in vivo *37*: 1922-1930 (2023)
doi:10.21873/invivo.13288

Review

Pathogenesis of Endometriosis: Focus on Adenogenesis-related Factors

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Abstract. *Endometriosis can be defined as the presence of the endometrium outside the uterine cavity. It affects approximately 10% of women of reproductive age and causes infertility, chronic pain, and deterioration of the quality of life. Since the identification of the disease, various pathogenetic mechanisms have been proposed, such as retrograde menstruation, coelomic metaplasia, hormonal imbalance, stem cell involvement, and alterations in epigenetic regulation. However, the underlying pathogenesis of endometriosis remains inadequately understood. Elucidation of the precise mechanism of the development and progression of endometriosis is crucial for effective treatment. This review presents the major pathogenetic theories of endometriosis based on current research studies with a major focus on the potential role of uterine factors.*

Endometriosis is characterized by the presence of endometrial tissue outside the uterus, often accompanied by chronic inflammation. The first documented description of endometriosis and its pathogenesis dates to 1860, when von Rokitansky observed the presence of active endometrial tissue outside the uterine cavity (1).

However, it was not until 1927 that a formal definition of endometriosis emerged when Sampson introduced the term "endometriosis" into medical terminology (2). According to his theory, the disease was attributed to a phenomenon known as "retrograde menstruation," which involves the backward flow of menstrual blood and subsequent implantation of endometrial cells within the peritoneal cavity (2).

This theory is the most shared in the literature but certainly not the only one, because despite extensive research, the precise reason why retrograde transport of menstrual blood, a common event in approximately 90% of women of reproductive age, results in the survival and growth of endometrial tissue outside the uterus in only a minority of women, remains elusive (3).

Furthermore, numerous studies have shed light on the distinctions between endometriotic cells and eutopic endometrial cells, supporting the theory of the development of endometriosis "*in situ*" from embryonic cell remnants or tissues during cellular migration (4). Interestingly, we have recently shown that eutopic and ectopic endometrium present differential expression of "adenogenesis related factors" (5). In addition, endometriosis is histologically characterized by the presence of endometrioid glandular structure and surrounding endometrial stroma, regardless of the tissue involved (6). It is unfortunate that despite extensive investigations the complex nature of this disease is still not fully understood.

This review aims to provide a comprehensive summary of recent advancements in our understanding of the pathobiology of endometriosis, with a specific focus on endometrial adenogenesis. A thorough literature review was conducted using PubMed and Google Scholar, searching for articles on the pathogenesis of endometriosis using the keywords 'endometriosis', 'pathogenesis', and 'review'. A total of over eight hundred articles published between 1975 and 2023 were identified, and close to one hundred articles were selected for detailed analysis.

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Key Words: Endometriosis, endometrium, uterus, adenogenesis, review.

Epidemiology

Endometriosis affects 5-10% of women of reproductive age (7) and more than 176 million women have endometriosis worldwide (8). Most endometriosis cases occur in women between the onset of menstruation (menarche) and menopause, with a peak incidence between the ages of 25 and 45 years (9). However, it should be noted that there are also cases of endometriosis in postmenopausal women and adolescents (10). The risk of developing endometriosis is lower in black women and higher in Asian women (11). Infertility is a relatively common symptom among women with endometriosis, with approximately 30% to 50% experiencing difficulties in conceiving (12). Endometriosis can significantly impact various aspects of social life, family dynamics, and sexual well-being (13). The presence of pain and associated physical dysfunction further diminishes the overall quality of life (14).

Interestingly, in a recent retrospective work from our research group on a large population of endometriosis patients, chronic fatigue syndrome, dyspareunia, and bowel disorders have been identified as primary symptoms of endometriosis, along with a lower incidence of urinary disorders and chronic pelvic pain, which are typically considered key symptoms of the condition (5).

Endometriosis is a highly significant issue not only in terms of medical and social impact but also from an economic perspective. The annual costs associated with endometriosis treatment in Europe range from 0.8 billion to 12.5 billion, varying by country, and are comparable to the costs of managing other chronic diseases such as diabetes (13).

Risk Factors

Various genetic, endocrine, immunological, microbiotic, and environmental factors have been reported to have positive or negative associations with the development of endometriosis.

Some factors associated with an increased risk include: Early menarche (before the age of 11) (15); shorter than 27-day menstrual cycles (16); low body mass index (17); small number of births; prolonged estrogen exposure (18); Asian ethnicity (19); and uterine outlet obstruction (16). However, cigarette smoking and higher parity are linked to a decreased risk (20).

Types of Endometrioses

Most diagnosed cases of endometriosis can be broadly classified into four principal subtypes:

1. superficial/peritoneal endometriosis that accounts for ~80% of endometriosis (21).

Focal lesions of endometriosis within the peritoneum are detected in 15-50% of women diagnosed with endometriosis (22).

2. ovarian endometriosis (cysts or ''endometrioma'').

Ovarian endometriosis is among the most prevalent manifestations of this condition and can affect 2-10% of women of reproductive age, with rates increasing up to 50% among patients undergoing infertility treatment (23).

3. Deep infiltrating endometriosis (DIE) (24, 25).

It is characterized by the infiltration of endometrioid glands into various pelvic organs, including ligaments, rectum, vagina, and bladder. Additionally, the infiltration of endometrial cells >5 mm below the surface of the peritoneum or connective tissue is a defining feature (25).

4. extra-pelvic localizations such as: abdominal organs, abdominal wall, diaphragm, pleura, and the central and peripheral nervous system (26).

Interestingly, in a recent retrospective work on more than four thousand patients with endometriosis, the clinical signs associated with endometriosis were most commonly observed in the rectovaginal septum, posterior wall of the uterus, left uterosacral ligament, and posterior fornix. When analyzing the exact anatomical localization of lesions through endoscopy and histological analysis, the highest incidence was found in the deep peritoneum, while the superficial peritoneum exhibited a significantly lower incidence. A similar distinction between superficial and deep tissues was also observed in both ovaries (27).

Diagnosis

Knowledge of population distributions, disease manifestations, and risk factors is limited to data for women in whom endometriosis is successfully diagnosed. Despite its high prevalence, endometriosis recognition is still inadequate and diagnosis time ranges from 4 to 11 years, with 65% of women being initially misdiagnosed (28). Rather, key symptoms that currently prompt surgical evaluation, such as pain and infertility, can have multiple causes. Up to now, none of the many biomarkers in peripheral blood proposed for endometriosis has been validated (29). Nisenblat and colleagues in 2016 (30) analyzed blood, urinary, and endometrial markers (alone or combined with imaging). The authors conclude that none could be evaluated in a meaningful way and that laparoscopy, with histological examination, remains the gold standard for the diagnosis of endometriosis and any non-invasive tests should only performed in a research setting.

A perfect diagnostic test for endometriosis should display high sensitivity and high specificity, so that no endometriosis patients would be lost, and no healthy patients would be selected for needless extra procedures. Our research group, by means of a proteomic 2D-gel analysis-based approach, has defined at least three potential diagnostic markers for endometriosis: zinc-alpha-2-glycoprotein, albumin, and complement C3 (31-33). ROC curve analyses established the non-overlapping diagnostic potential of these markers in a

robust cohort of endometriosis patients. Recently, a diagnostic test based on the analysis of microRNAs has been proposed and validated on a cohort of endometriosis patients (34).

Imaging

Ultrasound (US) examination is a fundamental diagnostic tool in the evaluation of endometriosis (35), especially transvaginal ultrasound (TVUS) (36). The utilization of dynamic ultrasonographic examination offers the potential to gather additional information that may not be easily obtained through other imaging techniques (35, 36). The International Deep Endometriosis Analysis group (37) suggests the following key steps to be followed during the examination:

1. Routine assessment of the uterus and adnexa to identify adenomyosis and the presence or absence of endometriomas.

2. Evaluation of transvaginal sonographic soft markers such as specific tenderness and ovarian mobility.

3. Assessment of the status of the Douglas pouch using the sliding sign.

4. Examination for deep infiltrating endometriosis (DIE) nodules in the anterior and posterior compartments.

These steps should be performed, although not necessarily in the specified order, with a partially filled bladder. According to Hoyos *et al*., "Computed tomography has no role in the routine evaluation of endometriosis except in very few particular scenarios" (38). magnetic resonance imaging. is commonly employed for the diagnosis of endometriosis (39). However, there is currently no consensus on the optimal MRI descriptors for deep endometriosis (DE). The guidelines from the European Society of Urogenital Radiology (ESUR) (40) recommend MRI as a secondary imaging technique following transvaginal ultrasound (TVUS) for evaluating endometriosis. Furthermore, ESUR recommends the use of MRI for preoperative staging to predict the presence of DE in multiple locations in cases where TVUS results are inconclusive or when a symptomatic patient has negative TVUS findings (40).

Nevertheless, to the best of our knowledge no marker has been identified, permitting, through MRI exam, the exact localization *in vivo* of the endometriotic lesions, both cystic and connective solid ones (41). Moreover, endometriotic lesions can have microscopic sizes (less than 1 cm) (42), which makes virtually impossible with the presently existing analysis methods to identify the *in vivo* localization of these lesions. Recently, our research group has identified anti-mullerian hormone as a suitable cellular target to allow detection *in vivo* of the exact localization of the endometriotic tissue in an animal model of ectopic transplant of endometriosis tissue (43). The data generated suggests the use of such marker for diagnosing *in vivo* endometriosis and for pinpointing and/or assessing the entity of the endometriosis lesions in endometriosis patients.

Laparoscopy

The predominantly intraabdominal location of the lesions, plus their small size, means that laparoscopic visualization, with histologic verification, remains the standard for diagnosis of the disease (25). This observation is valid, however, only for lesions present on the external bladder, intestinal and peritoneal surfaces. In fact, laparoscopy does not identify intra-organ lesions that do not emerge on the surface and do not deform the organs, just as it does not identify deep endometriosis lesions that may be present in the extraperitoneal areas of the reproductive system such as perirectal and vaginal nodules. Finally, this method cannot identify very small lesions such as, for example, microscopic adenomyosis (42). Therefore, there is a strong need for additional methods to complement the previously reported diagnostic tools.

Histology of Endometriosis

Histology is the central tenet of endometriosis' diagnosis: endometrial glands, endometrial stroma, and/or hemosiderin-laden macrophages. Despite the site of endometriosis, at microscopical examination, a pathologist should find at least 2 of the following 3 features (44):

1. Endometrial type glands: Müllerian type epithelium (can be atrophic to cycling endometrium), which can also show degenerative atypia (enlarged smudgy nuclei) or even metaplasia;

2. Endometrial type stroma: often contains fine capillary network, may undergo smooth muscle metaplasia, fibrosis (longstanding), and decidual change. In exceptional cases can be myxoid (particularly during pregnancy). A pathologist must be aware that the stroma may be the only identifiable histological component of the lesion (should be reported as "stromal endometriosis");

3. Evidence of chronic hemorrhage (hemosiderin laden or foamy macrophages) (45).

Figure 1 shows a typical histology of endometriosis.

Staging Endometriosis

At present, the American Society for Reproductive Medicine (ASRM) system, which was originally developed for endometriosis staging (46), has been implemented with the Enzian staging system (47-49) because it poorly correlates with pain symptoms, infertility, and excludes extra-pelvic lesions (46).

However, the World Endometriosis Society published a consensus statement to expand understanding of how this condition is classified (50); "Until better classification systems are developed, we propose a classification toolbox (that includes the revised American Society for Reproductive Medicine and, where appropriate, the Enzian and Endometriosis Fertility Index staging systems)" (50).

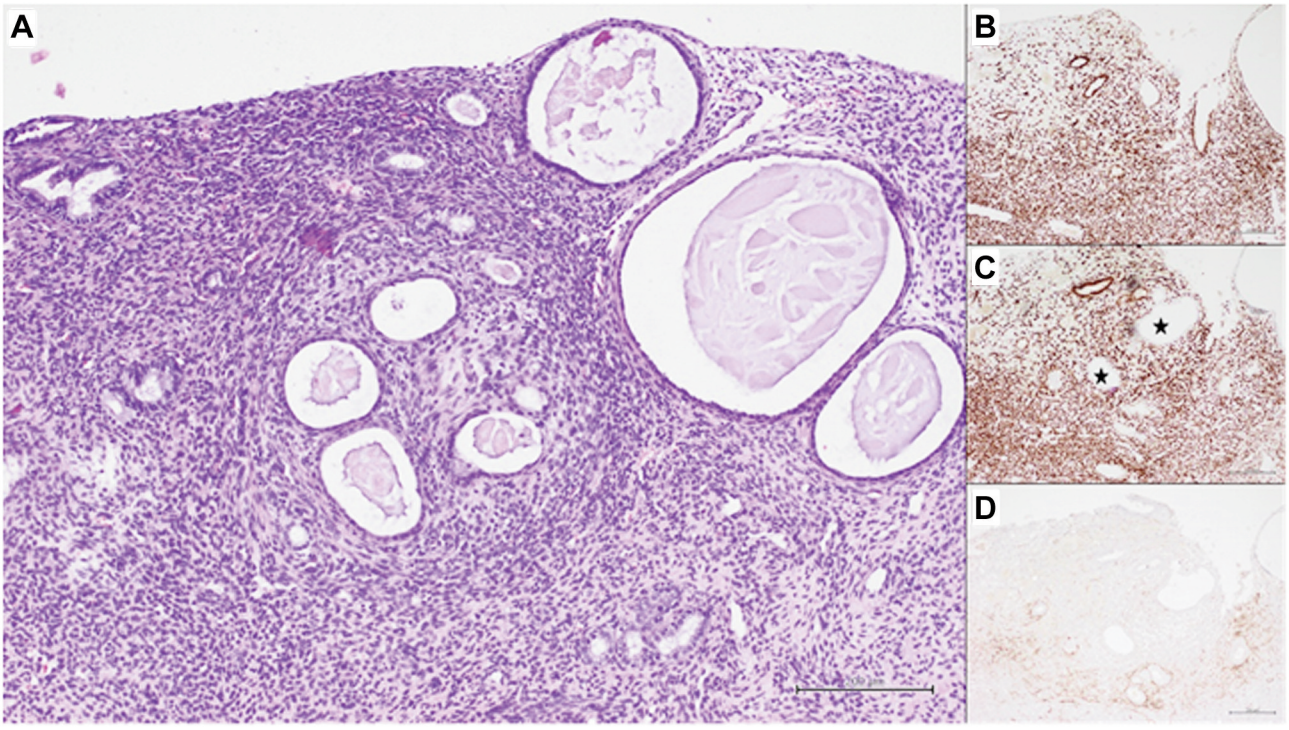

Figure 1. *Histological example of endometriosis. A) Histology shows several endometrioid glandular structures in a highly cellulated stromal background (Hematoxylin and Eosin, 10× magnification, scale bar 200 μm). B-D) Immunohistochemical analysis shows diffuse positivity for estrogen receptor (B), and for progesterone receptor (C) while few glands appear negative for progesterone receptor (C - black star), the endometrioid stroma is confirmed by positivity for CD10 (D) (Immunostaining, 20× magnification, scale bar 100 μm).*

Origin of Endometriosis

One of the most fascinating aspects of endometriosis is the survival and establishment of apparently normal endometrial tissue outside the uterus. Various theories have been proposed to elucidate the origin of endometriosis and to explain the mechanisms by which tissue can disperse throughout the body.

Retrograde menstruation model. In 1927, Sampson (51) proposed a retrograde flow of the menstrual mix of blood and endometrial tissue through the Fallopian tubes into the peritoneal cavity as the first step in the development of this disease. Sampson's theory finds support in data demonstrating that retrograde menstrual flow is a common occurrence in women. Furthermore, increased retrograde flow resulting from obstructive defects in the outflow tract significantly raises the prevalence of endometriosis (7). However, it is important to note that endometriosis can also be found outside the pelvic region, in women who have undergone hysterectomy, and even in men. This suggests that retrograde menstruation is not the sole pathway for the development of endometriosis (52, 53).

Celomic metaplasia model. This theory proposes a mechanism that would explain the presence of lesions on the peritoneum (54). It assumes that the original coelomic membrane undergoes metaplasia and forms endometrial stroma and glands.

The celomic metaplasia model could easily explain the formation of ovarian endometriosis/endometriomas. The mesothelium, originating from the coelomic epithelium that covers the ovary, possesses significant metaplastic potential. It can undergo invagination into the ovarian cortex, and these mesothelial inclusions have the potential to transform into endometriosis through metaplasia (55).

Endometrial stem cell recruitment model. The two primary theories regarding the origin of endometriosis stem cells propose that they either arise from the uterine endometrium or from bone marrow. Regardless of the site of origin, the microenvironment of the surrounding tissue, along with hormonal and other factors, contribute to the adhesion, invasion, inflammation, angiogenesis, and evasion of immunosurveillance necessary for the establishment of endometriosis.

In the normal endometrium, epithelial stem cells are predominantly found in the basalis layer, providing a

geographic protection against the effects of regular menstruation. These stem cells are considered to play a crucial role in regenerating the epithelium of the functional layer during the proliferative phase in response to estrogen.

The migration of endometrial stem cells is still a hypothesis, and various theories have been proposed to explain this process. One theory, based on Sampson's retrograde menstruation model, suggests that stem cells in the blood can reach the peritoneal cavity through the fallopian tubes. This theory is supported by evidence showing the presence of endometrial stem cells in menstrual blood (56). Another possible mechanism for stem cell migration to ectopic sites involves abnormal cell migration during the development of the female reproductive tract (56). Additionally, it is suggested that stem cells originating from the endometrium may passively enter the angiolymphatic space during menstruation and subsequently circulate throughout the body (57).

Bone-marrow stem cell recruitment model. According to Wang and colleagues (56) this variant stem cell recruitment model, follows the same rules of the endometrial stem cells, but is based on another source of stem cells, the bone marrow. Various populations of stem cells derived from the bone marrow, known as bone marrow-derived stem cells (BMDSCs), including mesenchymal stem cells, hematopoietic stem cells, and endothelial progenitor cells, can integrate into the endometrium and participate in tissue regeneration (58). The number of these cells circulating in the bloodstream may increase during the menstrual cycle and the proliferative phase of the endometrium (57). In summary, the model of the theory is the following: circulating BMDSCs deviate from their intended destination in the endometrium and instead migrate to soft tissues, leading to the development of endometriosis (57). The strength of this theory is that BMDSCs are thought to be the major source of stem cells that cause endometriosis outside of the peritoneal cavity, and they could also explain the rare endometriosis cases in men. However, each model seems to have conceptual flaws, and it is not possible to fit all the pieces of the puzzle. For instance, various studies have revealed the contrasting characteristics between endometriotic cells and eutopic endometrial cells. These include diminished responsiveness to progesterone (58), heightened resistance to apoptosis (59), and increased capacity for cell adhesion, migration, and invasion (60). Consequently, the traditional model of retrograde menstruation is now facing a critical challenge, necessitating the exploration of alternative models and paradigms. The embryonic rest model of endometriosis may represent one of these new paradigms.

Embryonic rest model. Similar to the theory of celomic metaplasia, this concept proposes that residual embryonic cells derived from the Wolffian or Müllerian ducts can undergo differentiation, giving rise to endometriotic lesions (61). According to this theory, these embryonic cells remain dormant until puberty, and upon estrogen stimulation, the development of endometriotic lesions commences. This theory is applicable not only to women with endometriosis but also to men, as the Wolffian ducts also harbor embryonic cells (61). Furthermore, this mechanism may provide an explanation for the common occurrence of endometriosis in the deep peritoneum and the Douglas pouch (27). Recently, our research group conducted a meticulous autopsy analysis, which revealed the presence of endometriotic structures in a significant number of female fetuses (62, 63). This observation has been successively confirmed by other research groups (64).

Role of Adenogenesis in Endometriosis

The molecular pathways involved in uterine adenogenesis have been clearly defined in the last years (65). Recently, a link has been proposed between uterine adenogenesis and development of endometriosis based on the observation of the reduced expression in endometriosis lesions compared to adult endometrium of DLx5 and Dlx6 gene products, two closely associated homeobox genes coding for transcription factors involved in the control of uterine adenogenesis (66). Alterations in the molecular pathways related to uterine adenogenesis in endometriosis is consistent with the embryogenetic model proposed for the pathogenesis of endometriosis.

However, the high recurrence rate of this disease in patients treated with antiestrogens or GnRH analogs indicates the existence of alternative pathways for cellular growth and differentiation (67). It is worth noting that there is limited research on the expression of these molecules in endometriosis compared to normal endometrium, and there are no studies analyzing them collectively.

Based on these observations, our research group developed research to better comprehend the complex ratio between adenogenesis and epithelial-mesenchymal interaction (4, 67). Table I comprehensively summarizes the results of all studies.

Indeed, both uterine development and the development of endometriosis rely, at least partially, on interactions between epithelial and mesenchymal cells. These interactions are reflected in the inherent differences observed between eutopic (normal) and ectopic (abnormal) endometrium (65, 66).

In this study, we conducted an analysis of immunohistochemical expression of PRL-R, GH, IGF-1, IGF-2, FGF-23, FGF-7, FGF-10, IFN-τ, in normal human endometrium and stroma. We compared their expression with that in the epithelium and stroma of 42 deep endometriosis samples (4, 68). Interestingly, we found that FGF-23 and IFN-τ showed significantly higher expression in the ectopic endometrial stroma compared to the eutopic endometrium, and there was also a higher expression of GH. Finally, we found a lower PRL-R expression in the ectopic endometrial epithelium compared to the eutopic one.

Table I. *Immunohistochemical comparison between the eutopic and ectopic endometrium.*

	Eutopic endometrium		Ectopic endometrium	
	Epithelial compound	Stromal compound	Epithelial compound	Stromal compound
FGF7	High	High	Low	Low
FGF10	High	High	Low	Low
FGF23	High	Low	High	High
IFN-τ	High	Low	High	High
HGF	High	High	Low	Low
PRL-R	High	Low	Low	Low
GH	Low	Low	High	Low
IGF1	High	High	Low	Low
IGF2	High	High	Low	Low

As mentioned earlier, it is widely acknowledged that the development of endometrial adenogenesis relies, at least partially, on the proper epithelial-mesenchymal interaction. Both PRL-R and GH hormones are known to contribute to this process through their autocrine/paracrine actions. Additionally, IGF1 and IGF2, which are downstream targets, are involved in regulating cellular growth and differentiation (69). The significance of prolactin family members in uterine development and endometrial adenogenesis has been well established (70).

Considering the role of GH in promoting cellular proliferation and reducing cell-cell adhesion, it is plausible to hypothesize that its higher expression during embryogenesis could facilitate individual cells to detach from their normal niche. This phenomenon may contribute to the formation of primitive endometriosis lesions (71). Interestingly, both PRL-R and IGF1 show clear over-expression in the serum and peritoneal fluid, respectively, of women with endometriosis (72). The data generated from our study suggest a potential role for PRL-R and IGF in the progression of endometriosis, rather than in the pathogenesis of the disease (62). On the contrary, this extracellular overexpression could potentially contribute to the development of a microenvironment that is favorable for the survival and growth of endometrial tissue outside the uterus. Consistent with other studies, we observed an increase in the expression of GH and PRL-R during the secretory phase of human endometrial samples (73).

Conversely, GH and PRL-R expression in the stromal and epithelial endometriotic tissues was not correlated with the proliferative or secretory phase. These findings suggest that certain factors involved in the development of endometriosis may be regulated differently respect to normal endometrial tissue and may not depend on female sex hormones for their formation and maintenance.

FGF-23 and IFN-τ have been identified as regulators of phosphate, calcium, and vitamin D signaling during the peri-implantation period of pregnancy (74). Several studies have associated low levels of vitamin D with endometriosis, suggesting a potential role of vitamin D deficiency in the development of the condition (75). Additionally, FGF-23 levels have been found to be associated with estrogen expression (76). It has been proposed that estrogen exposure, such as through estrogen therapy, might prevent or counteract the postmenopausal rise in serum FGF-23 and phosphorus levels (77).

In an *in vivo* model of developing neonatal ovine uterus, growth factors, including FGF-7, FGF-10, HGF, and their epithelial receptors, were found to play a crucial role in endometrial morphogenesis (78). Our research indicates a significant decrease in the expression of FGF-7, FGF-10, and HGF in both the epithelial and stromal components of ectopic endometrium. Considering the well-established role of these growth factors in promoting cellular proliferation and reducing cell-cell adhesion, it can be hypothesized that during embryogenesis, higher expression of these factors allows individual cells to detach from their original niche and contribute to the formation of primitive endometriosis lesions. The diminished expression of these factors in endometriosis may be linked to disease progression in adulthood, potentially influenced by the hyperestrogenic environment within endometriotic structures (79).

Finally, in our studies, we compared the immunohistochemical expression of these growth factors in relation to the different phases of the hormonal cycle in uterine tissue samples used as controls. Interestingly, we did not observe any correlation between the expression of these factors and changes in the ovarian cycle. Endometriosis is commonly referred to as an "estrogen-dependent" disorder, but based on our data, we propose that this definition should be updated to "steroid-dependent" to acknowledge the significance of other steroids and their receptors in regulating cellular processes in both eutopic and ectopic endometrium (4). In our opinion, this scientific evidence supports the embryogenetic theory in the pathogenesis of endometriosis.

Conclusion

Endometriosis is a chronic, hormonally dependent disease with a significant inflammatory component that affects millions of women worldwide (approximately 190 million). The condition greatly reduces their quality of life due to distressing symptoms and negative emotional experiences associated with overall health, diagnosis, and treatment side effects.

The pathogenesis of endometriosis is clearly complex, involving multiple factors and processes that occur concurrently. Over the years, numerous theories have been studied, but none has provided a comprehensive explanation for all aspects of the disease. The future understanding of endometriosis is likely to incorporate elements from various pathogenetic theories. In this context, exploring adenogenetic factors should be a research focus.

Only through a deeper understanding of the pathogenesis of this enigmatic yet prevalent reproductive disorder we can develop improved therapies and enhance the quality of life of women suffering from endometriosis.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

PGS and AB were responsible for conceptualization, methodology, formal analysis, and revision; MM and AR were responsible for writing and original draft preparation; PGS was responsible for funding acquisition.

Acknowledgements

This work was supported by the Fondazione Italiana Endometriosi (Grant: "Progetto Genomico"). The Authors would like to express their gratitude to Roberta Riposati and the entire staff of Fondazione Italiana Endometriosi for their invaluable assistance in our research endeavors at the Foundation.

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Received May 5, 2023
Revised June 11, 2023
Accepted June 12, 2023