 2022). The decrease in adhesion molecules and the increase in estradiol impair embryo attachment and invasion (Horton et al., 2019). Thus, adenomyosis negatively interferes with implantation and embryonic development, potentially causing damage to embryonic DNA (Juárez-Barber et al., 2022).

Scientific evidence points to strategies capable of improving endometrial receptivity in patients with adenomyosis

Scientific evidence indicates that strategies to improve endometrial receptivity in patients with adenomyosis involve both diagnostic advancements and targeted therapeutic interventions. Targeted next-generation sequencing can assist in identifying somatic alterations associated with the disease, allowing a better understanding of the involved mechanisms (Inoue et al., 2019). Techniques like endometrial biopsy combined with the analysis of the RPLP1 protein are considered less invasive and useful for diagnosis (Peterson et al., 2023). Furthermore, ultrasound and hysteroscopy show high reliability in gynecological evaluation and in identifying the causes of infertility (Alqahtani et al., 2023; Valenzuela-Islas, Frías-Mendívil & Luis-Zárate, 2017; Oliveira et al., 2015).

Hormonally, the modulation of estrogen and progesterone levels is vital to improving endometrial receptivity. Lowering estrogen and raising progesterone near the implantation window favors embryo attachment, with injectable progesterone being an effective strategy in this context (Pirtea et al., 2023). In cases of unexplained infertility, hormonal therapy is frequently indicated to improve endometrial thickness and receptivity (Singh et al., 2018). The use of selective progesterone receptor modulators, like UPA, promotes adjustments in hormone levels and reduces cell growth, although its effects are reversible (Whitaker et al., 2017).

Therapeutic strategies targeting specific molecular pathways have also been investigated. Inhibiting the PI3K/AKT/mTOR pathway, for instance, can be achieved with the use of metformin, reducing endometrial cell growth through AMPK activation (Driva et al., 2022). Other approaches include regulating proteins like Talin1 and Neuropilin 1, as well as intervening in the let-7a/Lin28B axis, which holds therapeutic potential in adenomyosis (Liu et al., 2022; Liu et al., 2020; Zhang et al., 2021). Moreover, targets like TIPE2 and the cGAS-STING pathway emerge as promising possibilities for disease treatment (Liu et al., 2020; Liu et al., 2022).

Surgically, intervention is considered the gold standard in many cases, especially when severe symptoms are present. Hysterectomy is often used for chronic conditions, while adenomyomectomy can be an alternative for patients who wish to preserve fertility (Camboni & Marbaix, 2021; Nougaret et al., 2021; Kishi et al., 2018). Surgery's efficacy is confirmed by histological analysis of uterine tissue (Morales-Vicente et al., 2021). Surgical procedures can also restore uterine anatomy and reduce inflammation, promoting a more suitable pelvic environment (Horng et al., 2014).

Other therapeutic approaches include the use of hormonal devices and medications. Etonogestrel implants and the levonorgestrel-releasing intrauterine system (LNG-IUS) demonstrate efficacy in reducing endometrial growth, pain, and menstrual flow (Zhang et al., 2019; Kim & Seong, 2013; Wang et al., 2025). The use of GnRH agonists also stands out, promoting the thinning of the junctional zone, reducing inflammation, and improving outcomes in assisted reproduction (Tanos et al., 2020; Munro, 2019). Therapies with mifepristone (MFP) and selective progesterone receptor modulators (SPRM) also help decrease vascularization and endometrial activity (Wagenfeld et al., 2014; Tsui et al., 2014).

Modulating specific cellular and molecular factors represents another promising line of treatment. Inhibiting genes like FMNL2 and PAK4 reduces cell migration and invasion, while interventions targeting proteins like annexin A2 can directly impact disease development (Li et al., 2019; Yi et al., 2015; Zhang et al., 2013). Additionally, the regulation of aquaporins and the use of CXCL12 for stem cell recruitment are strategies currently under investigation (Li et al., 2018; Critchley et al., 2020). Personalizing treatment based on the symptoms and individual characteristics of the patient is essential for better outcomes (Chodankar & Critchley, 2019; Silva et al., 2021).

Approaches aimed at improving endometrial receptivity encompass immunological and genetic interventions. Modulating cytokines such as TNF-α, IL-33, and IL-11 can improve endometrial function and implantation rates (Chen et al., 2022; Zhang et al., 2021; Liu et al., 2023). The use of biomarkers like circRNAs and miRNAs allows for non-invasive diagnostics and the prediction of reproductive outcomes (Hu et al., 2019; Juárez-Barber et al., 2022). Furthermore, therapies directed at genes like FOXO1, TCF21, and PDE4C, as well as TGFβ pathway inhibition, show potential in correcting abnormal decidualization (Peng et al., 2022; Wang et al., 2023; Monsivais et al., 2019). These strategies evidence a significant leap forward in the search for effective and personalized treatments for adenomyosis.

Conclusion

The analyzed results evidenced that adenomyosis is directly related to major hormonal alterations, mainly hyperestrogenism and progesterone resistance, factors that compromise endometrial functionality and favor disease progression. It was observed that these alterations stimulate chronic inflammatory processes, angiogenesis, and cell proliferation, in addition to promoting molecular imbalances that impair endometrial receptivity and embryo implantation. It was also identified that hormonal dysregulation interferes with gene expression and cellular communication, contributing to a uterine environment unfavorable to female fertility.

Furthermore, the studies demonstrated that therapeutic strategies focused on hormonal control, inflammation modulation, and improving endometrial receptivity show promising results in the management of adenomyosis. The use of progesterone, GnRH agonists, levonorgestrel-releasing devices, and therapies targeting specific molecular pathways has shown potential to reduce the disease's impacts on the endometrium and improve reproductive outcomes. Thus, it is concluded that an integrated understanding of the hormonal, inflammatory, and cellular mechanisms of adenomyosis is vital for the development of more effective and individualized diagnostic and therapeutic approaches.

References

SUDA, Kazuaki; TAKAHASHI, Kotaro; TAMURA, Ryo; SAITO, Kyota; YAMAGUCHI, Manako; YACHIDA, Nozomi; ADACHI, Sosuke; KASE, Hiroaki; OKUDA, Shujiro; YOSHIHARA, Kosuke; NAKAOKA, Hirofumi. Mutation profile and chromosomal abnormality in adenomyosis. Reproduction;170(2)2025 Aug 01.

VERCELLINI, Paolo; BANDINI, Veronica; VIGANÒ, Paola; DI STEFANO, Giorgia; MERLI, Camilla Erminia Maria; SOMIGLIANA, Edgardo. Proposal for targeted, neo-evolutionary-oriented, secondary prevention of early-onset endometriosis and adenomyosis. Part I: pathogenic aspects. Hum Reprod;39(1): 1-17, 2024 01 05.

ZIPPONI, Margherita; CACCIOTTOLA, Luciana; DOLMANS, Marie-Madeleine. Overview of crosstalk between stromal and epithelial cells in the pathogenesis of adenomyosis and shared features with deep endometriotic nodules. Hum Reprod;39(8): 1608-1617, 2024 08 01.

CHEN, Ya-Hui; ZHOU, Yan; XUE, Mei; SUN, Lin. Endometrioid adenocarcinoma caused by adenomyosis: A case report. Asian J Surg;47(4): 1921-1922, 2024 Apr.

CHAO, Angel; WU, Ren-Chin; LIN, Chiao-Yun; LEE, Lee-Yu; TSAI, Chia-Lung; LEE, Yun-Shien; WANG, Chin-Jung. Targeted next-generation sequencing for the detection of cancer-associated somatic mutations in adenomyosis. J Obstet Gynaecol;43(1): 2161352, 2023 Dec.

SHI, Jingwen; HUANG, Ying. Study on differentially expressed genes and participating pathways of ectopic endometrium in adenomyosis patients with different data sets. Genomics;115(3): 110619, 2023 05.

PETERSON, Riley; MINCHELLA, Paige; CUI, Wei; GRAHAM, Amanda; NOTHNICK, Warren B. RPLP1 Is Up-Regulated in Human Adenomyosis and Endometrial Adenocarcinoma Epithelial Cells and Is Essential for Cell Survival and Migration In Vitro. Int J Mol Sci;24(3)2023 Jan 31.

PIRTEA, Paul; DE ZIEGLER, Dominique; AYOUBI, Jean Marc. Reply of the authors: Endometrial receptivity in adenomyosis and/or endometriosis. Fertil Steril;120(4): 928, 2023 10.

YOSHIHARA, Kosuke. Pathogenesis of endometrium-related diseases based on genomic alterations in normal uterine endometrium. J Obstet Gynaecol Res;49(8): 2023-2030, 2023 Aug.

OHIRA, Satoshi; TACHIBANA, Ryota; YASAKI, Sayaka; TSUNEMI, Koji; UCHIYAMA, Natsuki; IKEDA, Eri; SANO, Kenji. Mucinous carcinoma originating from uterine adenomyosis: a case report. J Med Case Rep;17(1): 36, 2023 Feb 06.

WANG, Jing; WANG, Qingyuan; WANG, Wenyan; YANG, Jian; XIA, Jingxian; WEI, Yanan. Endometrioid adenocarcinoma arising in adenomyosis in a patient with pelvic organ prolapse-case report. BMC Womens Health;23(1): 150, 2023 03 30.

BIAN, Piao-Piao; LIU, Shao-Yan; LUO, Qiu-Ping; XIONG, Zhong-Tang. YTHDF2 is a novel diagnostic marker of endometrial adenocarcinoma and endometrial atypical hyperplasia/ intraepithelial neoplasia. Pathol Res Pract;234: 153919, 2022 Jun.

DRIVA, Tatiana S; SCHATZ, Christoph; SOBOCAN, Monika; HAYBAECK, Johannes. The Role of mTOR and eIF Signaling in Benign Endometrial Diseases. Int J Mol Sci;23(7)2022 Mar 22.

SINGH, Pushpa; METKARI, Siddhanath M; BHARTIYA, Deepa. Mice Uterine Stem Cells are Affected by Neonatal Endocrine Disruption & Initiate Uteropathies in Adult Life Independent of Circulatory Ovarian Hormones. Stem Cell Rev Rep;18(5): 1686-1701, 2022 06.

KHALID, Nagla Hussein Mohamed; AHMED, Itedal Abdelraheem Mohamed; AHMED, Samia Abdelgauom Fathelrahman. Evaluation of causes of female infertility using ultrasonography in Najran, Saudi Arabia. Afr J Reprod Health;26(5): 90-95, 2022 May.

WANG, Yi-Yi; DUAN, Hua; WANG, Sha; QUAN, Yong-Jun; HUANG, Jun-Hua; GUO, Zheng-Chen. Upregulated Talin1 synergistically boosts ß-estradiol-induced proliferation and pro-angiogenesis of eutopic and ectopic endometrial stromal cells in adenomyosis. Reprod Biol Endocrinol;19(1): 70, 2021 May 14.

CHODANKAR, Rohan R; MURRAY, Alison; NICOL, Moira; WHITAKER, Lucy H R; WILLIAMS, Alistair R W; CRITCHLEY, Hilary O D. The endometrial response to modulation of ligand-progesterone receptor pathways is reversible. Fertil Steril;116(3): 882-895, 2021 09.

HUANG, Jun-Hua; DUAN, Hua; WANG, Sha; WANG, Yi-Yi. Estrogen 17ß-estradiol accelerates the proliferation of uterine junctional zone smooth muscle cells via the let-7a/Lin28B axis in adenomyosis. Mol Med Rep;23(5)2021 May.

CAMBONI, Alessandra; MARBAIX, Etienne. Ectopic Endometrium: The Pathologist's Perspective. Int J Mol Sci;22(20)2021 Oct 11.

HUANG, Nan; XU, Liyan; QIU, Yafen; ZHAN, Jinlai; CHEN, Xiangjun. Down-regulated miR-124-3p enhanced the migration and epithelial-stromal transformation of endometrial stromal cells extracted from eutopic endometrium in subjects with adenomyosis by up-regulating Neuropilin 1. Tissue Cell;69: 101474, 2021 Apr.

WANG, Wenwen; ZHOU, Feng. Cervical HSIL Involving the Endometrium and Adenomyosis: A Case Report and Literature Review. J Coll Physicians Surg Pak;31(3): 337-339, 2021 Mar.

NOUGARET, Stephanie; CUNHA, Teresa Margarida; BENADLA, Nadia; NERON, Mathias; ROBBINS, Jessica B. Benign Uterine Disease: The Added Role of

Imaging. Obstet Gynecol Clin North Am;48(1): 193-214, 2021 Mar.

WON, Seyeon; HWANG, Ji Young; LEE, Nara; KIM, Miseon; KIM, Mi Kyoung; KIM, Mi-La; YUN, Bo Seong; SEONG, Seok Ju; JUNG, Yong Wook. Anti-Müllerian hormone level may predict successful pregnancy after adenomyomectomy in patients with infertility due to adenomyosis. Medicine (Baltimore);100(21): e26075, 2021 May 28.

MORALES-VICENTE, Ander; RAMOS-FERNÁNDEZ, Virginia; VIÑAS-ALBURQUERQUE, Teresa; GÓMEZ-DÍAZ, Norman; POZO, Santiago Domingo-Del; CRESPO-SIMÓ, Juana. Adenomiosis apendicular: reporte de dos casos. Rev. chil. obstet. ginecol.;86(3): 317-321, jun. 2021.

LIN, Yun; WANG, Luying; YE, Mingzhu; YU, Ke-Nan; SUN, Xin; XUE, Min; DENG, Xinliang. Activation of the cGAS-STING signaling pathway in adenomyosis patients. Immun Inflamm Dis;9(3): 932-942, 2021 09.

NIE, Lekai; ZOU, Hongli; MA, Xiaotian; CHENG, Lei; JIAO, Jun; WANG, Fenghua; LIANG, Weifeng; ZHANG, Peihai. A clinical observational study on the efficacy of subcutaneous etonogestrel implants for adenomyosis in 20 patients. Gynecol Endocrinol;37(8): 735-739, 2021 Aug.

NAKAI, Yudai; MAEDA, Eriko; KANDA, Tomonori; IKEMURA, Masako; USHIKU, Tetsuo; SASAJIMA, Yuko; ISSHIKI, Saiko; ABE, Osamu. Uterine adenomyosis with extensive glandular proliferation: case series of a rare imaging variant. Diagn Interv Radiol;26(3): 153-159, 2020 May.

CAPEZZUOLI, Tommaso; VANNUCCINI, Silvia; FANTAPPIÈ, Giulia; ORLANDI, Giulia; RIZZELLO, Francesca; COCCIA, Maria Elisabetta; PETRAGLIA, Felice. Ultrasound findings in infertile women with endometriosis: evidence of concomitant uterine disorders. Gynecol Endocrinol;36(9): 808-812, 2020 Sep.

LIU, Yuqiu; WANG, Xiaoyan; WAN, Lu; LIU, Xihong; YU, Huayun; ZHANG, Derui; SUN, Yingshuo; SHI, Yongyu; ZHANG, Lining; ZHOU, Huaiyu; WANG, Jianing; WEI, Zengtao. TIPE2 inhibits the migration and invasion of endometrial cells by targeting ß-catenin to reverse epithelial-mesenchymal transition. Hum Reprod;35(6): 1377-1390, 2020 06 01.

CHAO, Xiaopei; WU, Ming; MA, Shuiqing; TAN, Xianjie; ZHONG, Sen; BI, Yalan; WU, Huanwen; LANG, Jinghe; LI, Lei. The clinicopathological characteristics and survival outcomes of endometrial carcinoma coexisting with or arising in adenomyosis: A pilot study. Sci Rep;10(1): 5984, 2020 04 06.

CRITCHLEY, Hilary O D; BABAYEV, Elnur; BULUN, Serdar E; CLARK, Sandy; GARCIA-GRAU, Iolanda; GREGERSEN, Peter K; KILCOYNE, Aoife; KIM, Ji-Yong Julie; LAVENDER, Missy; MARSH, Erica E; MATTESON, Kristen A; MAYBIN, Jacqueline A; METZ, Christine N; MORENO, Inmaculada; SILK, Kami; SOMMER, Marni; SIMON, Carlos; TARIYAL, Ridhi; TAYLOR, Hugh S; WAGNER, Günter P; GRIFFITH, Linda G. Menstruation: science and society. Am J Obstet Gynecol;223(5): 624-664, 2020 11.

TANOS, Vasilios; LINGWOOD, Lee; BALAMI, Safinez. Junctional Zone Endometrium Morphological Characteristics and Functionality: Review of the Literature. Gynecol Obstet Invest;85(2): 107-117, 2020.

JIA, Liping; LIU, Yuzhu; HAN, Yixu; ZHOU, Xiaofei; WANG, Fahui. Differential expression and inhibitory effects of aquaporins on the development of adenomyosis. Mol Med Rep;22(5): 3840-3850, 2020 Nov.

MUNRO, Malcolm G. Uterine polyps, adenomyosis, leiomyomas, and endometrial receptivity. Fertil Steril;111(4): 629-640, 2019 04.

HUR, Christine; REHMER, Jenna; FLYCKT, Rebecca; FALCONE, Tommaso. Uterine Factor Infertility: A Clinical Review. Clin Obstet Gynecol;62(2): 257-270, 2019 06.

LI, You; ZHANG, Quan; LIU, Faying; ZHANG, Ziyu; ZOU, Yang; YANG, Bicheng; LUO, Yong; WANG, Liqun; HUANG, Ouping. Inhibition of formin like 2 promotes the transition of ectopic endometrial stromal cells to epithelial cells in adenomyosis through a MET-like process. Gene;710: 186-192, 2019 Aug 20.

LIU, Feng; LIU, Lixue; ZHENG, Jian. Expression of annexin A2 in adenomyosis and dysmenorrhea. Arch Gynecol Obstet;300(3): 711-716, 2019 09.

CHODANKAR, Rohan; CRITCHLEY, Hilary O D. Biomarkers in abnormal uterine bleeding. Biol Reprod;101(6): 1155-1166, 2019 12 24.

YEH, Chih-Ching; SU, Fu-Hsiung; TZENG, Chii-Ruey; MUO, Chih-Hsin; WANG, Wen-Chang. Women with adenomyosis are at higher risks of endometrial and thyroid cancers: A population-based historical cohort study. PLoS One;13(3): e0194011, 2018.

GHOSH, Adarsh; SINGH, Tulika; BAGGA, Rashmi; SRINIVASAN, Radhika; SINGLA, Veenu; KHANDELWAL, Niranjan. T2 relaxometry mapping in demonstrating layered uterine architecture: parameter optimization and utility in endometrial carcinoma and adenomyosis: a feasibility study. Br J Radiol;91(1081): 20170377, 2018 Jan.

YAZLIK, Murat Onur; TUNC, Arda Selin; COLAKOGLU, Hatice Esra; VURAL, Mehmet Rifat; KUPLULU, Sukru; POLAT, Ibrahim Mert; OZ, Burcu; KURT, Serdal; VURAL, Sevil Atalay. Effects of ovarian pathologies and uterine inflammations on adenomyosis in bitches Acta sci. vet.;46(supl): 1-7, 2018.

TSAI, Chia-Lung; LEE, Yun-Shien; CHAO, Angel; YEN, Chih-Feng; WANG, Hsin-Shih; WANG, Tzu-Hao. Associations between a single nucleotide polymorphism of stress-induced phosphoprotein 1 and endometriosis/adenomyosis. Taiwan J Obstet Gynecol;57(2): 270-275, 2018 Apr.

CUNNINGHAM, Ryan K; HORROW, Mindy M; SMITH, Ryan J; SPRINGER, Joseph. Adenomyosis: A Sonographic Diagnosis. Radiographics;38(5): 1576-1589, 2018.

HABIBA, Marwan; PLUCHINO, Nicola; PETIGNAT, Patrick; BIANCHI, Paola; BROSENS, Ivo A; BENAGIANO, Giuseppe. Adenomyosis and Endometrial Cancer: Literature Review. Gynecol Obstet Invest;83(4): 313-328, 2018.

VALENZUELA-ISLAS, HA; FRÍAS-MENDÍVIL, M; LUIS-ZÁRATE, H. Correlación entre hallazgos histeroscópicos y reportes histopatológicos en pacientes con sangrado uterino anormal. Ginecol. obstet. Méx;85(11): 748-754, mar. 2017.

JIANG, Zhongyong; XU, Wanqing; DAN, Gang; LIU, Yuan; XIONG, Jie. P53 and Murine Double Mimute 2 (MDM2) Expression Changes and Significance in Different Types of Endometrial Lesions. Med Sci Monit;22: 4786-4793, 2016 Dec 07.

GUO, Jing; CHEN, Li; LUO, Ning; LI, Caixia; CHEN, Rong; QU, Xiaoyan; LIU, Mingmin; KANG, Le; CHENG, Zhongping. LPS/TLR4-mediated stromal cells acquire an invasive phenotype and are implicated in the pathogenesis of adenomyosis. Sci Rep;6: 21416, 2016 Feb 22.

HANA PARK; SUNG-HOON KIM; YOO-MI CHO; HYO-JIN IHM; YOUNG-SANG OH; SEUNG-HWA HONG; HEE-DONG CHAE; CHUNG-HOON KIM; BYUNG-MOON KANG. Increased expression of nuclear factor kappa-B p65 subunit in adenomyosis Obstetrics & Gynecology Science;: 123-129, 2016.

SZEGEDI, S; KOPPAN, M; VARGA, T; KOVACS, K; TINNEBERG, H R; BODIS, J. Endometrioid adenocarcinoma arising from adenomyosis: a case report. Eur J Gynaecol Oncol;37(6): 858-860, 2016.

WHITAKER, Lucy; CRITCHLEY, Hilary O D. Abnormal uterine bleeding. Best Pract Res Clin Obstet Gynaecol;34: 54-65, 2016 Jul.

YI, Kyong Wook; KIM, Sung Hoon; IHM, Hyo Jin; OH, Young Sang; CHAE, Hee Dong; KIM, Chung-Hoon; KANG, Byung Moon. Increased expression of p21-activated kinase 4 in adenomyosis and its regulation of matrix metalloproteinase-2 and -9 in endometrial cells. Fertil Steril;103(4): 1089-1097.e2, 2015 Apr.

YUN, Bo Hyon; JEON, Young Eun; SEO, Seok Kyo; PARK, Joo Hyun; YOON, Sun Och; CHO, SiHyun; CHOI, Young Sik; LEE, Byung Seok. Effects of a Levonorgestrel-Releasing Intrauterine System on the Expression of Steroid Receptor Coregulators in Adenomyosis. Reprod Sci;22(12): 1539-48, 2015 Dec.

REKHI, Bharat; MENON, Santosh; MAHESHWARI, Amita. Complex papillary hyperplasia of the endometrium: an uncommon case report with cytopathological features and diagnostic implications. Diagn Cytopathol;43(2): 163-8, 2015 Feb.

HORNG, Huann-Cheng; CHEN, Ching-Hui; CHEN, Chih-Yao; TSUI, Kuan-Hao; LIU, Wei-Min; WANG, Peng-Hui; CHANG, Wen-Hsun; HUANG, Ben-Shian; SUN, Hsu-Dong; CHANG, Ting-Chang; CHANG, Wei-Chun; YEN, Ming-Shyen. Uterine-sparing surgery for adenomyosis and/or adenomyoma. Taiwan J Obstet Gynecol;53(1): 3-7, 2014 Mar.

BENAGIANO, Giuseppe; BASTIANELLI, Carlo; FARRIS, Manuela; BROSENS, Ivo. Selective progesterone receptor modulators: an update. Expert Opin Pharmacother;15(10): 1403-15, 2014 Jul.

TSUI, Kuan-Hao; LEE, Wen-Ling; CHEN, Chih-Yao; SHEU, Bor-Chin; YEN, Ming-Shyen; CHANG, Ting-Chang; WANG, Peng-Hui. Medical treatment for adenomyosis and/or adenomyoma. Taiwan J Obstet Gynecol;53(4): 459-65, 2014 Dec.

BATT, Ronald E; YEH, John. Müllerianosis: four developmental (embryonic) mullerian diseases. Reprod Sci;20(9): 1030-7, 2013 Sep.

OH, Na-Jung; RYU, Ki-Young; JUNG, Cha-Nam; YI, Sang Yeop; KIM, Se-Ryun. Expression of endothelial nitric oxide synthase in the uterus of patients with leiomyoma or adenomyosis. J Obstet Gynaecol Res;39(2): 536-42, 2013 Feb.

MUSA, Fernanda; FREY, Melissa K; IM, H Beatrice; CHEKMAREVA, Marina; ELLENSON, Lora H; HOLCOMB, Kevin. Does the presence of adenomyosis and lymphovascular space invasion affect lymph node status in patients with endometrioid adenocarcinoma of the endometrium? Am J Obstet Gynecol;207(5): 417.e1-6, 2012 Nov.

MI-LA KIM; SEOK-JU SEONG. Clinical applications of levonorgestrel-releasing intrauterine system (LNG-IUS: Mirena(R)) in gynecologic diseases. Korean Journal of Gynecologic Endoscopy and Minimally Invasive Surgery;: 1-6, 2011.

LASMAR, Ricardo Bassil; BARROZO, Paulo Roberto Mussel; PARENTE, Raphael Câmara Medeiros; LASMAR, Bernardo Portugal; ROSA, Daniela Baltar da; PENNA, Ivan Araujo; DIAS, Rogério. Avaliação histeroscópica em pacientes com infertilidade. Rev. bras. ginecol. obstet;32(8): 393-397, ago. 2010.

YUN-SIN KIM; MI-SOOK LEE; SUNG-CHUL LIM; JANG-SHIN SOHN; CHAE-HONG SUH. Overexpression of p53 Protein in Endometrial Hyperplasia and Adenocarcinoma Korean Journal of Pathology;: 655-661, 1997.

BAI, Y.; LIANG, J.; LIU, W.; WANG, F.; LI, C. Possible roles of HLA-G regulating immune cells in pregnancy and endometrial diseases via KIR2DL4. Journal of Reproductive Immunology, v. 142, p. 103176, 2020.

DAI, Y.; YUAN, Z.; FAN, W.; LIN, Z. Molecular mechanism of aberrant decidualization in adenomyosis leading to reduced endometrial receptivity. Frontiers in Endocrinology, v. 15, p. 1435177, 2025.

DE ZIEGLER, D.; PIRTEA, P.; GALLIANO, D.; CICINELLI, E.; MELDRUM, D. Optimal uterine anatomy and physiology necessary for normal implantation and placentation. Fertility and Sterility, v. 105, n. 4, p. 844-854, 2016.

DUAN, J.; ZHOU, X.; ZHU, H.; ZHOU, M.; LIU, M.; ZHOU, Y.; LI, W.; XU, B.; ZHANG, A. Decreased expression of LEF1 caused defective decidualization by inhibiting IL-11 expression in patients with adenomyosis. Molecular Medicine, v. 31, n. 1, p. 10, 2025.

GUO, S.; LI, Z.; YAN, L.; SUN, Y.; FENG, Y. GnRH agonist improves pregnancy outcome in mice with induced adenomyosis by restoring endometrial receptivity. Drug Design, Development and Therapy, v. 12, p. 1621-1631, 2018.

HARMSEN, M. J.; ARDUÇ, A.; BLEEKER, M. C. G.; JUFFERMANS, L. J. M.; GRIFFIOEN, A. W.; JORDANOVA, E. S.; HUIRNE, J. A. F. Increased angiogenesis and lymphangiogenesis in adenomyosis visualized by multiplex immunohistochemistry. International Journal of Molecular Sciences, v. 23, n. 15, p. 8434, 2022.

HE, B.; TENG, X. M.; HAO, F.; ZHAO, M.; CHEN, Z. Q.; LI, K. M.; YAN, Q. Decreased intracellular IL-33 impairs endometrial receptivity in women with adenomyosis. Frontiers in Endocrinology, v. 13, p. 928024, 2022.

HORTON, J.; STERRENBURG, M.; LANE, S.; MAHESHWARI, A.; LI, T. C.; CHEONG, Y. Reproductive, obstetric, and perinatal outcomes of women with adenomyosis and endometriosis: a systematic review and meta-analysis. Human Reproduction Update, v. 25, n. 5, p. 592-632, 2019.

HU, S.; WANG, Y.; YAO, G.; SUN, Y. The expression changes of circular RNAs between LH +2 and LH +7 human endometrium. Acta Biochimica et Biophysica Sinica, v. 51, n. 12, p. 1296-1299, 2019.

JUÁREZ-BARBER, E.; SEGURA-BENÍTEZ, M.; CARBAJO-GARCÍA, M. C.; BAS-RIVAS, A.; FAUS, A.; VIDAL, C.; GILES, J.; LABARTA, E.; PELLICER, A.; CERVELLÓ, I.; FERRERO, H. Extracellular vesicles secreted by adenomyosis endometrial organoids contain miRNAs involved in embryo implantation and pregnancy. Reproductive Biomedicine Online, v. 46, n. 3, p. 470-481, 2023.

LI, D.; JIANG, W.; JIANG, Y.; WANG, S.; FANG, J.; ZHU, L.; ZHU, Y.; YAN, G.; SUN, H.; CHEN, L.; ZHANG, N. Preliminary functional inquiry of lncRNA ENST00000433673 in embryo implantation using bioinformatics analysis. Systems Biology in Reproductive Medicine, v. 65, n. 2, p. 164-173, 2019.

LIU, M.; LI, Y.; YUAN, Y.; JIANG, M.; YIN, P.; YANG, D. Peri-implantation treatment with TNF-α inhibitor for endometriosis and/or adenomyosis women undergoing frozen-thawed embryo transfer: a retrospective cohort study. Journal of Reproductive Immunology, v. 167, p. 104415, 2025.

MUNRO, M. G. Uterine polyps, adenomyosis, leiomyomas, and endometrial receptivity. Fertility and Sterility, v. 111, n. 4, p. 629-640, 2019.

PENG, Y.; LIU, X.; JIN, Z.; LIU, H.; XU, C. Scribble downregulation in adenomyosis compromises endometrial stromal decidualization by decreasing FOXO1 expression. Human Reproduction, v. 37, n. 1, p. 93-108, 2022.

PIRTEA, P.; DE ZIEGLER, D.; AYOUBI, J. M. Endometrial receptivity in adenomyosis and/or endometriosis. Fertility and Sterility, v. 119, n. 5, p. 741-745, 2023.

PRAŠNIKAR, E.; KUNEJ, T.; GORENJAK, M.; POTOČNIK, U.; KOVAČIČ, B.; KNEZ, J. Transcriptomics of receptive endometrium in women with sonographic features of adenomyosis. Reproductive Biology and Endocrinology, v. 20, n. 1, p. 2, 2022.

STRATOPOULOU, C. A.; ROSSI, M.; BEAUSSART, C.; ZIPPONI, M.; CAMBONI, A.; DONNEZ, J.; DOLMANS, M. M. Generation of epithelial-stromal assembloids as an advanced in vitro model of impaired adenomyosis-related endometrial receptivity. Fertility and Sterility, v. 123, n. 2, p. 350-360, 2025.

TANOS, V.; LINGWOOD, L.; BALAMI, S. Junctional zone endometrium morphological characteristics and functionality: review of the literature. Gynecologic and Obstetric Investigation, v. 85, n. 2, p. 107-117, 2020.

UNSER, A. C.; MONSIVAIS, D. Integral roles of the TGFβ signaling pathway in uterine function and disease. Endocrinology, v. 166, n. 3, 2025.

WU, H. M.; TSAI, T. C.; LIU, S. M.; PAI, A. H.; CHEN, L. H. The current understanding of molecular mechanisms in adenomyosis-associated infertility and the treatment strategy for assisted reproductive technology. International Journal of Molecular Sciences, v. 25, n. 16, p. 8937, 2024.

YU, R.; WEI, C.; LI, G.; OUYANG, J.; LIU, N.; GU, N.; LIN, Y.; XU, H. Aberrant TCF21 upregulation in adenomyosis impairs endometrial decidualization by increasing PDE4C expression. Biochimica et Biophysica Acta: Molecular Basis of Disease, v. 1871, n. 1, p. 167526, 2025.

Access this Article in Online

Website: www.ijarm.com

Subject: Endocrinology

Quick Response Code

DOI:10.22192/ijamr.2026.13.07.003

How to cite this article:
Bianca Borges, João Ronaldo Tavares. (2026). Embryonic origin of Adenomyosis: A systematic review of molecular and clinical evidence. Int. J. Adv. Multidiscip. Res. 13(7): 44-59.
DOI: http://dx.doi.org/10.22192/ijamr.2026.13.07.003