

Adenomyosis and Endometrial Cancer: Literature Review

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Keywords

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Abstract

To confirm the origin of cancer found in both the endometrium and the myometrium is difficult. Cancer may spread from the endometrium into adenomyotic foci or vice versa. Also, premalignant changes may arise at either or both sites. Investigating disease origin enhances our understanding of pathophysiology and prognosis. Additional critical questions are whether women with adenomyosis have a higher risk of endometrial cancer; whether the invasive properties and prognosis of cancer in adenomyosis differ from those arising in the eutopic endometrium and whether the ectopic glandular tissue in adenomyosis becomes altered in the presence of eutopic endometrial cancer. A final question is

whether cancer arising within adenomyosis carries a worse prognosis because of its location within the myometrium and the possibility that the presence of adenomyosis facilitates invasion of cancer arising in the eutopic endometrium. The present review explores currently available literature in an attempt to answer these questions and to examine clinical presentations, diagnostic criteria, pathogenesis and prognosis.

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Introduction

Uterine adenomyosis is defined by the presence of endometrial glands and stroma within the myometrium [1]. Both adenomyosis and type 1 endometrial cancer have been linked to sex steroid action. The gene expression profile suggests a role of cancer, cell death and cell cycle net-

works in adenomyosis [2]. More recently, the expression of microRNA-17 was shown to be significantly increased and mRNA of Phosphatase and Tensin Homolog (PTEN-mRNA) to be reduced in adenomyosis [3]. The gene encoding the PTEN protein has been identified as a tumour suppressor that is mutated in a large number of cancers. Also, the relationship between PTEN and endometrial cancer is well documented [4]. Endometrioid endometrial cancers frequently contain mutations in the PIK3-mTOR signalling pathway, including mutations in PTEN and in Phosphatidylinositol 3-kinase catalytic subunit (PIK3CA). The gene encoding this protein has been found to be linked to cancer. Other genes that may be implicated in both diseases include *KRAS* (a gene providing instructions for making a protein called K-Ras that is part of a signalling pathway known as the RAS/MAPK and has been found to be oncogenic) and *BCL2* (a member of the family of proteins that regulate apoptosis, which is important within the AKT/PIK3 signalling pathway) [2, 5, 6]. These features raise questions about a possible link between the 2 diseases.

When examining the possible link between adenomyosis and endometrial cancer, 3 possibilities must be considered: whether malignant changes start in the endometrium lining the uterine cavity (eutopic endometrium) and spread to nests of adenomyosis; whether malignancy starts in an adenomyotic focus (ectopic endometrium) and spreads to the eutopic endometrium; or whether cancer or premalignant changes arise at both sites because of carcinogenesis having a wider field effect [7].

Further critical questions are whether women with adenomyosis have a higher risk of endometrial cancer; whether the invasive properties and prognosis of cancer in adenomyosis differ from cancer arising in the eutopic endometrium and whether adenomyosis predisposes to cancer arising in glands embedded within the myometrium. Despite the relatively high incidence of both adenomyosis and endometrial cancer, published information addressing their possible relation is inconclusive. One theory of the genesis of adenomyosis is linked to increased “invasiveness” of endometrial glands and stroma resulting in the identification of this tissue within the myometrium [8]. This theory is consistent with an increased risk of cancer. Endometrial glands within adenomyosis exhibit histological continuity with eutopic endometrium, which may facilitate cancer spread. On the other hand, the inconsistent response of ectopic endometrium to progestogens can also be a factor in carcinogenesis [9].

To confirm the origin of cancer found in both the endometrium and the myometrium is difficult, as disease presence can represent cancer spread from either site. For

example, Winkelman and Robinson [7] described a case where cancer was present in both the endometrium of the lower uterine segment and deep within the myometrium in adenomyotic foci. They considered the predominantly deep spread and the lymphatic involvement as evidence of an important contribution from adenomyosis, but such propositions are speculative.

Here, we examine literature relevant to these questions and after a historical overview present up-to-date evidence. Our objective is to assess the current state of knowledge of the relationship between cancer and adenomyosis, as can be gathered both from classic data and recent modern methodology.

Material and Methods

We searched Scopus and PubMed (NLM) databases from inception to April 1, 2017 using the terms “adenomyosis, Unique MeSH ID: D062788” and “cancer, Unique MeSH ID: D009369,” “carcinoma, Unique MeSH ID: D002277” or “adenocarcinoma, Unique MeSH ID: D000230” and obtained all available publications with no limitations on language or date of publication. Where applicable, the review followed the guidance of EQUATOR network following the PRISMA statement [10]. Identified articles from each database were added and duplicates were removed.

Results

Scopus yielded 818, 479, and 183 references for the first, second and third combinations respectively. After removing duplicates, 1,022 articles remained. Medline search yielded 954, 235, and 128 references for the first, second and third combinations, respectively, and a total of 984 articles remained after removal of duplicates. The 2 datasets were merged yielding 2006 articles of which 1,528 remained after removal of duplicates. Selecting with the search term “case report” yielded 140 articles, most of which were eliminated on manual search (Table 1). In the end, we undertook a manual search of the whole dataset of 1,528 articles. We also performed a Medline search using the term “adenomyosis” combined with “adenocarcinoma” in any field. This yielded 662 references, which we searched manually to identify relevant case reports. We then searched the bibliography of identified articles for early publications of case reports. In the end, between 1897 and 2017, we identified 78 case reports in 68 articles that describe a case of carcinoma arising from adenomyotic foci, thus suggesting an association between endometrial cancer and adenomyosis (Table 1).

Table 1. Identified articles from scopus and medline search

Database	Search terms	Sum	Total
Scopus	Adenomyosis + cancer (<i>n</i> = 818) Adenomyosis + carcinoma (<i>n</i> = 479) Adenomyosis + adenocarcinoma (<i>n</i> = 183)	1,022	1,528
Medline	Adenomyosis + cancer (<i>n</i> = 954) Adenomyosis + carcinoma (<i>n</i> = 235) Adenomyosis + adenocarcinoma (<i>n</i> = 128)	984	

Table 2. Historical landmarks concerning malignancy in adenomyosis

Reference	Case description
Rolly [12], 1897	First report of a case of cancer arising in an adenomyoma. A 54-year-old woman with metastatic disease and benign eutopic endometrium. Rolly argued that cancer may not become symptomatic till it reaches an advanced stage.
Cullen [13], 1900	Concluded that adenocarcinoma could extend to a fibroid only in the very rare instances where ectopic endometrial glands are scattered through a myoma. Cullen denied finding any instances of adenomyoma becoming carcinomatous (page 410). Described a case with co-existing fibroid, adenomyoma and adenocarcinoma (page 459).
Cullen [14], 1908	Wrote that adenocarcinoma very rarely arises in an adenomyoma and stated that only 2 cases were found by von Recklinghausen [15] and 1 case was suspected by Meyer [16].
Lockyer [17], 1918	Stated that, “adenomyomata may become malignant, but they do so very rarely” However, this conclusion was in part based on the assumption – that would not be accepted today – of a link between chronic inflammatory processes, such as chronic salpingitis and malignancy.
Andrews [18], 1921	Presented a case of endometrial cancer arising in an “adenomyoma,” manifesting with postmenopausal bleeding. The endometrium was atrophic. Cancerous and non-cancerous endometria were found in an adenomyoma.
Borowski [19], 1929	Described malignant glands in an adenomyoma and reviewed 19 cases, including his own. The review also included cases of sarcoma.

Historical Overview

The presence of a relation between adenomyosis and endometrial cancer was suspected even before the term “adenomyosis” was coined in 1925 by Frankl [11]. Table 2 outlines the important landmarks in early publications till 1930.

It is important to mention that at the end of the 19th century and up to the 1920s, the distinction was blurred between what we today identify as “myoma,” “adenomyoma,” “adenomyosis,” “endometriosis” (excluding ovarian endometrioma, then named “chocolate cyst”). Nonetheless, it appears that Cullen [13] did observe both an adenocarcinoma invading adenomyosis and a fibroid, as well as an adenocarcinoma arising from an adenomyoma. By 1930, the distinction between adenomyosis and endo-

metriosis had been widely accepted and therefore, we can presume that all cases published thereafter concern malignant changes in adenomyotic foci.

Endometrial Cancer Arising within Adenomyotic Foci

A number of case reports of cancer arising from adenomyosis have been reported since the above summarized early observation. These are reported in Table 3. A possible non-random association with endometrial cancer was proposed soon after adenomyosis was identified as a specific condition. Dreyfuss [20] noted that considering the histolytic and hyperplastic activity of adenomyosis and endometriosis, the possibility of cancer seems very likely indeed. Despite this, he noted that only isolated cas-

Table 3. Cases of coexistence of adenomyosis and endometrial cancer published after 1930

Reference	Case description
Frankl [11], 1932	One case out of 127 cases of adenomyosis (information available for 94 cases. A 41-year-old nulliparous woman with regular painful periods. Nulliparous woman, underwent vaginal hysterectomy. Noted to have severe perimetritis. Myometrium in the posterior wall contained irregular pattern epithelium with possible subserosal cancer in adenomyosis.
Cirio [21], 1933*	One case report. Reviewed by Kumar and Anderson [22].
Rockstroh [23], 1936	Reported cancer in 2 out of 327 cases of adenomyosis. Fifty five-year-old, 1.5 years of infrequent bleeding. Tumour mass filling the cavity and down to the isthmus with areas of infiltration. Microscopically, adenomyosis containing malignant cells with invasion into the myometrium. Thirty five-year-old, hysterectomized for a tumour mass. Microscopically, nests of adenomyosis invading myometrium up to the serosa with adenocarcinoma. Cancer was also identified in the endometrium. Origin of cancer was uncertain in either cases.
Bertone [24], 1936*	One case report. Reviewed by Kumar and Anderson [22].
Frankl [25], 1937*	One case report. Detail not accessible.
Grayzel [26], 1938	Forty-four years old woman with irregular bleeding and severe pain. Cylindrical cancer arising in an adenomyoma: well-preserved glandular acini surrounded by typical endometrial stroma in the tumour nodule coexisted with a low-grade adenocarcinoma of endometrium, with no involvement of the myometrium.
Smith and Masson [27], 1939 *	A case of cancer arising from an ectopic endometriotic nest associated with a squamous cell cancer of the cervix. Details not accessible.
Dreyfuss [20], 1940	Identified one case where cancer may have originated in adenomyosis but noted that no definitive proof was possible.
Da Silva Horta [28], 1941*	One case report. Reviewed by Kumar and Anderson [22].
Dubrausky and Niendorf [29], 1951	A case where only the stroma of the adenomyotic lesion was the site of malignant transformation; the endometrium was in the proliferative phase.
Elsner [30], 1951*	A case of adenocarcinoma in adenomyotic lesion, with hyperplasia in eutopic endometrium. Details not accessible.
Olsen [31], 1955	One case of a 51-year-old who had lung metastatic disease at the time of diagnosis
Kumar and Anderson [22], 1958	Cast doubt on the exact pathology in most early cases as reviewed by Borowski [19], as instances of squamous metaplasia in an adenomyoma, metastatic cancer, or sarcoma were mistaken for malignancy originating in the adenomyoma. Reported one case (54-year-old) premenopausal woman presenting with irregular bleeding, discomfort and a mass in left lower quadrant. Had multiple foci of adenocarcinoma rising in adenomyosis, and adenocarcinoma of the endometrium and in an endometrial polyp. The concomitant presence of benign adenomyosis and early malignant changes and the lack of direct connection between the eutopic endometrial cancer and cancer in adenomyosis and the presence of typical endometrial stroma around carcinomatous adenomyosis favoured origin in adenomyosis.
Colman and Rosenthal [32], 1959	Cast doubt about the origin of all cases of cancer in adenomyosis reported till 1959 except 3:2 reported by Cullen [14] and the one by Polano [33].
Greene [34], 1961	One case in a 52-year-old with perimenopausal bleeding that persisted for more than 5 years prior to hysterectomy. Patient also had a granulosa-theca cell tumour. Unclear if this was an instance of atypical hyperplasia.
Dockerty [35], 1962	One case with cancer within adenomyosis and atrophic eutopic endometrium in a 59-year-old woman.
Zych and Pieczonka [36], 1973*	A case in a Polish publication. Details not accessible.

Table 3. (continued)

Reference	Case description
Baril et al. [37], 1973*	One case in a French publication. Quoted by Kay et al. [38].
Hernandez and Woodruff [39], 1980	Six cases of cancer in adenomyosis amongst 204 hysterectomies for endometrial cancer.
Zanetti et al. [40], 1981*	One case in an Italian publication in a postmenopausal woman. Quoted by Ramael et al. [41].
Kay et al. [38], 1988	Seventy five-year-old with intramural endometrial (adeno-squamous) cancer arising from a large polypoid adenomyoma. The central mass exhibited cystic degeneration. Atrophic eutopic endometrium may account for 6 years delay and paraaortic nodal involvement at surgery.
Ramael et al. [41], 1992	Sixty eight-year-old presenting with postmenopausal bleeding. Identified with papillary adenocarcinoma with benign eutopic endometrium following hysterectomy.
Zhang [42], 1992*	One case in a Chinese publication. Details not accessible.
Mori et al. [43], 1994	Sixty three-year-old with postmenopausal bleeding. Identified with a 3.5 cm uterine mass. Adenocarcinoma with areas of clear cell tumour. Atrophic endometrium.
Kuwashima et al. [44], 1994	First: 54-year-old with abdominal mass. Tumour spread to ovaries and lymph nodes. The uterine lumen contained a large tumour mass from the posterior uterine wall. There was “no apparent tumour” in the endometrium. Endometrial histology the endometrium contained “upward infiltration focally” whereas the rest was atrophic. Second 61-year-old with abnormal bleeding identified with smears suspicious of cancer. The posterior uterine wall contained a 5 × 5 cm intramural nodule, minimal invasion of tumour in the endometrium. Endometrioid cancer scattered throughout the myometrium with papillary pattern.
Sasaki et al. [45], 2001	Found 17 cases documented since 1980 (including their own report). 53-year-old postmenopausal with benign endometrium and adenocarcinoma suspected on cervical smear. Adenocarcinoma involving adenomyotic foci, the serosa and lymph nodes but not the eutopic endometrium.
Koshiyama et al, [46], 2002	Four cases: Forty eight-year-old premenopausal with abnormal bleeding, MRI consistent with adenomyosis, small endometrial polyp with adenocarcinoma. Sixty two-year-old postmenopausal with vaginal discharge. MRI suggested fibroids. Adenocarcinoma on histology. Benign eutopic endometrium. Seventy two-year-old with dull pain. MRI 7 cm pelvic mass possibly ovarian. Histology proved adenocarcinoma. Developed metastatic disease after three months. Benign eutopic endometrium. Sixty nine-year-old with postmenopausal bleeding. MRI 7.5 cm solid and cystic tumour proved adenocarcinoma. Benign eutopic endometrium.
Rubod et al. [47], 2004	Sixty two-year-old postmenopausal woman using HRT presented with pelvic pain and dyspareunia with extensive pelvic adhesions and metastases. Multifocal cancer identified in adenomyosis (unclear from the report if the endometrium was affected).
Couto et al. [48], 2004	Sixty two-year-old with postmenopausal bleeding. She had endometrial hyperplasia with atypia on curettage and adenomyosis on MRI. Hysterectomy proved EAC arising in a focus of adenomyosis with myometrial invasion. Eutopic endometrium was atrophic. The authors recorded the case as stage 1c, but pointed out the difficulty of using the FIGO classification.
Takeuchi et al. [49], 2004	Sixty seven-year-old woman presenting with backache and lower abdominal pain. Had a large immobile pelvic mass adherent to the rectosigmoid and adenocarcinoma in the myometrium invading the rectum with lymph node metastases. There was adenomyosis and atrophic endometrium.

Table 3. (continued)

Reference	Case description
Takeuchi et al. [50], 2006	A 56-year-old with endometrioid adenocarcinoma arising in adenomyosis in a septate uterus. Presented with lower abdominal pain and a pelvic mass. The endometrium was atrophic but the serosa was affected by tumour invasion. Pelvic and paraaortic lymph node affection.
Hsu et al. [51], 2006	Forty seven-year-old premenopausal woman with heavy periods. Initially diagnosed with fibroids. Lesion (suspected adenomyosis) debulked at surgery. Had endometrioid adenocarcinoma and transitional stages from benign adenomyosis and benign proliferative endometrium.
Puppa et al. [52], 2007	Fifty seven-year-old woman identified with fibroids and adenomyosis. Few ectopic glands exhibited moderately differentiated adenocarcinoma. The eutopic endometrium was tumour free. She developed metastatic disease a few months later.
Motohara et al. [53], 2008	Forty one-year-old premenopausal with heavy menstrual bleeding. MRI diagnosed a fibroid and adenomyosis. About 12 years later, adenomyoma had increased markedly in size and became poorly demarcated. Hysterectomy identified adenomyosis with transitional stages to poorly differentiated cancer. The eutopic endometrium was atrophic.
Ohta et al. [54], 2008	Fifty four-year-old with heavy periods. After 1 year follow up, suspected ovarian cancer with metastatic disease. Giant 11 × 11 × 10 cm uterine mass containing altered blood and an 8 × 7 × 8 cm solid component containing clear cell carcinoma. Uterus contained adenomyosis and the eutopic endometrium was proliferative.
Hirabayashi et al. [55], 2009	Seventy three-year-old presented with weight loss and fever, no vaginal bleeding. Histology proved clear cell cancer from adenomyosis. Endometrium small foci of lymphatic involvement in the atopic mucosa with no connection to those in the myometrium.
Kazandi et al. [56], 2010	Fifty nine-year-old postmenopausal woman with pelvic pain, a 15 × 10 cm solid mass from the uterine fundus adherent to the sigmoid colon. Histologically endometrioid adenocarcinoma with no endometrial involvement.
Boes et al. [57], 2011	Sixty four-year-old postmenopausal woman with vaginal bleeding and dull pelvic pain. Small endometrial polyp with well-differentiated endometrioid cancer with squamous differentiation (adenoacanthoma) invading the myometrium. Extensive adenomyosis and adenoacanthoma invading >1/2 the myometrium. The endometrium was proliferative.
Jeong et al. [58], 2011	Fifty two-year-old with postmenopausal bleeding and back pain. Diagnosed with degenerated fibroid on MRI. 4 × 3 cm myometrial mass proved clear cell carcinoma in adenomyosis. A focal clear cell carcinoma was identified in the myometrium.
Long et al. [59], 2012	Postmenopausal with a 10 cm cancerous mass in the posterior myometrium – atypical hyperplasia in the eutopic endometrium.
Koike et al. [60], 2013	Review article reported that 44 cases of endometrial carcinomas arising from adenomyosis have been documented in 19 publications.
Bae et al. [61], 2014	Fifty five-year-old who received herbal remedy for menopausal hot flushes. Identified with a 12 × 12 × 15 cm mass. Adenocarcinoma in adenomyosis, adherent to bowel but no endometrial involvement.
Taga et al. [62], 2014	Fifty seven-year-old postmenopausal woman presenting with bleeding and had suspicious cells on cervical smear. The endometrium was benign. CA125 was elevated. Cancer was located within the myometrium adjacent to adenomyosis.
Masri et al. [63], 2015	Forty three-year-old with abdominal distension identified with a large fibroid uterus (20 weeks size) and a large ovarian cyst (30 weeks size). Histopathology identified foci of endometrioid adenocarcinoma in the myometrium. The endometrium was benign proliferative.
Andino and Cole [64], 2015	Forty six-year-old premenopausal with dysmenorrhea and abnormal bleeding. Unexpected finding of adenocarcinoma in adenomyosis.

Table 3. (continued)

Reference	Case description
Mori et al. [65], 2015	Sixty seven-year-old asymptomatic with 11 cm cystic pelvic lesion. Histology endometrioid adenocarcinoma arising from cystic adenomyosis. The endometrium was benign.
Baba et al. [66], 2016	Forty-year-old with a history of fibroids. MRI identified 7.2 cm cystic uterine mass which contained 2 nodular structures. Features suggested adenomyotic cyst. This proved an adenomyotic cyst with small foci of in situ clear cell adenocarcinoma.
Lu et al. [67], 2016	Sixty four-year-old with lower abdominal pain, identified with 2.5 × 2.6 cm left parametrial mass and 4 × 2.1 × 3.2 cm left sided cyst. Diagnosed with adenocarcinoma of the left adnexa. Fifty five-year old with postmenopausal bleeding curettage proved serous carcinoma. Fifty five-year-old with bleeding. Past subtotal hysterectomy for adenomyosis. Curettage of the endocervix proved endometrioid cancer. The cases do not fulfil the strict diagnostic criteria, but the authors believed the cases to arise from adenomyosis.

* Full text not available for these case reports.

es have been reported and that the origin of the cancer in these few cases was under dispute (Table 3).

The early history of cancer arising from adenomyosis was reconstructed by Kumar and Anderson [22] who again cast doubts on the origin of most early cases reported till then. They argued that it is necessary to demonstrate either transitional stages or continuity between benign and malignant endometrium within adenomyotic nodules in order to make a convincing case for the origin of malignancy. Kumar and Anderson [22] stated that cancer origin from adenomyosis could be demonstrated beyond reasonable doubt in only 2 cases [12, 19] out of the 26 cases reported prior to 1930. For the period between 1930 and 1958, they identified 7 cases as representing adenocarcinoma arising from adenomyotic foci [21, 24, 26, 30].

Sampson's original criteria for diagnosing cancer originating from endometriosis [68] were modified by Colman and Rosenthal [32] and applied to adenomyosis. They proposed that in order to pose a diagnosis of cancer arising within adenomyosis, the following 3 criteria should be met: (a) The cancer must be absent from a normal surrounding endometrium, (b) The cancer must be seen to arise from the adenomyotic epithelium without invasion from another source (c) Endometrial stromal cells must be present in order to support the diagnosis of adenomyosis. Using these criteria, they reported in 50 consecutive cases of adenomyosis, the presence within the ectopic foci of one case each of carcinoma in situ, atypical epithelium, atypical hyperplasia with cystic

changes and polypoid proliferation in glands. There were 4 cases of coexistent endometrial adenocarcinoma (EAC), which they believed to have originated in the ectopic endometrium [32]. Uterine cancer is usually diagnosed following investigation for abnormal uterine bleeding, whereas cancer within adenomyosis is unlikely to manifest with bleeding abnormalities until it has progressed towards the cavity and the first of the above criteria would no longer be fulfilled. Also, Hendrickson and Kempson [69] argued that when adenocarcinoma is present in both the endometrium and adenomyotic foci, it is impossible to determine which is the primary site and that one can be certain of a primary cancer in an adenomyotic nodule only if the overlying eutopic endometrium is normal. They acknowledge that the use of this strict criterion renders the diagnosis "vanishing rare."

It should be pointed out that the above criteria were not universally adopted. Hernandez and Woodruff [39], for example, reported that they identified adenomyosis in 21 (10%) out of the 204 hysterectomies carried out for endometrial cancer between 1955 and 1974 and that 2 out of the 21 cases had atypical hyperplasia and 6 had adenocarcinoma in adenomyosis. Lu et al. [67] argued that these criteria are too strict. Indeed, they would not apply to any of their 3 cases.

The most common cancer reported in adenomyosis is endometrioid. Other rare malignancies identified in adenomyosis or its variants include adenosarcoma [70] and endometrioid adenocarcinoma arising from subserosal cystic adenomyosis [65, 71]. The exact number of cases

reported in literature is difficult to determine as classification of many of the cases has been disputed, but considering the authors' original classification, the total number of cases of malignancy originating in adenomyosis is in the region of 78 cases. These include 6 cases of clear cell carcinoma and 3 serous carcinomas.

The potential evolution of adenomyotic foci towards cancer has been extensively investigated by Japanese researchers. Still, Takai et al. [72] concluded that both its incidence and prevalence remain unknown. According to Hirai et al. [73], there are no known epidemiological factors involved in the evolution of cancer, although a possible role of unopposed hyper-oestrogenism has long been suspected.

Clinical Presentations and Diagnosis

From the above description, it appears that although the majority of reported cases were diagnosed early following investigation for abnormal uterine bleeding (mostly postmenopausal bleeding), in a number of instances, the diagnosis was made only in advanced disease or in the presence of metastasis. Late presentation is not surprising and was referred to more than a century ago by Rolly [12]. Cancer deep within the myometrium may not manifest itself until the local pelvic growth is advanced or in the presence of distant metastases. However, it is to be noted that cancer was suspected in most cases based on the results of endometrial histology or, more recently, based on imaging that detected large pelvic masses or de novo growth after the menopause.

In 1986, Woodruff et al. [74] reported on 2 cases of post-menopausal adenocarcinoma arising from adenomyotic foci that were detected through persistent atypical vaginal cytology, though eutopic endometrium was unaffected (inactive in one instance and hyperplastic with small polyps in the other). A case with positive preoperative endometrial cytology containing many atypical papillary clusters with features of adenocarcinoma was reported by Sasaki et al. [45] who maintained that the origin of the cells was uncertain. Also, Kawana et al. [75] described a case where three-dimensional clusters of malignant cells were found in endometrial cytology. Repeated curettage failed to show malignant changes in the endometrium. They speculated that malignant cells might come from "surface holes connecting carcinoma foci of adenomyotic glands in the myometrium." The same year, Koshiyama et al. [46] reported on 4 cases of adenocarcinoma arising from adenomyosis (1 pre- and 3 post-menopausal); endometrial and cervical cytology in the pre-menopausal woman were negative. In contrast, Griffin et al. [76] found a cervical smear positive for adeno-

carcinoma in a post-menopausal woman in whom endometrial curettage had shown no evidence of disease. EAC arising in an adenomyoma was found at hysterectomy.

It is important to note that there were many instances of diagnostic delays before the cancer was finally diagnosed [54]. Some of the reports indicate extensive local spread and metastases without endometrial involvement [41, 46]. Patients may present with pelvic pain rather than with the classical symptom of bleeding. Here, imaging including MRI or ultrasound can be useful, but require an index of suspicion. Particularly important would be an increase in the size of myometrial lesions in postmenopausal women [38]. The identification of cancerous cells or atypia in cytology is rare but should always be investigated.

MRI provides an important modern diagnostic tool. In theory, this technique might be able to identify cases where malignant changes originate in adenomyotic lesions [77, 78]. Using techniques such as gadolinium or dynamic contrast-enhanced sequence can improve visualisation of the inner myometrium, the so-called myometrium junctional zone (JZ) [79]. The presence of a disruption of the JZ is essential for diagnosing myometrial invasion. Thus, an intact but thickened JZ in the presence of suspicious myometrial lesions may suggest malignancy arising within adenomyosis. However, the features may be difficult to distinguish from adenomyosis unless observations show increase in size after the menopause or in the presence of abnormal cytology or other indicators. The number of case reports of cancer within adenomyosis is small, which is perhaps surprising, given the incidence of adenomyosis. But it should be considered that the low number of reported cases might be secondary to the method of detection, which still relies on endometrial biopsy. It is possible that wider availability and use of non-invasive imaging will enable a better understanding of the association.

An important observation from more recent case reports is that the lesions can resemble degenerated fibroids both clinically and radiologically, including MRI. The symptoms include postmenopausal bleeding or discharge and less commonly abnormal menstrual bleeding in younger women. Patients can also present with vague lower abdominal pain or discomfort. The exact diagnosis is often made only after a hysterectomy is performed. Hysterectomy could be difficult because of pelvic adhesions or disease spread. The diagnosis is often made late, as demonstrated by the extent of the disease at the time of diagnosis and in some cases by the relatively short course to recurrence. This suggests the need for a higher index of suspicion in the presence of atypical radiological features and/or elevated CA125. Histologically most cases of

cancer in adenomyosis were endometrioid and less frequently were serous, clear-cell or poorly differentiated adenocarcinoma.

Adenomyosis in Patients with Endometrial Cancer

Incidence

Early reports suggested that adenomyosis is linked to increased incidence and severity of endometrial cancer. Giammalvo and Kaplan [80] reviewed all early descriptions of coexisting adenomyosis (identified in their article as “endometriosis interna”) and endometrial cancer and looked for a possible relation between the 2 in their series of patients with cancer. The series consisted of 120 cases of EAC and controls without malignancy (264 uteri); adenomyosis coexisted in 33% of EAC specimens and in 18% of non-EAC cases. They were able to identify several additional reports [81–84].

Histological Features of Adenomyosis in Patients with Endometrial Cancer

Understanding whether ectopic glandular tissue in adenomyosis is altered in the presence of eutopic endometrial cancer can advance our knowledge of the pathophysiology of cancer and of the likelihood of malignant changes in the ectopic endometrium.

Hayata and Kawashima [85] did not find pre-malignant changes in the ectopic endometrium in women with early endometrial cancer. Conversely, Taskin et al. [86] identified abnormal changes in the ectopic glandular epithelium in women with endometrial cancer. In their group, 28 out of the 84 women with endometrial cancer had adenomyosis. The stage of the disease was not reported separately for these 28 women and it is not clear if any of them had non-endometrioid cancer. Nevertheless, in 13 of these cases, the ectopic endometrium was of basal type, 8 cases had simple cystic or complex hyperplasia, 1 patient had squamous morula formation with simple hyperplasia and 7 patients had atypical hyperplasia to cancer in situ. Foci of atypia were located in the deeper myometrium in 2 cases. There were no cases of invasive cancer in the adenomyotic foci. They also reported that cellular tumour antigen p53 was expressed in the ectopic glands in 4 cases with atypical complex hyperplasia, in 2 cases with simple hyperplasia and in one case with basal type endometrium. The findings are consistent with the hypothesis that hyperplastic and atypical changes in adenomyosis might be due to micro-environmental influences rather than direct invasion [86, 87].

Kucera et al. [88] identified adenomyosis in 87 out of a series of 205 patients who had early endometrioid endometrial cancer. Six of these cases had cancer within adenomyosis. The histotype of the tumour in adenomyosis correlated with the eutopic endometrial cancer in 3 out of the 6 cases. In the remaining 3 cases, cancer grade was higher in the eutopic endometrium. Among the group with adenomyosis, 25 (28.7%) had glandular hyperplasia without atypia, 18 (20.7%) had atypical complex hyperplasia, 6 (6.8%) had malignant changes, 21 (24.1%) had atrophy and 17 (19.5%) had no pathological features. Interestingly, while myometrial invasion was deeper than 50% of myometrial thickness in 5 of the 6 cases, whenever there was cancer in the adenomyotic foci, no stromal invasion was found into the myometrium adjacent to these malignant foci. This was interpreted as suggestive of the existence of a similar mechanism of carcinogenesis in adenomyotic foci and in the eutopic endometrium.

Clinical Consequences

Marcus [89] compared a series of 100 consecutive cases of adenocarcinoma of the endometrium and a control group of 100 patients who had a hysterectomy for benign causes. The depth of invasion of cancer and adenomyosis was classed as slight, moderate or extensive if glands were present within the inner, middle or outer thirds of the myometrium. They reported adenomyosis in 60% of cases with EAC compared to 39% of controls. Forty per cent of women with EAC had moderate or extensive adenomyosis compared to 14% of the control group. Adenomyosis and endometrial hyperplasia coexisted in 39% of cases of EAC compared to 7% of the controls. However, the characteristics of the control group were not provided, which limits conclusions from the study beyond the known relation between endometrial hyperplasia and cancer. In his study, Marcus [89] identified hyperplasia in the adenomyotic glands in 15 out of 39 cases with endometrial cancer and in 3 out of 7 of the control cases and concluded that a cause and effect relationship between adenomyosis and endometrial cancer cannot be deduced from the data.

In 2001, Koshiyama et al. [90] reported that postmenopausal women with endometrioid cancer had a higher incidence of fibroids and adenomyosis compared to postmenopausal women who had a hysterectomy for prolapse. Three years later, the same group reviewed all cases of endometrial cancer treated at their hospital between 1989 and 2001 ($n = 179$) and identified adenomyosis in 29 (16%), endometriosis in 12 (7%) and fibroids in 51 (28%) cases [88]. Patients with coexisting adenomyosis or endometriosis were younger and included a higher

percentage of pre-menopausal women compared to those with no concomitant pathology; they also tended to have less advanced disease.

In a retrospective study, Kucera et al. [88] identified adenomyosis in 88 (40%) out of 219 uterine specimens from women who underwent a hysterectomy for early endometrial cancer. The majority ($n = 205$) had endometrioid adenocarcinoma, 10 had clear cell carcinoma and 4 had papillary serous carcinoma. There is one report of a case of Mullerian Mucinous Borderline tumour believed to have occurred from adenomyosis [92].

Musa et al. [93] reviewed 2,346 hysterectomy specimens and identified EAC in 197 cases (8.4%). Adenomyosis was present in 42% of the 2,346 hysterectomy specimens and in 66% of those with EAC. The coexistence of adenomyosis was again higher (75%) when considering endometrioid adenocarcinoma. There were no significant differences among EAC patients with and without adenomyosis with regards to age or body mass index, but those without adenomyosis were more likely to have diabetes. Adenomyosis was associated with lower tumour grade, less myometrial invasion, negative lympho-vascular space invasion and negative lymph node invasion. This may be because adenomyosis was associated with endometrioid tumours that were hormonally responsive, well differentiated and more likely to be diagnosed early [94]. A significant difficulty is that the incidence of adenomyosis in control hysterectomy specimens is necessarily influenced by the indication for surgery and also by the diagnostic criteria and the degree of diligence in identifying adenomyosis.

Other investigators attempted to assess the relation between cancer and adenomyosis by examining the incidence of associated pathology identified in uteri containing adenomyosis. This is also problematic because adenomyosis was not the primary indication for hysterectomy in women with cancer and, in most instances, it was not the indication for surgery.

Gün et al. [95] evaluated hysterectomy specimens from 472 women to determine the frequency of the presence of adenomyosis in relation to other pathologies. Adenomyosis was found in 98 cases (20.8% of the total) and in 28 of them (28.5%), it represented the sole pathology. The most common accompanying pathology findings associated with adenomyosis were uterine fibroids ($n = 51$, 52%), uterine polyps ($n = 16$, 16.3%) and endometrial cancer ($n = 11$, 11.2%). The association between the adenomyosis and endometrial cancer was not statistically significant. In the study by Nomellini et al. [96], there were no cases of endometrial cancer among 94 women who underwent a hysterectomy and in whom the presence of adenomyosis was proven.

Hayata and Kawashima [85] identified adenomyosis in 8 out of 20 cases of early endometrial cancer (Stages 1A and 1B). The ectopic endometrium was benign in all cases that had adenomyosis. There was one case of focal cystic glandular endometrial hyperplasia. There were 2 other cases with atypical glandular epithelium within the myometrium, but as these were not surrounded by stroma, they considered this to be evidence of invasion rather than malignant transformation in adenomyosis. In the same study, there were no cases of malignant changes in 100 cases of adenomyosis [94]. It has been argued – based on small-scale studies – that the presence of carcinoma in situ within adenomyosis does not adversely affect prognosis [72]. Nevertheless, distinguishing hyperplastic and atypical changes in adenomyosis from cancer invasion within the myometrium is of prognostic significance.

Kairi-Vassilatou et al. [97] examined 135 consecutive hysterectomy specimens with adenomyosis and 82 cases of EAC. Endometrial hyperplasia and fibroids were identified, respectively, in 47 (34.8%) and 86 (63.7%) of cases with adenomyosis. Adenomyosis coexisted in 31 (37.8%) cases with endometrial cancer and in 4 cases malignant changes were also present in foci of adenomyosis. In one case, the malignancy arose in a focus of adenomyosis.

The high incidence of adenomyosis in women with endometrioid cancer is a factor of the prevalence of adenomyosis. But the information whether adenomyosis is linked to an increased risk of malignancy remains uncertain. Improved reporting of adenomyosis in hysterectomy or by imaging may enable better understanding of the link.

Prognosis

It is unclear whether adenomyosis affects the prognosis of endometrial cancer. There is a possibility that the presence of adenomyosis can facilitate cancer spread along the mucosa. Alternatively, cancer may arise within deep adenomyosis. On the other hand, hypertrophied myometrium can offer a degree of protection against the spread especially of eutopic cancer. There is paucity of data relevant to understanding this issue. Critically, adenomyosis has not been consistently sought or reported in cases with cancer and, indeed, classifications of endometrial cancer do not take the presence of adenomyosis into account.

Hall et al. [98] compared the prognosis of endometrial cancer in women with and without adenomyosis. Out of the 52 women with stage 1 endometrial cancer with coexisting adenomyosis included in the study, 21 (40%) had no myometrial invasion, 24 (46%) had invasion confined to the inner third of the myometrium, 5 (10%) had invasion to the mid-myometrium, and 2 (4%) had invasion to

the outer myometrium. There were 9 cases with adenocarcinoma in adenomyosis without evidence of myometrial invasion (7 cases involved the inner third of the myometrium, and 2 cases involved the middle third) and 2 cases where the depth of cancer in the adenomyosis was greater than the depth of myometrial invasion (in 1 case that involved the outer third of the myometrium and in the other involved the inner third). The 5-year survival rate for women with cancer in adenomyosis was 100%, compared to 96% for the whole group [35]. However, the series is too small to derive firm conclusions.

Jacques and Lawrence [99] reported a better 5-year survival in 23 cases of stage I (18 grade 1 and 5 grade 2) endometrial cancers with myometrial involvement limited to adenomyotic foci compared to endometrial cancers with myometrial invasion at the corresponding depth. This group comprised 21 cases of EAC, one case of adeno-acanthoma and another of an adeno-squamous carcinoma.

Mittal and Barwick [94] compared cases with cancer extending into adenomyosis compared to cancer invading within the myometrium. They identified 18 cases in which cancer affected adenomyotic foci without myometrial invasion and 43 cases of cancers invading the myometrium. Half the women who had cancer within adenomyosis had a history of postmenopausal oestrogens use compared to 19% in those with myometrial invasion. Those with cancer within adenomyosis were more likely to have low-grade cancer. There were no cancer-related deaths in the absence of myometrial invasion and 8 deaths in cases with myometrial invasion after a minimum follow-up of 5 years.

Hirai et al. [73] reported on 286 surgically treated patients with EAC (Stage I–III). There was a tendency for EAC coexisting with adenomyosis to be associated with endometrial hyperplasia to be diagnosed as less invasive and to have a more favourable prognosis. Koshiyama et al. [90] found no difference in prognosis in the presence or absence of adenomyosis in 179 patients with stage I adenocarcinoma.

In the 2 similar and probably overlapping publications by Ismiil et al. [100, 101], histological samples from patients with Grade I EAC were compared based on the presence or absence of adenomyosis. Myometrial invasion was more common and occurred at a greater depth in the presence of adenomyosis.

Taneichi et al. [102] investigated the occurrence and the prognostic role of myometrial invasion in 362 cases of endometrioid adenocarcinoma with associated adenomyosis. Uterine adenomyosis was associated with deep myometrial invasion in stage I endometrioid adenocarcinoma; but this did not affect the recurrence or mortality

rates. Similar finding was reported in a cohort of Stage I–IV endometrial cancer and endometrial hyperplasia patients [103]. They reported that the presence of adenomyosis was significantly associated with grade 1–2 tumours, earlier stage disease and lower likelihood of deep myometrial or cervical invasion. The presence of adenomyosis was an independent prognostic factor associated with a decreased risk of recurrence after surgery. Interestingly, they also reported that endometrial hyperplasia was linked to a significantly increased incidence of adenomyosis when compared with type I endometrial cancer.

Musa et al. [93] investigated the effect of adenomyosis on lymphatic spread. The presence of adenomyosis was associated with lower grade cancer, less myometrial invasion, negative lymphovascular space invasion and negative lymph node involvement. Adenomyosis was associated with improved survival but not if tumour grade and depth of invasion were taken into account. Their analysis suggested that the presence of adenomyosis was associated with a lower risk of lymph node metastasis in EAC patients who had lymphovascular space invasion. One possible mechanism is that adenomyosis enables lower grade cancer with less invasive potential to access the lymphovascular space, but these cancers will not have the same potential to metastasize.

Gizzo et al. [104] reviewed 289 patients with endometrioid cancer. They identified within their cohort 37 patients with concomitant invasion of adenomyotic foci. FIGO Stage 1 comprised 83.8% of the specimens with concomitant involvement in adenomyosis compared to 68.7% of cases with no adenomyosis. The presence of adenomyosis was associated with lower FIGO stages, myometrial invasion, lympho-vascular space and lymph node involvement and tumour size.

Predisposing Factors

As early as 1934, Jeffcoates and Potter [105] hypothesised that “an over-production of oestrin by the ovary is the most important factor in the development of endometriomata in any site”. They stated: “since the ectopic endometrium reacts to ovarian hormones in exactly the same way as does the uterine mucosa, its histologic appearance permits an estimation of ovarian function, normal or otherwise.” This view was strongly opposed by Novak and de Lima [106], since there was no evidence of secretory changes in the ectopic endometrium in adenomyosis in the cases they examined, regardless of the phase of the cycle. They thus, concluded that the ectopic endometrium is of an immature type capable of responding to the effect of oestrogens but not to progesterone.

It is notable that malignant changes in adenomyosis are relatively rare despite the high incidence of adenomyosis and the assumed relation to hyper-oestrogenism. One possible explanation is the association between adenomyosis and pregnancy [106]. Pregnancy increases the risk of adenomyosis but may be protective against endometrial cancer [107]. Elevated progesterone concentrations [102, 104] or endometrial shedding at the time of delivery may play a part [108, 109]. Here again, the limitations of available literature render it impossible to reach reliable conclusions.

A possible role for selective oestrogen receptor modulators in malignancy in adenomyosis was suggested based on one case of cancer in a 61-year-old woman who presented with postmenopausal bleeding while taking tamoxifen. At surgery, multiple adenomyotic foci were seen. One contained a papillary serous carcinoma. There was no malignancy in the eutopic endometrium, the peritoneum or the adnexa [110].

While reported cases of cancer originating or confined to adenomyosis are rare, very few also included a description of pre-malignant changes in the adjacent endometrium. Features identified in these lesions include expression of oestrogen and progesterone receptors, cyclooxygenase-2, CA-125 and focal expression of aromatase [52], supporting the hypothesis of the existence of hyperplasia-cancer sequence in the ectopic endometrium. On the contrary, advanced poorly differentiated adenocarcinoma stained positively for p53, but not ER or PR [86].

The identification of cancer in adenomyotic glands raises a question about their origin. A surface spread theory proposes that extension within the glands is favoured because of the lower resistance to spread compared to invasion through the endometrial-myometrial junction. According to this hypothesis, carcinomas in adenomyosis would be associated with a poorer prognosis than cancer without adenomyosis involvement [32, 99]. The other possibility is that cancer in adenomyotic glands arises from within the ectopic epithelium from malignant precursors. As reported above, Colman and Rosenthal [32] argued in support of this theory because of the finding of premalignant changes within adenomyosis.

Recently, Abushahin et al. [111] published a series of 5 cases of serous endometrial intraepithelial carcinoma (SEIC) arising in patients with multiple adenomyotic foci, where only some of the nests of ectopic cells were affected by SEIC, whereas others contained lesions identified as endometrial glandular dysplasia. In one case, an invasive endometrial serous carcinoma was present without any direct spatial connection with adenomyotic foci affected by SEIC; in 2 specimens, 2

types of lesions were separated by at least 5 mm, but SEIC was present in both eutopic and ectopic endometria; in the remaining 2 cases, eutopic endometrium was “resting” without any detectable cancer or precancerous lesions.

A recent population-based, prospective study, investigated the risk of developing gynaecological malignancies among patients with adenomyosis [112]. The cohort included 768 women with adenomyosis but no coexisting endometriosis. Adenomyosis was associated with an increased risk of developing endometrial cancer (adjusted Hazard Ratio [HR] 5.13; 95% CI 1.36–19.40) and ovarian cancer (adjusted HR 5.50; 95% CI 1.95–15.50) compared to the control population. The markedly increased incidence of endometrial cancer in this cohort highlights the need to better understand the biology of the endometrium in adenomyosis and the complexity of molecular interactions between the endometrium and myometrium [113, 114].

Early diagnosis of cancer arising within adenomyosis will necessarily rely on maintaining an index of suspicion especially in the presence of elevated CA125 and the use of modern diagnostics including MRI. In postmenopausal women, the presence of a myometrial lesion particularly one that increases in the size, recurrent unexplained bleeding, the identification of abnormal cells on cytology or the *de novo* symptom of dull pelvic pain could act as triggers for surveillance.

Conclusion

Because of its high incidence, adenomyosis is frequently associated with endometrial cancer. The incidence of adenomyosis in women with endometrioid adenocarcinoma ranges between 10 and 70% [71]. The exact prevalence is difficult to determine because of the relatively small case series available and because of the lack of consistency in diagnosing adenomyosis [113].

Current opinion indicates that adenomyosis-associated endometrial cancer has better prognosis, but this may be a factor of the early stage at which it is detected. Understanding the true impact is perhaps hampered by the fact that the currently used classifications do not take the presence of adenomyosis or of cancer within adenomyosis into account. Moreover, endometrial cancer series investigating the prognostic value of adenomyosis often lacks adequate statistical power or adjustment for other risk factors.

The information about whether cancer within adenomyosis in the absence of stromal invasion carries the same

significance as myometrial invasion to the same depth is unclear. It is also not clear whether cancer within adenomyosis alters the risk of deep myometrial infiltration. Some studies have suggested an increased risk [115], while others suggested a lower risk [93, 103]. Ismiil et al. [100] found that patients who had cancer involvement within adenomyosis were more likely to have myometrial involvement. They speculated that involvement within adenomyosis confers invasive advantage, possibly because of the increased surface area of interface with the myometrium. This raises the question of how to define myometrial invasion in cases with adenomyosis. This question is of both academic and clinical interest, given the prognostic significance of myometrial invasion in endometrial cancer.

Abnormal histological features within adenomyosis foci provide a further challenge. It has been argued, based on small-scale studies, that the presence of carcinoma in situ within adenomyosis does not adversely affect prognosis [94]. But distinguishing hyperplastic and atypical changes in adenomyosis from invasion of cancer within the myometrium may be of prognostic significance.

The reported cases of clear cell and serous carcinoma are consistent with the recognised incidence in the endometrium. These rare tumour types are biologically distinct from the more common endometrioid carcinoma and generally carry a worse prognosis. Endometrial serous carcinoma is recognised with a higher propensity to lymphovascular invasion and spread [116]. Endometrioid cancer is linked to alterations in *PTEN* gene silencing, defects in DNA mismatch repair genes, microsatellite instability and mutations in *KRAS* and of β -catenin. On the other hand, clear cell and serous cancers are linked to p53 gene muta-

tion, p16 gene inactivation, low E-cadherin, Her-2/neu overexpression, STK15 amplification and loss of heterozygosity on several chromosomes [100]. No literature exists that specifically addressed the molecular distinction in cases arising from adenomyosis. PIK3-AKT-mTOR and the CTNNB1 signalling pathways have been linked to endometrioid cancer [5, 6], and genetic and epigenetic alterations affecting these pathways have also been shown in adenomyosis [3, 117]. But while genetic and epigenetic studies have suggested convergence in the mechanisms involved in cancer and adenomyosis, the infrequent occurrence of cancer in adenomyosis may be related to the similarities between adenomyosis and to the basal layer in the endometrium, which is less responsive to steroids [118].

Although the diagnosis of adenomyosis is feasible following hysterectomy, improvements of non-invasive diagnostic techniques may enable preoperative and longitudinal evaluation of affected patients. This is relevant to further investigate whether the presence of adenomyosis represents a risk factor for gynaecological malignancies. Moreover, non-invasive techniques may enable the prompt diagnosis of cancer arising deep within the myometrium. And although available literature suggests that this as a rare occurrence, the exact incidence cannot be determined because of the factors discussed in this article.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

References

- Frankl O: Adenomyosis uteri. *Am J Obstet Gynecol* 1925;10:680–684.
- Hever A, Roth RB, Hevezi PA, Lee J, Willhite D, White EC, et al: Molecular characterization of human adenomyosis. *Mol Hum Reprod* 2006;12:737–748.
- Hu H, Li H, He Y: MicroRNA-17 downregulates expression of the PTEN gene to promote the occurrence and development of adenomyosis. *Exp Ther Med* 2017;14:3805–3811.
- Mutter GL, Lin MC, Fitzgerald JT, Kum JB, Baak JP, Lees JA, et al: Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. *J Natl Cancer Inst* 2000;92:924–930.
- Roddy E, Chapman J: Genomic insights in gynecologic cancer. *Curr Probl Cancer* 2017;41:8–36.
- Markowska A, Pawalowska M, Lubin J, Markowska J: Signalling pathways in endometrial cancer. *Contemp Oncol (Pozn)* 2014;18:143–148.
- Winkelman J, Robinson R: Adenocarcinoma of endometrium involving adenomyosis. Report of an unusual case and review of the literature. *Cancer* 1966;19:901–908.
- Benagiano G, Brosens I: The endometrium in adenomyosis. *Womens Health (Lond)* 2012;8:301–312.
- Benagiano G, Habiba M, Brosens I: The pathophysiology of uterine adenomyosis: an update. *Fertil Steril* 2012;98:572–579.
- Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- Frankl O: Weitere Beiträge zur Klinik und Bemerkungen zur Pathologie der Adenomyosis uteri [Additional clinical descriptions and comments on the pathology of adenomyosis uteri]. *Zentralbl Gynäkol* 1932;56:902–927.
- Rolly F: Ueber einen Fall von Adenomyoma uteri mit Uebergang in Carcinom und Metastasenbildung. [About a case of uterine adenomyoma with transition to carcinoma and metastasis] *Archiv Pathol Anat Physiol Klinische Med* 1897;150:555–582.
- Cullen TS: Cancer of the Uterus: Its Pathology, Symptomatology, Diagnosis, and Treatment: Also the Pathology of Diseases of the Endometrium. New York, D. Appleton and Company, 1900.
- Cullen TS: Adenomyoma of the Uterus. Philadelphia, W.B. Saunders Company, 1908.

- 15 von Recklinghausen F: Die Adenomyome und Cystadenome der Uterus und Tubenwandung: ihre Abkunft von Resten des Wolff'schen Körpers [The Adenomyomas and Cystadenomas of the Uterus and Tubal Wall: Their Origin from the Remains of Wolff's Body]. Berlin, Verlag von August Hirschwald, 1896.
- 16 Meyer R: Ueber Drüsen, Cysten und Adenome im Myometrium bei Erwachsenen. *Ztschr Geburtsh Gynäk* 1900;43.
- 17 Lockyer C: Fibroids and Allied Tumours (Myoma and Adenomyoma). London, Mac-Millan, 1918.
- 18 Andrews HR: Case of carcinoma of the uterus originating in an adenomyoma. *Proc R Soc med* 1921;14:321–324.
- 19 Borowski P: Über maligne adenomyome des uterus [About a case of a malignant adenomyoma of the uterus]. *Zeit Geburtshilfe Gynäkol* 1929;95:311–328.
- 20 Dreyfuss ML: Pathologic and clinical aspects of adenomyosis and endometriosis: a survey of 224 cases. *Am J Obstet Gynecol* 1940;39:95–99.
- 21 Cirio CR: La degeneracion cancerosa en la endometriosis [Malignant degeneration in endometriosis]. *Rev Sud-Am Endocrin Immun Quimiother* 1933;16:555–560.
- 22 Kumar D, Anderson W: Malignancy in endometriosis interna. *J Obstet Gynaecol Br Emp* 1958;65:435–437.
- 23 Rockstroh H: Über begleitende und über ursächlich bedeutsame Erkrankungen der Adenomyosis uteri interna, insbesondere Fälle von Carcinoma adenomatosum uteri und Fälle von Granulosazelltumour des Ovars mit Adenomyosis uteri interna [On the accompanying and caused significant diseases of uterine adenomyosis interna in particular cases of carcinoma uteri adenomatosum and cases of granulosa cell tumours of ovaries with uterine adenomyosis interna]. *Zentralbl Gynäkol* 1936;60:550–559.
- 24 Bertone G: Endometrioma maligno dell'utero e delle ovaie diffuso al sigma colico. [Malignant uterine endometrioma diffusing to the uterus, ovaries and colic sigma] *Arch Scie med (Turin)* 1936;61:521–527.
- 25 Frankl O: Adenomyosis und endometriosis [Adenomyosis and endometriosis]. *Ztschr Geburtsh Gynäkol* 1937;115:1–14.
- 26 Grayzel D: Carcinoma arising in an adenomyoma of the uterus. *Am J Obstet Gynecol* 1938;35:690–693.
- 27 Smith CY, Masson JC: Carcinoma in an adenomyomata of the uterus and a squamous-cell epithelioma of the cervix: report of case. *Proc Mayo Clinic* 1939;14:476–478.
- 28 Da Silva Horta J: Adenomyome de l'utérus, transformation maligne de la partie épithéliale [Uterine adenomyoma, malignant degeneration of the epithelial portion]. *Lisboa Méd* 1941;18:643–656.
- 29 Dubrausky V, Niendorf F: Über die maligne entartung heterotoper korpus-chleimhautwucherungen [On the malignant growth of heterotopic endometrial proliferation in the corpus uteri]. *Zeit Geburtshilfe Gynäkol* 1951;134:213–226.
- 30 Elsner P: Zur Frage des malignen karzinomatös entarteten adenomyoms [On the question of malignant carcinomatous adenomyoma]. *Zeit Geburtshilfe Gynäkol* 1951;134:185–199.
- 31 Olsen K: An unusual case of adenocarcinoma-adenomyosis of the uterus with diffuse embolic lung metastases. *Acta Obstet Gynecol Scand* 1955;34:269–272.
- 32 Colman HI, Rosenthal AH: Carcinoma developing in areas of adenomyosis. *Obstet Gynecol* 1959;14:342–348.
- 33 Polano O: Zur Pathologie des uterus [On the pathology of the uterus]. *Ztschr Geburtsh Gynäk* 1910;67:413–429.
- 34 Greene JW Jr: Carcinoma arising in adenomyosis associated with a feminizing mesenchymoma of the broad ligament. A case report. *Am J Obstet Gynecol* 1961;81:272–276.
- 35 Dockerty MB: Malignancy complicating endometriosis. Pathologic features in 9 cases. *Am J Obstet Gynecol* 1962;83:175–179.
- 36 Zych G, Pieczonka L: Text in polish [Case of adenocarcinoma in uterine adenomyosis. Role of gynecography (GC) in detecting palpable lesions in myometrium]. *Pol Tyg Lek* 1973;28:451–453.
- 37 Baril A, Boucheron S, La Selve A: Transformation adeno-carcinomatose isolée d'une adényomose utérine [Isolated adenocarcinomatous transformation of uterine adenomyosis]. *Sem Hop* 1979;55:301–304.
- 38 Kay S, Frable WJ, Goplerud DR: Endometrial carcinoma arising in a large polypoid adenomyoma of the uterus. *Int J Gynecol Pathol* 1988;7:391–398.
- 39 Hernandez E, Woodruff JD: Endometrial adenocarcinoma arising in adenomyosis. *Am J Obstet Gynecol* 1980;138:827–832.
- 40 Zanetti G, Dall'Ara P, Scarani P: Adenocarcinoma sviluppato su adenomiosi dopo estrogeno terapia in menopausa [Adenocarcinoma arising in adenomyosis after estrogen therapy in the menopause]. *Pathologica* 1981;73:233–240.
- 41 Ramael M, De Neubourg DE, Van Steelandt H, Scalliet P, Buytaert P, Van Marck E: Endometrial papillary carcinoma arising in a focus of adenomyosis. *J Obstet Gynaecol* 1992;12:278–279.
- 42 Zhang SQ: Adenoacanthoma developing in adenomyosis uteri. *Chin Med J (Engl)* 1992;105:343–346.
- 43 Mori Y, Inoue Y, Sakai K, Koizumi M, Okamura N, Sato K, et al: [Primary clear cell carcinoma arising in cystic adenomyosis of the uterus – a case report]. *Nihon Sanka Fujinka Gakkai Zasshi* 1994;46:915–917.
- 44 Kuwashima Y, Uehara T, Kishi K, Tajima H, Shiromizu K, Matsuzawa M, et al: Intramural adenocarcinoma of the uterus, arisen from adenomyosis uteri, showing unique histologic appearances. Report of two cases. *Eur J Gynaecol Oncol* 1994;15:418–423.
- 45 Sasaki T, Sugiyama T, Nanjo H, Hoshi N, Murakami M, Sugita A, et al: Endometrioid adenocarcinoma arising from adenomyosis: report and immunohistochemical analysis of an unusual case. *Pathol Int* 2001;51:308–313.
- 46 Koshiyama M, zuSuki A, Ozawa M, Fujita K, Sakakibara A, Kawamura M, et al: Adenocarcinomas arising from uterine adenomyosis: a report of four cases. *Int J Gynecol Pathol* 2002;21:239–245.
- 47 Rubod C, Narducci F, Delattre C, Decocq J, Verbert A, Delahousse G: Adénocarcinome endométrioïde résultant de foyers d'adényomose. À propos d'un cas et revue de la littérature [Endometrioid adenocarcinoma arising from adenomyosis. A case report and literature review]. *J Gynecol Obstet Biol Reprod (Paris)* 2004;33:140–144.
- 48 Couto D, Mota F, Silva T, de Oliveira C: Adenocarcinoma arising in adenomyosis: report of an unusual case. *Acta Obstet Gynecol Scand* 2004;83:406–408.
- 49 Takeuchi K, Yamanaka Y, Hamana S, Ohara N, Maruo T: Invasive adenocarcinoma arising from uterine adenomyosis involving the rectosigmoid colon. *Int J Gynecol Cancer* 2004;14:1004–1006.
- 50 Takeuchi K, Tateiwa H, Hamana S, Yoshida S, Kitazawa S, Maruo T: Invasive adenocarcinoma arising from adenomyosis in a septate uterus. *Acta Obstetrica et Gynecologica Scandinavica* 2006;85:1146–1147.
- 51 Hsu MI, Chou SY, Lin SE, Liang SJ, Chiu HC, Hsu CS: Very early stage adenocarcinoma arising from adenomyosis in the uterus. *Taiwan J Obstet Gynecol* 2006;45:346–349.
- 52 Puppa G, Shozu M, Perin T, Nomura K, Gloghini A, Campagnutta E, et al: Small primary adenocarcinoma in adenomyosis with nodal metastasis: a case report. *BMC Cancer* 2007;7:103.
- 53 Motohara K, Tashiro H, Ohtake H, Saito F, Ohba T, Katabuchi H: Endometrioid adenocarcinoma arising in adenomyosis: elucidation by periodic magnetic resonance imaging evaluations. *Int J Clin Oncol* 2008;13:266–270.
- 54 Ohta Y, Hamatani S, Suzuki T, Ikeda K, Kiyokawa K, Shiokawa A, et al: Clear cell adenocarcinoma arising from a giant cystic adenomyosis: a case report with immunohistochemical analysis of laminin-5 gamma2 chain and p53 overexpression. *Pathol Res Pract* 2008;204:677–682.
- 55 Hirabayashi K, Yasuda M, Kajiwara H, Nakamura N, Sato S, Nishijima Y, et al: Clear cell adenocarcinoma arising from adenomyosis. *Int J Gynecol Pathol* 2009;28:262–266.
- 56 Kazandi M, Zeybek B, Terek MC, Zekioglu O, Ozdemir N, Oztekin K: Grade 2 endometrioid adenocarcinoma arising from adenomyosis of the uterus: report of a case. *Eur J Gynaecol Oncol* 2010;31:719–721.
- 57 Boes AS, Toussey T, Vandenput I, Timmerman D, Vergote I, Moerman P, et al: Pitfall in the diagnosis of endometrial cancer: case report of an endometrioid adenocarcinoma arising from uterine adenomyosis. *Eur J Gynaecol Oncol* 2011;32:431–434.

- 58 Jeong Shin Y, Se-Eun C, Sung CO, Choi CH, Bae D: Clear cell adenocarcinoma arising from adenomyosis mimicking leiomyoma: a case report. *Korean J Obstet Gynecol* 2011;54:561–565.
- 59 Long M, Hu CY, Wu N, LP W: Malignant transformation of endometrial carcinoma with adenomyosis in 1 case. *Med J NDFN* 2012;33:521–526.
- 60 Koike N, Tsunemi T, Uekuri C, Akasaka J, Ito F, Shigemitsu A, et al: Pathogenesis and malignant transformation of adenomyosis (review). *Oncol Rep* 2013;29:861–867.
- 61 Bae HS, Kim IS, Kang JS, Song JY: Endometrioid adenocarcinoma arising from adenomyosis after black cohosh with St John's wort. *J Obstet Gynaecol* 2014;34:213–214.
- 62 Taga S, Sawada M, Nagai A, Yamamoto D, Hayase R: A case of endometrioid adenocarcinoma arising from adenomyosis. *Case Rep Obstet Gynecol* 2014;2014:569295.
- 63 Masri MA, Omar B, Low WH, Omar J, Yong CM, Ganesalingam M: Endometrioid adenocarcinoma arising from adenomyosis: a rare event: EP9.34 [Abstract]. *Int J Obstet Gynaecol* 2015;122(suppl 1):143.
- 64 Andino MA, Cole LM: A case of adenocarcinoma arising from adenomyosis. *J Obstet Gynaecol Res* 2015;41(suppl1):143.
- 65 Mori M, Furusawa A, Kino N, Uno M, Ozaki Y, Yasugi T: Rare case of endometrioid adenocarcinoma arising from cystic adenomyosis. *J Obstet Gynaecol Res* 2015;41:324–328.
- 66 Baba A, Yamazoe S, Dogru M, Ogawa M, Takamatsu K, Miyauchi J: Clear cell adenocarcinoma arising from adenomyotic cyst: a case report and literature review. *J Obstet Gynaecol Res* 2016;42:217–223.
- 67 Lu B, Chen Q, Zhang X, Cheng L: Serous carcinoma arising from uterine adenomyosis/adenomyotic cyst of the cervical stump: a report of 3 cases. *Diagn Pathol* 2016;11:46–54.
- 68 Sampson JA: Endometrial carcinoma of the ovary arising in endometrial tissue in that organ. *Am J Obstet Gynecol* 1925;9:111–114.
- 69 Hendrickson MR, Kempson RL: Endometrial epithelial metaplasias: proliferations frequently misdiagnosed as adenocarcinoma. Report of 89 cases and proposed classification. *Am J Surg Pathol* 1980;4:525–542.
- 70 Jha P, Ansari C, Coakley FV, Wang ZJ, Yeh BM, Rabban J, et al: Case report: Imaging of Mullerian adenosarcoma arising in adenomyosis. *Clin Radiol* 2009;64:645–648.
- 71 Heo SH, Lee KH, Kim JW, Jeong YY: Unusual manifestation of endometrioid adenocarcinoma arising from subserosal cystic adenomyosis of the uterus: emphasis on MRI and positron emission tomography CT findings. *Br J Radiol* 2011;84:e210–e212.
- 72 Takai N, Akizuki S, Nasu K, Etoh Y, Miyakawa I: Endometrioid adenocarcinoma arising from adenomyosis. *Gynecol Obstet Invest* 1999;48:141–144.
- 73 Hirai M, Hirono M, Oosaki T, Hayashi Y, Yoshihara T, Matsuzaki O: Prognostic factors relating to survival in uterine endometrioid carcinoma. *Int J Gynaecol Obstet* 1999;66:155–562.
- 74 Woodruff JD, Erozan YS, Genadry R: Adenocarcinoma arising in adenomyosis detected by atypical cytology. *Obstet Gynecol* 1986;67:145–148.
- 75 Kawana K, Shirai T, Jimbo H, Yoshida M, Takahashi M, Shiromizu K, et al: Endometrial cytology in early diagnosis of adenocarcinoma arising from adenomyosis uteri. *Acta Cytol* 2002;46:612–614.
- 76 Griffin M, Parai S, Ghatage P, Dimakulangan A: Papillary serous carcinoma of the uterus arising in an adenomyoma. *Acta Cytol* 1996;40:849–850.
- 77 Sala E, Crawford R, Senior E, Shaw A, Simcock B, Vrotsou K, et al: Added value of dynamic contrast-enhanced magnetic resonance imaging in predicting advanced stage disease in patients with endometrial carcinoma. *Int J Gynecol Cancer* 2009;19:141–146.
- 78 Cao K, Gao M, Sun YS, Li YL, Sun Y, Gao YN, et al: Apparent diffusion coefficient of diffusion weighted MRI in endometrial carcinoma—relationship with local invasiveness. *Eur J Radiol* 2012;81:1926–1930.
- 79 Nasi F, Fiocchi F, Pecchi A, Rivasi F, Torricelli P: MRI evaluation of myometrial invasion by endometrial carcinoma. Comparison between fast-spin-echo T2w and coronal-FMPSPGR Gadolinium-Dota-enhanced sequences. *Radiol Med* 2005;110:199–210.
- 80 Giammalvo JT, Kaplan K: The incidence of endometriosis interna in 120 cases of carcinoma of the endometrium. *Am J Obstet Gynecol* 1958;75:161–166.
- 81 Smith GV: A clinical and pathologic study of 159 cases treated at the clinic of the free hospital for women. *Am J Obstet Gynecol* 1929;17:806–814.
- 82 Skamnakis SN: Uber gleichzeitiges Vorkommen von Adenomyosis uteri interna mit anderen pathologischen Veranderungen des Genitales, insbesondere mit Carcinoma uteri [Occurrence of adenomyosis uteri interna with other pathological genital changes, especially with carcinoma uteri]. *Zentralbl Gynäkol* 1938;62:414–423.
- 83 Fallas R, Rosenblum G: Endometriosis: a study of 260 private hospital cases. *Am J Obstet Gynecol* 1940;39:964–975.
- 84 Hunter WC, Smith LL, Reiner WC: Uterine adenomyosis; incidence, symptoms, and pathology in 1,856 hysterectomies. *Am J Obstet Gynecol* 1947;53:663–668.
- 85 Hayata T, Kawashima Y: Clinicopathologic study of eight cases of uterine body cancers associated with endometriosis interna (uterine adenomyosis). *Am J Obstet Gynecol* 1987;156:663–666.
- 86 Taskin M, Lallas TA, Shevchuk M, Barber HR: P53 expression in adenomyosis in endometrial carcinoma patients. *Gynecol Oncol* 1996;62:241–246.
- 87 Lochhead P, Chan AT, Nishihara R, Fuchs CS, Beck AH, Giovannucci E, et al: Etiologic field effect: reappraisal of the field effect concept in cancer predisposition and progression. *Mod Pathol* 2015;28:14–29.
- 88 Kucera E, Hejda V, Dankovcik R, Valha P, Dudas M, Feyereisl J: Malignant changes in adenomyosis in patients with endometrioid adenocarcinoma. *Eur J Gynaecol Oncol* 2011;32:182–184.
- 89 Marcus CC: Relationship of adenomyosis uteri to endometrial hyperplasia and endometrial carcinoma. *Am J Obstet Gynecol* 1961;82:408–416.
- 90 Koshiyama M, Morita Y, Fujii H, Kobashi Y, Yoshida M: Gynecologic malignancies accompanied by benign hormone-dependent diseases. *Menopause* 2001;8:149–150.
- 91 Koshiyama M, Okamoto T, Ueta M: The relationship between endometrial carcinoma and coexistent adenomyosis uteri, endometriosis externa and myoma uteri. *Cancer Detect Prev* 2004;28:94–98.
- 92 Kawamura K, Kaneki E, Ogawa S, Imamura H, Ohishi Y, Kobayashi H, et al: Primary uterine mullerian mucinous borderline tumor (MMBT) associated with adenomyosis: a case report. *Int J Gynecol Pathol* 2014;33:146–150.
- 93 Musa F, Frey MK, Im HB, Chekmareva M, El-lenson LH, Holcomb K: 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* 2012;207:417.e1–e6.
- 94 Mittal KR, Barwick KW: Endometrial adenocarcinoma involving adenomyosis without true myometrial invasion is characterized by frequent preceding estrogen therapy, low histologic grades, and excellent prognosis. *Gynecol Oncol* 1993;49:197–201.
- 95 Gün I, Oner O, Bodur S, Ozdamar O, Atay V: Is adenomyosis associated with the risk of endometrial cancer? *Medicinski Glasnik* 2012;9:268–272.
- 96 Nomelini RS, Ferreira FA, Borges RC, Adad SJ, Murta EF: Frequency of endometriosis and adenomyosis in patients with leiomyomas, gynecologic premalignant, and malignant neoplasias. *Clin Exp Obstet Gynecol* 2013;40:40–44.
- 97 Kairi-Vassilatou E, Kontogianni K, Salamalekis M, Sykiotis K, Kondi-Pafitis A: A clinicopathological study of the relationship between adenomyosis and other hormone-dependent uterine lesions. *Eur J Gynaecol Oncol* 2004;25:222–224.
- 98 Hall JB, Young RH, Nelson JH Jr: The prognostic significance of adenomyosis in endometrial carcinoma. *Gynecol Oncol* 1984;17:32–40.
- 99 Jacques SM, Lawrence WD: Endometrial adenocarcinoma with variable-level myometrial involvement limited to adenomyosis: a clinicopathologic study of 23 cases. *Gynecol Oncol* 1990;37:401–407.

- 100 Ismiil N, Rasty G, Ghorab Z, Nofech-Mozes S, Bernardini M, Ackerman I, et al: Adenomyosis involved by endometrial adenocarcinoma is a significant risk factor for deep myometrial invasion. *Ann Diagn Pathol* 2007;11:252–257.
- 101 Ismiil ND, Rasty G, Ghorab Z, Nofech-Mozes S, Bernardini M, Thomas G, et al: Adenomyosis is associated with myometrial invasion by FIGO 1 endometrial adenocarcinoma. *Int J Gynecol Pathol* 2007;26:278–283.
- 102 Taneichi A, Fujiwara H, Takahashi Y, Takei Y, Machida S, Saga Y, et al: Influences of uterine adenomyosis on muscle invasion and prognosis of endometrioid adenocarcinoma. *Int J Gynecol Cancer* 2014;24:1429–1433.
- 103 Matsuo K, Cahoon SS, Gualtieri M, Scannell CA, Jung CE, Takano T, et al: Significance of adenomyosis on tumor progression and survival outcome of endometrial cancer. *Ann Surg Oncol* 2014;21:4246–4255.
- 104 Gizzo S, Patrelli TS, Dall’asta A, DI Gangi S, Giordano G, Migliavacca C, et al: Coexistence of adenomyosis and endometrioid endometrial cancer: role in surgical guidance and prognosis estimation. *Oncol Lett* 2016;11:1213–1219.
- 105 Jeffcoates TN, Potter AL: Endometriosis as a manifestation of ovarian dysfunction. *J Obstet Gynaecol Brit Emp* 1934;41:684–707.
- 106 Novak E, De Lima OA: A correlative study of adenomyosis and pelvic endometriosis, with special reference to the hormonal reaction of ectopic endometrium. *Am J obstet Gynecol* 1948;56:634–644.
- 107 Ichikawa Y, Takano K, Higa S, Tanabe M, Wada A, Sugita M, et al: Endometrial carcinoma coexisting with pregnancy, presumed to derive from adenomyosis: a case report. *Int J Gynecol Cancer* 2001;11:488–490.
- 108 Parazzini F, Negri E, La Vecchia C, Benzi G, Chiapparino F, Polatti A, et al: Role of reproductive factors on the risk of endometrial cancer. *Int J Cancer* 1998;76:784–786.
- 109 Kodama S, Tanaka K, Tokunaga A, Sudo N, Takahashi T, Matsui K: Multivariate analysis of prognostic factors in patients with ovarian cancer stage I and II. *Int J Gynaecol Obstet* 1997;56:147–153.
- 110 Izadi-Mood N, Samadi N, Sarmadi S, Eftekhari Z: Papillary serous carcinoma arising from adenomyosis presenting as intramural leiomyoma. *Arch Iran Med* 2007;10:258–260.
- 111 Abushahin N, Zhang T, Chiang S, Zhang X, Hatch K, Zheng W: Serous endometrial intraepithelial carcinoma arising in adenomyosis: a report of 5 cases. *Int J Gynecol Pathol* 2011;30:271–281.
- 112 Kok VC, Tsai HJ, Su CF, Lee CK: The risks for ovarian, endometrial, breast, colorectal, and other cancers in women with newly diagnosed endometriosis or adenomyosis: a population-based study. *Int J Gynecol Cancer* 2015;25:968–976.
- 113 Benagiano G, Brosens I, Habiba M: Adenomyosis: a life-cycle approach. *Reprod Biomed Online* 2015;30:220–232.
- 114 Verit FF, Yucel O: Endometriosis, leiomyoma and adenomyosis: the risk of gynecologic malignancy. *Asian Pac J Cancer Prev* 2013;14:5589–5597.
- 115 Ismiil N, Ghorab Z, Covens A, Nofech-Mozes S, Saad R, Dube V, et al: Intraoperative margin assessment of the radical trachelectomy specimen. *Gynecol Oncol* 2009;113:42–46.
- 116 Wei JJ, Paintal A, Keh P: Histologic and immunohistochemical analyses of endometrial carcinomas: experiences from endometrial biopsies in 358 consultation cases. *Arch Pathol Lab Med* 2013;137:1574–1583.
- 117 Yen CF, Huang SJ, Lee CL, Wang HS, Liao SK: Molecular characteristics of the endometrium in uterine adenomyosis and Its biochemical microenvironment. *Reprod Sci* 2017;24:1346–1361.
- 118 Mehaseb MK, Panchal R, Taylor AH, Brown L, Bell SC, Habiba M: Estrogen and progesterone receptor isoform distribution through the menstrual cycle in uteri with and without adenomyosis. *Fertil Steril* 2011;95:2228–2235.