Review article

Relationship between adenomyosis and endometriosis; Different phenotypes of a single disease?

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\textbf{A B S T R A C T}

Adenomyosis and endometriosis are common gynecological disorders, but their pathophysiology is still under debate. The aim of this review is to discuss whether adenomyosis and endometriosis represent two different entities or different phenotypes of a single disease. We searched PubMed electronic databases published between January 2000 and April 2020. Endometriosis is classified into three phenotypes; superficial peritoneal disease (SUP), ovarian endometriosis (OMA) and deep infiltrating endometriosis (DIE) lesions. Adenomyosis presents several different subtypes, including intrinsic adenomyosis, extrinsic adenomyosis, adenomyosis externa and focal adenomyosis located in the outer myometrium (FAOM). Human uterus is embryologically composed of archimetra, originating from the Müllerian duct, and neometra, arising from the non-Müllerian duct, and endometriosis and endometriosis are diseases of archimetra. The outer myometrial layer of the uterus is composed of highly differentiated smooth muscle cells (SMCs), while the inner myometrial cells are immature. Inappropriate uterine contractions can cause retrograde menstruation and chronic inflammation in the pelvic cavity, then influencing the development of pelvic endometriosis. Furthermore, hyperperistalsis results in physiological and pathological changes to the endometrial-myometrial junctional barrier, allowing invagination of the normal endometrial tissue into the inner myometrial layer. This can trigger the development of intrinsic adenomyosis. There are insufficient data available to draw conclusions, but extrinsic adenomyosis may result from pelvic endometriosis and FAOM from rectal and bladder DIE/adenomyosis externa. In conclusions, this paper contributes to the debate in the possibility that adenomyosis and endometriosis represent different phenotypes of a single disease.

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Introduction

Endometriosis is a common gynecological disease, characterized by the presence of endometrial tissue outside the uterus, and the main clinical manifestations are pelvic pain and infertility [1–3]. Uterine adenomyosis is characterized by the presence of endometrial glands and stromas within the myometrium and is usually associated with pelvic pain, abnormal uterine bleeding or infertility [4–6]. Poor quality of life due to delayed diagnosis is a major problem for treatment of these disorders. Recent advances in imaging such as transvaginal ultrasound (TVS) and magnetic resonance imaging (MRI) contribute significantly to diagnostic accuracy in the field of reproductive medicine. Endometriosis is classified into three phenotypes; superficial peritoneal disease (SUP), ovarian endometrioma (OMA) and deep endometriosis (DIE) lesions [1]. On the other hand, adenomyosis presents several different subtypes, including intrinsic adenomyosis, extrinsic adenomyosis, adenomyosis externa and focal adenomyosis located in the outer myometrium (FAOM) [5,7,8]. However, these classifications are not yet fully agreed internationally. Generally, adenomyosis and endometriosis share a number of clinical, biological and molecular features, but they are considered to be two different entities [2]. In the area of basic research, the molecular mechanism of survival, adhesion, proliferation, invasion and fibrogenesis pathways in ectopic endometrium is currently being studied through genomic approaches [9]. Some researchers have noted that adenomyosis and endometriosis are independent disorders because they show different gene expression and pathogenic signaling pathways [10,11]. The fact that gene expression is different in both disorders suggests that each disease may occur with different gene expression, or that exposure to different environments results in altered gene expression through epigenetic changes [10,11]. Some researchers have shown that genetic alterations may be epigenetically regulated [10,11]. It is currently unknown whether these genetic and epigenetic abnormalities are affected by the microenvironmental changes and lead to the development of disease. Thus, it remains unclear whether two diseases are genetically determined, microenvironmentally induced, or both.

Understanding the relationship between imaging, epidemiology, molecular biology and biochemical microenvironments can provide new insights into the undetermined pathophysiology. Several articles discuss etiology, pathogenesis, diagnostics, classification, symptom severity and medical and surgical management options for adenomyosis and endometriosis [1,2,7,12]. However, there has been insufficient information on the relevance of the pathophysiology of each phenotype. The aim of this review is to discuss whether adenomyosis and endometriosis represent two different entities or different phenotypes of a single disease. The current review article provides some of the insights provided by the pioneering researchers and the latest updates on the relationship between adenomyosis and endometriosis, and concludes with our personal opinion.

Methods

Search strategy and selection criteria

A computerized literature search was performed to identify relevant studies reported in the English language. We searched PubMed and Google Scholar electronic databases published between January 2000 and April 2020, combining the keywords ‘adenomyosis’, ‘endometriosis’, ‘pathogenesis’, ‘classification’, ‘subtype’, ‘phenotype’, and ‘fibrosis’. A variety of combinations of these terms were used, depending on which database was searched (Table 1). Furthermore, the references of each article were searched to identify potentially relevant studies. Publications of original studies, review articles and some guidelines were included, while those documenting opinions, points of view or anecdotes were excluded.

Table 1
The number of articles hit by searching for each keyword alone or in combination.

<table>
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<tr>
<th>Key words</th>
<th>No. of refs.</th>
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<tr>
<td>adenomyosis</td>
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<td>70</td>
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<td>adenomyosis</td>
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<tr>
<td>endometriosis</td>
<td>pathogenesis</td>
<td>classification</td>
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Each keyword alone or in combination was used to search by applying the filters of the title and the publication years between 2000 and 2020. Table shows the number of articles searched by keywords and the number of eligible articles among them and that, for example, the number of articles hit by searching for keywords for ‘adenomyosis AND pathogenesis’ AND ‘classification’ is 70. Among the 79 articles, 41 articles were eligible.
Results

The current knowledge of uterine structure and function

Proper knowledge of the embryology of the female reproductive system is essential to understand the etiology and pathogenesis of mysterious reproductive disorders, adenomyosis and endometriosis [7]. The female reproductive system develops from a pair of paramesonephric or Müllerian ducts of mese
dermal origin [13] and derives from mesoderm, primordial germ cells, coelomic epithelium, and mesenchyme [14]. The Müllerian ducts arise as an invagination of thickened coelomic epithelium and develop the upper two-thirds of the vagina, the cervix, uterus and both fallopian tubes [13,14]. The human uterus is composed of three layers such as endometrium, myometrium and perimetryrium, also termed the serosa. The endometrium and myometrial layer of the uterus are formed from mesoderm [14]. The developmental origins are different between the inner and outer structures of the uterus [7,15]. The myometrium is divided into the inner and outer portions of the uterine wall, and the inner portion is defined as the subendometrial myometrium or stratum subvasculare. The outer part consists of the stratum vasculare and supravasculare. The inner structure, which includes the endometrium, subendometrial functional zone (JZ) and the underlying stratum subvasculare of the myome
trium, is called ‘archmetra’ and originates from the Müllerian duct [7,15]. On the other hand, the outer structures of the uterus, the stratum vasculare and supravasculare of the myometrium, arise from the non-Müllerian duct and is referred to as ‘neometra’ [7,15]. Histopathological examination showed clear differences in cell density and stereotypical changes in nuclear size between the inner and outer myometria, but the transition is gradual and there is no distinct zonation [16]. The archmetra and the neometra exhibit different pathophysiological functions on hormone receptor expression, hormone sensitivity, smooth muscle cell development and uterine contractility [15].

The biomechanical function and remodeling of the uterus are required for normal reproductive processes such as menstrua
tion, fertility, gestation, and childbirth [17,18]. The female reproductive organ undergoes dynamic morphological, function-
al, biochemical and molecular changes in response to estrogen and progesterone [17]. There are at least two types of uterine contractions: sustained uterine contraction and uterine peristalsis [17]. The former is focal and sporadic bulging of the myometrium with sufficient strength, which mainly depends on the contraction of the outer myometrial layer of the uterus [17]. The outer myometrium is composed of terminally differentiated smooth muscle cells, which can produce cytoskel
etal proteins, allowing for large uterine contractions [19]. This layer is necessary to structurally strengthen the uterus, protect the fetus from external forces and allow continuous uterine contractions due to labor. On the other hand, the latter is rhythmic and wavelike movements of the subendometrial myometrium associated with contractions of the inner myome
trium [17]. The direction of the uterine contractions is retrograde (cervix to fundus) for sperm transport during ovulation and anterograde (fundus to cervix) for discharge of menstrual blood [17,20]. The inner myometrium including archmetra allows uterine peristalsis [19]. Thus, the human uterus is composed of smooth muscle cells with morphological, functional and phenotypic differences. Since the inner myometrium consists of undifferentiated smooth muscle cells, repeated childbirths and abortions can trigger tissue damage [19]. Therefore, uterine hyperperistalsis and persistent uterine contraction may induce micro trauma, inflammation, cell proliferation, extracellular matrix production and fibrosis at the level of the archmetra [21].

Pathogenesis of uterine adenomyosis: a lesson from gallbladder adenomyosis

The term ‘adenomyoma’ was proposed by Karl von Rokitansky in 1860 [22]. In 1921 Thomas Stephen Cullen pathologically discovered a mucosal invasion into the myometrium and in 1925 Oskar Frankl named it adenomyosis [22]. In 1927 John Albertson Sampson proposed the term ‘endometriosis’ when endometrial tissue is located outside the uterus [23]. Adenomyosis shares a number of similarities with endometriosis and is used to be called ‘endometriosis interna’ in 1956 [9,24]. So far, various subtypes such as intrinsic adenomyosis, extrinsic adenomyosis, adeno
dyosis externa, FAOM have been proposed. This proposal does not reach agreement on an international evidence-based standardization system for the classification of adenomyosis. Further, deeply infiltrating endometriosis can be defined as endometriosis infiltrating deeper than 5 mm under the peritoneal surface and is classified as three types I, II and III depending on the disease extent [25]. Type III is the most severe lesion suggested to be caused by adenomyosis externa [25]. As originally suggested by Cullen, the definition ‘deeper than 5 mm’ was changed to ‘adenomyosis externa’ [7]. Thus, each of these types of adeno
dyosis is not an exclusive classification.

To understand the pathogenesis of uterine adenomyosis, we investigate where and how adenomyosis occurs in organs other than the uterus. PubMed and Google Scholar databases were searched for the keyword ‘adenomyosis’, which identified two diseases: uterine adenomyosis and gallbladder adenomyosis (adenomyomatosis). The gallbladder wall histologically consists of the layers of the mucosa, submucosa, muscular wall and serosa [26]. Gallbladder adenomyosis/adenomyomatosis is a disease characterized by epithelial proliferation and hypertrophy of the muscular layer, leading to epithelial infolding within the underlying muscular layer and subsequent formation of the so-called Rokitansky-Aschoff sinus [26]. This disease results from a functional obstruction to the outflow of bile [27]. The prevalence of this disease in cholecystectomy samples ranges from 1% to 9%, with no gender difference [28]. The incidence is higher in the 50 s and older [28].

Next, we investigated the pathogenesis of gallbladder adenomyosis/adenomyomatosis. The layers of the mucosa and muscular wall of gallbladder are subjected to dynamic forces such as mechanical stretch. Biophysical forces due to high transmural pressures by impaired bile drainage can cause mucosal invagination through the muscularis as an intramural diverticula [27]. The elevated pressure and mechanical stretch expose cells to excessive load, which may lead to pathological consequences through the formation of inflammation [28]. Increased gallbladder pressure probably causes an inflammatory disorder such as cholecystitis [27]. Thus, inflammation can trigger cellular events that further promote an epithelial-mesenchymal transition (EMT) in the Rokitansky-Aschoff sinuses, leading to gallbladder adenomyosis [29]. The classification of gallbladder adenomyosis subdivides into three groups: diffuse, segmental or localized [27]. The diffuse type is reportedly associated with a stronger inflammatory response than the segmental or localized type [29]. Common pathophysio-
logical abnormalities can translate the lessons learned from the etiology of gallbladder adenomyosis into uterine adenomyosis. We speculate that, like gallbladder adenomyosis, both biophysical forces and inflammation are involved in the development of uterine adenomyosis.

Phenotypic similarities and differences between adenomyosis and endometriosis

Uterine adenomyosis and endometriosis are two different diseases, but often coexist and their clinical features are similar [2].
The age-of-onset distributions vary depending on the subtype of two diseases. SUP and OMA were more common than DIE in juvenile endometriosis [30]. Adenomyosis is a common disease found in women in the transitional period of perimenopause [4]. Like endometriosis, adenomyosis has come to be classified into subtypes. We discuss how each subtype of adenomyosis is associated with endometriosis phenotypes. The classification of adenomyosis is summarized in a recent paper [31]. Sampson divided adenomyosis into 3 groups according to the origin or pathogenesis: invasion from within the uterus; invasion from outside the uterus; and misplaced endometrial tissue (originating from embryonic pluripotent Müllerian remnants) in the uterine wall [32]. This theory, in turn, led to Kishi’s classification criteria in 2012 [5]. Subtypes of adenomyosis with different localization (e.g., intrinsic or extrinsic) have been reported [5,9,31]. Intrinsic adenomyosis occurs at the inner myometrium and is characterized by higher ages, multiparity and a history of curettage [5]. In extrinsic adenomyosis, it takes a considerable amount of time for basal endometrial tissue to cross the JZ barrier, invade the muscular layer, and ultimately form distinct lesions. Extrinsic adenomyosis occurs at the outer myometrium and is characterized by a strong relationship with pelvic endometriosis [5]. Therefore, extrinsic adenomyosis may be more common in younger ages and nulliparous women. This idea is supported by clinical data [5].

Furthermore, patients with adenomyosis are categorized either as diffuse or focal. The diffuse type of adenomyosis is mainly related to deep diffuse internal adenomyosis [7]. Focal type includes focal adenomyosis, adenomyoma, and cystic adenomyosis [7]. Multiple factors such as the number, volume and location of adenomyotic lesions and thickness of the abdominal wall are considered to contribute to the severity of a variety of clinical sequelae. Sofic et al. reported that approximately 80% of the patients have diffuse adenomyosis, while ~20% has focal type [6]. Diffuse adenomyosis was observed in one-third of patients with endometriosis and healthy controls, suggesting that the presence of endometriosis does not change the incidence of diffuse adenomyosis [8]. Furthermore, among women with endometriosis, the prevalence of diffuse adenomyosis did not differ significantly in the endometriosis phenotypes (SUP, 20.0%; OMA, 45.2% and DIE, 35.5%; P = 0.068) [8]. In contrast, FAOM was observed more frequently in women with endometriosis than in controls (50.2% vs. 5.4%; P < 0.001), and was significantly associated with the DIE phenotype (SUP, 7.5%; OMA, 19.3% and DIE, 66.3%) [8]. Kahn et al. reaffirmed the fact that FAOM is frequently associated with DIE [33]. This suggests that FAOM might originate from the invasion of adjacent DIE lesions [7]. The interrelationship between FAOM and adenomyosis externa is poorly understood, so it is unclear whether these disorders all result from infiltration of adjacent DIE lesions. As described in Fig. 1, there might be two or more different pathogenic origins in adenomyosis: invagination of the endometrium into the inner myometrial layer, and invasion from adjacent endometriosis, including DIE lesions. However, there is limited information on the relationships between the extent of the lesions and symptom severity and the presence of concomitant pathologies.

Adenomyosis and endometriosis as an archimetra disease

Two main theories have been proposed to explain the pathogenesis of adenomyosis: invasion and metaplasia [12].

Fig. 1. Theory of “Different phenotypes of a single disease”. Uterine contraction and hyperperistalsis cause the efflux of endometrium into the peritoneal cavity, and contribute to implantation of endometrial tissue and formation of endometriotic lesions at ectopic sites, resulting in the development of SUP, OMA and some DIE. Part of the rectovaginal DIE is derived from the metaplasia of the Müllerian remnant. Extrinsic adenomyosis may arise secondarily through pelvic endometriosis. FAOM can result from rectal and bladder DIE/adenomyosis externa. Evidence suggests that SUP, OMA and extrinsic adenomyosis occur in relatively young women and show TGF-dependent fibrosis. The ReTIAR and EMID hypotheses show uterine contraction also induces microtrauma at the EMI, leading to intrinsic adenomyosis with time. Intrinsic adenomyosis is frequently found in women in the transitional period of menopause and shows TGF-dependent fibrosis. The mechanism of fibrogenesis may differ depending on the site of lesion and time course. SUP, superficial peritoneal disease; OMA, ovarian endometrioma; DIE, deep infiltrating endometriosis; A. externa, Adenomyosis externa; Intrinsic A., Intrinsic adenomyosis; Extrinsic A., Extrinsic adenomyosis; FAOM, Focal adenomyosis located in the outer myometrium; ReTIAR, Repeated tissue injury and repair; EMT, Epithelial-mesenchymal transition; EMID, Endometrial-myometrial interface disruption; and BMDSCs, Bone marrow-derived stem cells.
Leyendecker and Guo and their colleagues have indicated that repeated tissue injury and repair (ReTIAR) play a pivotal role in endometriosis and adenomyosis, which accelerates EMT and fibroblast-to-myofibroblast transdifferentiation (FMT), leading ultimately to tissue fibrosis [7,34–38] (Fig. 1). Since multiparity, previous abortion, and dilatation and curettage are risk of having adenomyosis (especially intrinsic type), iatrogenic trauma is considered one of the pathogenic mechanisms. Uduwela et al. reported that endometrial-myometrial interface (EMI) of the uterus lacks an intervening tissue layer, and the endometrium is in direct contact with the myometrium, making it vulnerable to invasion by the endometrium [39]. Based on the current understanding of wound healing, a new EMD (endometrial-myometrial interface disruption) theory for an old hypothesis reappeared to explain adenomyosis [7,39,40] (Fig. 1). This theory also includes the mechanisms of tissue fibrosis due to EMT and recruitment of bone marrow-derived stem cells (BMSCs) [7]. Chronic injury and subsequent inflammation can trigger EMT through the release of some inducers, such as transforming growth factor (TGF)-β and hypoxia-induced factor-1 (HIF-1A) [41]. Inflammation and activated platelets also promote EMT-induced smooth muscle metaplasia and play an important role in the pathogenesis of adenomyosis [42]. The authors noted that estrogen up-regulates the TGF-β and smooth muscle α-actin mRNA expression and causes ReTIAR/EMD through uterine contractions, and ReTIAR/EMD further promotes estrogen production [7,35]. If tight physiological regulation fails to clear the prolonged activation of ReTIAR/EMD, a vicious circle is formed between uterine contraction and aberrant estrogen production, promoting the further development of adenomyosis [7,15,35]. Injury or trauma might be an important initial event that induces the cellular responses of the archimeta [15]. Thus, uterine auto-traumatization is considered the initial events in the disease development. This concept is similar to the biophysical force theory proposed for the etiology of gallbladder adenomyosis [27–29]. This suggests that adenomyosis can develop in both gallbladder and uterus possibly due to high transmural pressures. Subsequent tissue damage, repair, inflammation, and metaplasia are considered to be a series of cascades for adenomyosis development. However, this concept can explain the mechanisms involving the intrinsic adenomyosis, but not for the extrinsic adenomyosis [5,19].

Retrograde menstruation theory can explain the pathogenesis of endometriosis, but not adenomyosis. Therefore, the two diseases came to be considered as different entities, but not distinct forms of the same entity [2]. However, several studies suggest that both diseases may cause similar changes in the eutopic endometrium and the inner portion of the myometrium [2,15,43–45]. As described previously, in 1998, Leyendecker et al. recognized endometriosis and adenomyosis as a disease of the endometrial-subendometrial unit or archimeta and considered them as a hyperreaction to cell proliferation and inflammatory defense by peristalsis [15]. Surprisingly, changes in the inner myometrium are frequently present even in women with endometriosis [44]. In fact, the maximum thickness of JZ in patients with endometriosis without adenomyosis was significantly greater than in healthy women without adenomyosis and endometriosis (6.5 ± 1.9 mm vs. 4.8 ± 1.0 mm; P < .001) [45]. The expansion of the JZ was more pronounced in older than in younger women [43]. JZ thickness and its alterations are not correlated with American Society of Reproductive Medicine staging methods [43,45]. The inner myometrium or JZ is altered in both diseases, and alterations are much more marked in adenomyosis than in endometriosis [2]. A JZ thickness >12 mm is today considered sufficient for diagnosis of adenomyosis [2]. The results of the previous study indicate that JZ thickening is already present when endometriosis is clinically diagnosed [45]. As the ReTIAR and EMD hypotheses show, excessive peristalsis causes imagination of the endometrium into the inner myometrial layer. However, this change is microscopic and clinically invisible. As the endometrial invagination progresses, the development of adenomyosis becomes more pronounced over time. Excessive uterine peristalsis not only causes intrinsic adenomyosis, but at the same time frequent menstrual reflux can also promote endometriosis [35,46]. The results of these studies provide support to the notion that adenomyosis and endometriosis are primarily an archimeta disease [43].

**Dynamic interactions between adenomyosis and endometriosis in the fibrotic microenvironment**

Elevated intrauterine pressure and hyperperistalsis can cause endometrial tissue damage and menstrual reflux, leading to tissue remodeling. This process contributes to the occurrence of inflammation, angiogenesis, and fibrogenesis, which are key pathobiological processes in the progression of nodular formation in adenomyosis and adhesions in endometriosis [47]. A complex interaction of inflammatory cytokines, adhesion molecules, fibrotic growth factors, oxidative stress, immune response, and the EMT is involved in the process of fibrogenesis [48]. All types of adenomyosis and endometriosis commonly have an aspect of fibrotic disease irrespective of their localization [47]. This chapter reviews the potential markers available for characterizing smooth muscle cell phenotype and fibrogenesis in normal uterus, adenomyosis, and endometriosis.

**Expression and cell localization of fibrosis markers in normal uterus**

Uterine SMCs are essential for maintaining tissue integrity and homeostasis. In addition to contraction, SMCs can exert important functions such as proliferation, adhesion, migration and fibrosis. The whole myometrium of the uterus was uniformly immunostained with α-smooth muscle actin (α-SMA) in non-pregnant [19] and pregnant women [49]. In contrast, the other SMC markers such as desmin, smoothelin, and myosin heavy chain (MHC) were not stained uniformly throughout the uterus. Desmin, smoothelin, and MHC were localized only in the SMCs of the most outer myometrium [19]. However, the rest of the myometrium was negative, or very weakly positive for these markers. Smooth muscle MHC, the motor protein that takes part in SMC contraction, is a very late marker of SMC differentiation [50]. Desmin, the major protein component of the cytoplasmic intermediate filaments, is linked with contractile functions of uterine muscle cells [51]. Furthermore, smoothelin is expressed in contractile SMC only [52]. These experiments showed that the outer myometrial layer of the uterus is composed of highly differentiated SMCs, while the inner myometrial cells are immature.

**Expression and cell localization of fibrosis markers in adenomyosis**

Immunostaining for α-SMA and desmin was consistent with areas of myometrial hyperplasia and hypertrophy in adenomyosis lesions [16]. There was no significant difference in the immunostaining patterns of desmin, smoothelin and MHC between the intrinsic and extrinsic adenomyosis [19]. The SMCs dedifferentiate in response to extracellular cues such as tissue damage and inflammation [53]. Dedifferentiated SMCs are proliferative, migratory, less contractile, and can contribute to fibrogenesis [53]. Nonmuscle myosin IIB (NM-IIB) is a dedifferentiation marker for SMCs and is upregulated in scar fibroblasts correlated with increased collagen matrix contraction [34]. NM-IIB is overexpressed in SMCs of extrinsic adenomyosis, but not in control uterus or intrinsic adenomyosis [19]. The phosphorylated TGF-β type 1 receptor and its downstream SMAD signaling are activated in...
extrinsic adenomyosis, whereas intrinsic adenomyosis causes fibrosis possibly through the TGF-β-dependent mechanism [19,47]. The molecular characteristics and mechanism of fibrosis may depend on the localization of adenomyosis and the degree of SMC differentiation.

Expression and cell localization of fibrosis markers in endometriosis

Among the three phenotypes of endometriosis (SUP, OMA and DIE), DIE is characterized by the presence of nodular lesions largely composed of dense fibrous tissue. DIE such as the rectovaginal endometriotic nodule is a different disease from SUP with respect to the expression of cytokeratin, vimentin, estrogen receptor and progesterone receptor [3]. Donnez et al. reported that rectovaginal DIE probably originates from the metaplasia of Müllerian rests rather than the implantation of regurgitated endometrial cells [3]. Therefore, rectovaginal DIE must be called rectovaginal adenomyosis or adenomyoma [3]. The serosa of the posterior wall of the uterus is anatomically in contact with the rectovaginal DIE. Therefore, the ectopic endometrial tissue of DIE easily invades the uterine serosa and the outer myometrial layer, leading to the formation of FAOM. A literature search was conducted to retrieve articles that evaluated the SMC markers on endometriosis-associated fibrosis. A smooth muscle component and fibrosis are more abundant in endometriotic lesions than in unaffected areas [55]. The expression of desmin and MHC are upregulated in all endometriosis phenotypes [56]. In particular, DIE lesions contain myofibroblast-like cells that express multiple markers of fibromuscular differentiation, such as Vimentin, desmin, α-SMA, and MHC [57]. TGF-β1 is increased in peritoneal fluid, serum, ectopic endometrium and peritoneum in women with endometriosis compared to women without endometriosis [58]. Endometrial epithelial cells in red lesions may undergo an EMT-like process in a TGF-β1-rich microenvironment [59]. Immunohistochemistry revealed that SUP and OMA are more dependent on TGF-β-induced signaling pathway than DIE [58]. The in vitro assay system using endometriotic stromal cells revealed that TGF-β1 is associated with fibrosis in endometriotic lesions through upregulation of type I collagen and angiogenesis factors [60]. DIE may show decreased EMT and elevated E-cadherin expression as the terminal stage of fibrosis [58]. DIE is composed of fibromuscular nodular lesions, and may be controlled by TGF-β-independent mechanism. These results show that intrinsic adenomyosis and DIE have similarities in the process of fibrosis. Intrinsic adenomyosis and DIE show TGF-β-independent fibrosis, suggesting the similarities in the process of fibrosis.

Discussion

This review summarizes our view on the pathogenesis of adenomyosis and endometriosis (Fig. 1). This paper has two added values. One is an attempt to elucidate the pathophysiology of endometriosis and adenomyosis based on differences in uterine anatomy (archimetric and neometra). Secondly, since a disease called adenomyosis occurs in the uterus and gallbladder, the etiology of uterine adenomyosis was estimated based on the pathophysiology of gallbladder adenomyosis. Inappropriate uterine contractions or hyperperistalsis may produce retrograde bleeding and cause chronic inflammation [46]. Inflammation is an essential and complex biological process that protects the body from potential harm caused by tissues injury or damage. When contractile triggers are not cleared, inflammation is not properly controlled, impaired wound healing, adhesion or fibrosis occurs via activation of TGFβ-dependent and -independent signaling, resulting in reproductive disorders, such as adenomyosis and endometriosis [41]. In addition, these adverse intrauterine environments result in physiological changes to the endo-myometrial junction, which causes destruction of the EMI barrier over time, allowing invagination of the normal endometrial tissue into the inner myometrial layer [7,15,34-40]. This may trigger the development and progression of intrinsic adenomyosis. On the other hand, extrinsic adenomyosis may result from pelvic endometriosis. Prevalence of SUP, OMA, and extrinsic adenomyosis was higher in younger women while intrinsic adenomyosis and adenomyosis externa/DIE are more common in women in their 40 s. Furthermore, SUP, OMA and extrinsic adenomyosis are regulated by TGF-β-dependent fibrosis, whereas intrinsic adenomyosis and DIE are often TGF-β-independent [19,47]. Rectal and bladder endometriosis may be involved in the development of FAOM.

In conclusion, the interrelationship between the two diseases is considered to be two sides of the same coin. We have debated the possibility that adenomyosis and endometriosis represent different phenotypes of a single disease.

Conclusion

Adenomyosis and endometriosis are common gynecological disorders, but their pathophysiology is still under debate. The aim of this review is to discuss whether adenomyosis and endometriosis represent two different entities or different phenotypes of a single disease. This paper support the possibility that adenomyosis and endometriosis represent different phenotypes of a single disease.

Statement of ethics

Not applicable.

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Author contributions

Shogo Imanaka, Mika Nagayasu, and Mai Kimura performed the literature search and collected data using the Web database. Sachio Maruyama and Hiroshi Kobayashi made substantial contribution to conception of the study. Shogo Imanaka and Sachio Maruyama contributed to the study design and interpretation of included research studies. The final version of the manuscript has been read and approved by all authors.

Patient consent for publication

Not applicable.

Declaration of Competing Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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