# Role of Hormones in Common Benign Uterine Lesions: Endometrial Polyps, Leiomyomas, and Adenomyosis


**Myriam Kossaï and Frédérique Penault-Llorca**

## 1 Introduction

Leiomyoma, adenomyosis, and endometrial polyps are benign uterine neoplasms or disorders. They are considered a specific entity in the PALM-COEIN FIGO [1]. They are absent before menarche and regress rapidly after menopause, indicating that sex steroid hormones (estrogen and progesterone) play a pivotal role in the development of these diseases. Estrogen and progesterone are secreted mainly by the ovaries and in smaller amounts by the adrenal glands. They are secreted cyclically during the reproductive life and are required for the process of implantation, which is the result of a series of complex interactions between the decidualized endometrium and the early embryo [2].

Leiomyoma, adenomyosis, and endometrial polyps seem to develop in the context of hormonal imbalances, in association with various factors ranging from genetic factors to modifiable lifestyle factors. In this chapter we define these entities and describe our current knowledge regarding their etiopathogenesis and the influence of sex steroid hormones on their development. Available and emerging therapy is presented for each disease.

M. Kossaï (✉) · F. Penault-Llorca (✉)
Department of Pathology and Molecular Pathology, Centre Jean Perrin, Clermont-Ferrand, France

UMR INSERM 1240, Universite Clermont Auvergne, Clermont-Ferrand, France
e-mail: myriam.kossai@clermont.unicancer.fr; frederique.penault-llorca@clermont.unicancer.fr



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## 2 Leiomyoma

### *2.1 Definition, Epidemiology, Clinical Features*

Uterine leiomyomas (ULs), often called fibroids or myomas, are benign smooth muscle tumors. They are the most common neoplasms in women, occurring in >70% of women worldwide [3, 4], but the true incidence is certainly underestimated. Histological studies on a series of uteri serially examined, resected for noncancerous conditions, showed that 56–77% of women had ULs [3, 5]. They mostly affect women during their reproductive age. Black women are particularly affected by ULs, with a higher prevalence and a two- to threefold incidence, occurring at a younger age than in Caucasian, Asian, and Hispanic women [4, 6, 7].

ULs occur in the uterine body (Fig. 1) but can develop in the cervix, uterine ligaments, and, rarely, the ovary and fallopian tube. A FIGO classification system has been established, based on tumor location (Fig. 2) [8]. They are well-demarcated lesions consisting of interlacing bundles of smooth muscle cells separated by substantial extracellular matrix (ECM) (Fig. 3). Histological examination defines the malignant potential of ULs by the assessment of nuclear grade and atypia, the count of mitoses, and the presence or absence of coagulative necrosis. Several subtypes have been described such as myxoid, epithelioid, cellular, and degenerated ULs (Fig. 4). Despite a low mitotic index, some subtypes present unusual growth patterns, commonly attributed to malignant lesions. These are diffuse leiomyomatosis, intravascular leiomyomatosis, benign metastasizing ULs, and disseminated peritoneal leiomyomatosis. For example, intravascular leiomyomatosis is a condition in which benign smooth muscle cells are present within the lumen of veins, which could spread to the heart without invading other tissues. Disseminated peritoneal

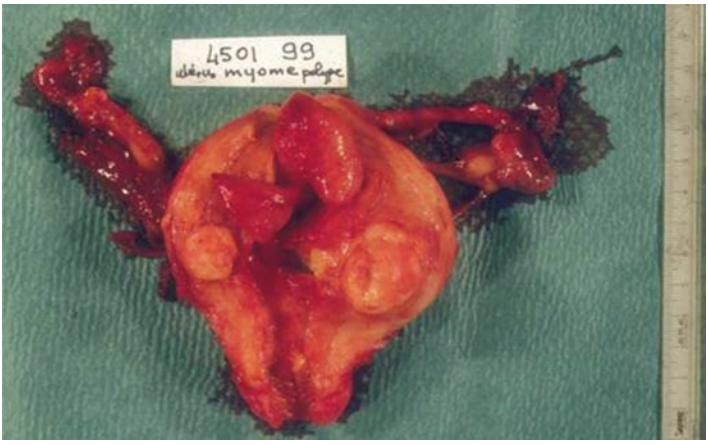


**Fig. 1** Uterine leiomyomata (submucosal, intramural, and subserosal) and endometrial polyp

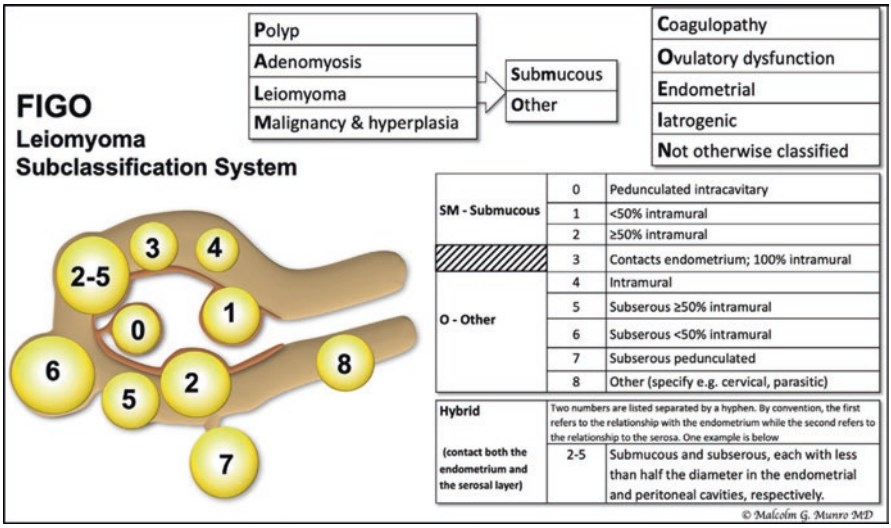


**Fig. 2** The FIGO leiomyoma classification system. (From Munro et al. Int J Gynaecol Obstet. 2011)

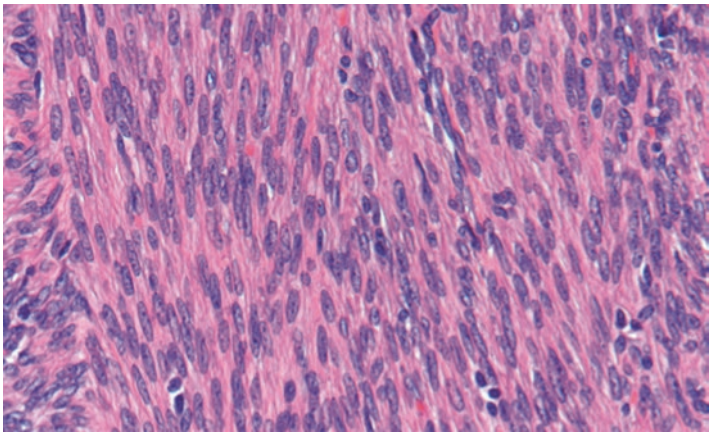

**Fig. 3** Leiomyoma composed of spindle-shaped smooth muscle cells, with uniform, regular nuclei. H&E ×40

leiomyomatosis exhibits small nodular deposits of benign smooth muscle throughout the superficial subperitoneal tissues without tissue invasion.

Clinically, ULs are symptomatic in about one third of women over 30 years, rising to more than 40% in women over 40 years. They present with a variety of symptoms due mostly to their local mass effect. Heavy menstrual bleeding and pelvic pressure are the most common symptoms. Chronic pelvic pain, pressure upon adjacent organs resulting in incontinence, increased urinary frequency, and constipation

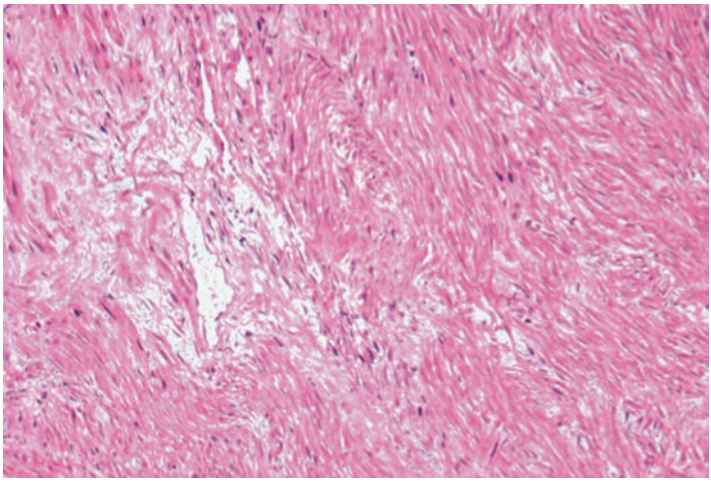

**Fig. 4** Microscopic section of a leiomyoma with degenerative changes. H&E ×40

are commonly described. ULs can also cause problems related to pregnancy including infertility, early pregnancy loss, and later pregnancy complications [9]. The disease is more severe in black women compared to white women, with larger and more numerous tumors [7, 10].

The severity of symptoms depends on the number, size and location of the tumors in the uterus. ULs are often multiple and demonstrate a large heterogeneity even within the same woman, presenting several ULs showing different growth rates [3, 11].

As a consequence, ULs represent a major indication of hysterectomy and an important public health burden. As an example, the estimated annual healthcare-related costs of ULs range from 6 to 34 billion USD in the United States [12].

## *2.2 Risk Factors and Etiopathogenesis*

A variety of risk factors that can overlap have been identified, from genetic and epigenetic factors to modifiable lifestyle factors [13, 14]. Increasing age until age of menopause and ethnicity (African ancestry) are the main factors. Family history of ULs, time since last birth, high blood pressure, obesity, soybean milk and food additive consumption, and vitamin C deficiency are other factors. Pregnancy (with a risk that decreases with an increasing number of pregnancies), oral contraceptive use, and smoking in women with a low BMI may lower the risk of ULs.

Other pathogenetic factors have also been reported such as growth factors, cytokines, chemokines, and extracellular matrix components. The role of steroid hormones remains decisive for the development and growth of ULs.

The ULs' etiology is unclear, certainly multifactorial; ULs derive from a proliferation of a single clone of smooth muscle cells [15, 16]. The myometrium and ULs contain multipotent somatic stem cells that represent a reservoir supporting growth and self-renewal [17]. Stem cells from ULs carry genetic mutations, whereas the myometrium does not, suggesting that a mutation as a first "hit" is required for the genesis of UL from a myometrial stem cell. Among genetic alterations, 12 trisomy, deletions in 7q, and mutations in genes encoding high mobility group AT-hook 2 (*HMGA2*) or mediator complex subunit 12 (*MED12*) have been reported [18–20]. The latter one is frequent, found in around 70% of ULs. In addition to sporadic alterations, ULs are a feature of hereditary leiomyomatosis and renal cancer syndrome (HLRCC) caused by heterozygous germline mutations in fumarate hydratase (*FH*) [21, 22].

ULs seem to develop in response to the menstrual cyclic steroid hormones. Estrogen and progesterone and their nuclear receptors (ER and PR, respectively) stimulate the genesis and growth of ULs. Messenger RNA and protein, estrogen and progesterone, and their receptor levels are higher in UL compared to those in normal myometrium [23–26]. Stem cells derived from ULs express low levels of estrogen and progesterone compared with UL cells or normal myometrial cells [27]. The growth of UL cells requires the surrounding myometrial cells with higher levels of steroid hormone receptors and their ligands, potentially mediated in a paracrine fashion [17]. Some studies showed that estrogen and progesterone activate several pathways such as the WNT/β-catenin pathway, leading to the stimulation of various transcription factors and downstream signaling, ultimately giving rise to the clonal proliferation of ULs [28–31]. Ovarian estrogen and estrogen induced locally by the aromatase activity are key regulators in UL cells. Aromatase inhibitors are efficient in reducing significantly UL size, showing that local aromatase activity is essential [32].

Progesterone is essential for maintenance and growth of ULs and, according to some studies, appears to be an even more important regulator than estrogen [33–36]. A study suggested that estrogen maintains PR levels and that progesterone, by interacting receptors, promotes UL growth [37]. Progesterone and progesterone receptors influence proliferation of ULs by regulating expression of growth factor signaling proteins such as epidermal growth factor (EGF) and signaling pathways. Progesterone receptors can directly bind to antiapoptotic BCL-2 promoter preventing apoptosis in UL cells [38–40]. The use of antiprogestins or selective progesterone receptor modulators in clinical trials provides yet the strongest evidence for the effect of progesterone on UL growth. Indeed, these treatments induced a decreased tumor size [35, 36, 41–44].

## *2.3 Treatment*

Regarding UL treatment, there are no standard guidelines due to a lack of randomized controlled trials. Studies comparing treatment options are rare and follow-up investigation is often missing. The strategy depends on the presence or absence of

symptoms and their nature (heavy menstrual bleeding, bulk symptoms, or both). For women with asymptomatic ULs, it is generally recommended to have follow-up evaluations. There is an exception for women with submucosal ULs who want future childbearing: hysteroscopic resection is indicated even if ULs are asymptomatic, according to some guidelines [45]. Although surgical interventions had historically been the mainstay in UL treatment, therapeutic options for symptomatic ULs also include medical and radiological procedures. However, a systematic review pointed out the lack of high-quality evidence supporting the effectiveness of most medical treatments [46].

### 2.3.1 Medical Treatment

For UL-related heavy bleeding, nonsteroid treatments include antifibrinolytics (tranexamic acid) and nonsteroidal anti-inflammatory drugs (NSAIDs) that have shown to be effective [47]. NSAIDs also reduce pain.

Contraceptive associate synthetic analogues of progesterone and estrogen are widely prescribed for the treatment of UL-related heavy menstrual bleeding.

Progesterone receptor agents are intended to reduce heavy menstrual bleeding by reducing endometrial hyperplasia associated with ULs. They include antiprogestins (mifepristone), selective progesterone receptor modulators (SPRMs, ulipristal acetate UPA), and levonorgestrel intrauterine device (LNG-IUD). UPA showed to be effective in decreasing ULs and uterine volume and improved symptoms such as pain and bleeding, most patients achieving amenorrhea [35, 36]. Because of specific pathological SPRM-related endometrial changes, an intermittent regimen is recommended [48]. These are also used for preoperative treatment of ULs. Hence, SPRMs are becoming the standard medical option for ULs with bulk symptoms. Studies assessing mifepristone showed a decrease in size of ULs and the total uterine volume at the completion of the period of active treatment. UL-related symptoms affecting the quality of life were also substantially improved [49, 50]. LNG-IUDs have been shown to reduce bleeding and to restore hemoglobin levels in women with ULs (except those that are submucosal) [51]. Mifepristone and LNG-IUDs have not been approved as therapy for ULs; further clinical trials to support their use are required [52].

Gonadotropin-releasing hormone (GnRH) agonists reduce the size of ULs and the overall uterine volume associated with a reduction of bleeding reported in some studies [53, 54]. Other symptoms such as pelvic pain and pressure, urinary frequency, and constipation were consistently ameliorated. Despite these positive effects, this treatment causes numerous side effects mimicking menopause, including vasomotor effects and bone mineral density loss, although some of these can be improved with hormonal “add-back” therapy using estrogens. Another problem resides in the fact that ULs recur following discontinuation of treatment. Hence, this drug is recommended for preoperative management for short periods [45, 55]. GnRH antagonists have similar effects with GnRH agonists with an immediate

effect, avoiding the "flare-up" [56]. They reduce UL volume, but they do not improve bleeding and are not considered as an effective treatment for ULs.

Selective estrogen receptor modulator (SERM) raloxifene was assessed in randomized trial showing inconsistent results [57, 58]. Aromatase inhibitors showed to be effective in reducing ULs and uterine volume as well as symptoms [59]. Those agents are not currently supported for the treatments of ULs.

### 2.3.2 Interventional Procedures for ULs

Several studies randomized women to uterine artery embolization (UAE) procedure; this is a conservative approach and should be considered for women with symptomatic ULs. ULs and uterine volume decreased significantly as well as symptoms after UAE, regardless of the embolization agent or size of particles used to occlude the UL arteries [60]. The EMMY trial was a long-term follow-up report from the "Embolization for the Treatment of Symptomatic Uterine Fibroid Tumors" study and confirmed that ULs and uterine volume reductions persist up to 5 years after UAE; however, 28% (23/81) of women underwent subsequent hysterectomy [61].

Magnetic resonance-guided focused ultrasound (MRgFUS) is a noninvasive thermoablative technique, also effective in reducing UL size and symptoms, but remains experimental [62].

Laparoscopic radiofrequency UL ablation with intra-abdominal ultrasound guidance has been approved for the treatment of ULs with bulk symptoms [63, 64]. In addition, this procedure seems to result in less intraoperative blood loss and a shorter hospital stay, compared to myomectomy.

Myolysis using energy delivery systems based upon radiofrequency electricity or supercooled cryoprobes and laparoscopic ligations of the uterine arteries are other techniques used for women with UL-related bulk symptoms, but they need to be validated in clinical trials [45, 65].

### 2.3.3 Surgical Treatment

For women with intrauterine ULs (FIGO type 0, type 1, or type 2 up to 4 cm), myomectomy seems to be the best option for the treatment of UL-related bleeding [45]. It can be performed by hysteroscopy, laparoscopy or laparotomy. This technique removes ULs and preserves the uterus. However, patients must be informed that the symptoms may persist and ULs may recur, requiring further surgery. It is recommended in asymptomatic women who desire future fertility given its minimal morbidity.

Endometrial ablation is a minimally invasive procedure to be considered for women who wish to preserve fertility but as a second option after medical treatment since this technique increases the risk for extrauterine pregnancy [66].

Definitive hysterectomy is used following the failure of medical treatment in women with FIGO type 3 and higher ULs. It is recommended for women who do not intend to get pregnant. This method showed significant improvement in quality of life [45].

## 3 Adenomyosis

### *3.1 Definition, Epidemiology, Clinical Features*

Adenomyosis is not considered a neoplasm but an endometrial disorder described as "the benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic non-neoplastic, endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium" (Fig. 5) [67]. It was initially described by Carl von Rokitansky in 1860, before endometriosis, but the term was first used by Frankl in 1925. The endometrial-myometrial junction is irregular, the involvement of the superficial myometrium by endometrial mucosa occurring to varying degrees. Consequently "adenomyosis" is not well defined. The distance to which the endometrial tissue extends into the myometrium has been expressed as a number of microscopic fields from the junction. It has been commonly suggested that the diagnosis is based on a myometrial depth of ≥2.5 mm on one microscopic field at ten times magnification from the junction [68].

Adenomyosis occurs mostly in the late reproductive years, and its prevalence varies widely, with an average rate of 20–25% [69]. Recent studies showed that this condition is not particularly associated with other uterine disorders or neoplasms such as leiomyoma and prolapse [70].

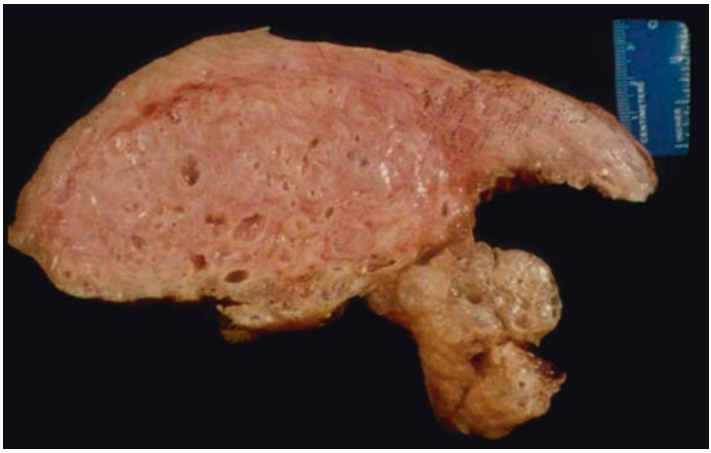

**Fig. 5** Extensive adenomyosis in uterine cross section, with sponge-like appearance due to endometrial glands and their cystic hyperplasia (gross image)

Dysmenorrhea and dyspareunia are the most common symptoms, but the patient can be asymptomatic [71]. Pain, heavy periods, and infertility are other reported symptoms.

Until recently, adenomyosis could only be diagnosed by histology on hysterectomy. With the improvement of high-resolution ultrasound and the development of magnetic resonance imaging (MRI), the diagnosis of adenomyosis can now be relatively reliably made without a hysterectomy [72–74].

## *3.2 Risk Factors, Etiopathogenesis*

Age, multiparity, and prior uterine surgery are the main risk factors involved in the etiology of adenomyosis [75]. The development of adenomyosis is influenced by steroids, but the pathogenetic mechanisms of adenomyosis remain unclear. Other factors which have been proposed to play a role in the etiopathogenesis of adenomyosis are inflammation, altered cell proliferation, and neoangiogenesis [76].

Regarding adenomyosis etiology, there are two main theories. Adenomyosis may develop from invagination of the endometrial basalis into the myometrium, through an altered or absent junctional zone [77]. This altered junctional zone presents week smooth muscle fibers that have loosened their tissue cohesion [78]. The invagination is due to activation of the tissue injury and repair (TIAR) mechanism, resulting in a local supraphysiological estrogen production in eutopic and ectopic endometrium in patients with adenomyosis. A higher level of estrogen was detected in menstrual blood but not in peripheral blood in women with this disease, corroborating these findings [79].

Gene polymorphisms such as catechol-O-methyltransferase (COMT), cytochrome P450–1B1 (CYP1B1), and COX-2 have been associated with the risk of developing adenomyosis [80, 81]. Progesterone and estrogen have antagonist effects. Some studies demonstrated that some epigenetic aberrations in progesterone receptor genes lead to a reduction or a loss of the progesterone receptor activity in women with adenomyosis [82, 83]. This hormonal deregulation indirectly increases estrogen-induced proliferation.

Postmenopausal women with breast cancer treated with tamoxifen have a higher rate of adenomyosis than those untreated [84]. By its estrogenic action, tamoxifen may promote the development of adenomyosis or its persistency in postmenopause [85]. Hence, hyperestrogenism promotes hyperperistalsis and increases local damage allowing the invagination of endometrial tissue into the myometrium [86–88].

The cycle of auto-traumatization worsens with each menstrual cycle, increasing the disruption of the muscular fibers and the “invasion” of the endometrium into the muscular uterine wall. Also, cesarean section, increased birth rates, and prior uterine surgery are risk factors for adenomyosis, supporting that tissue trauma plays a role in the pathogenesis of this disease [89–92].

The other hypothesis suggests that adenomyosis may originate from the differentiation of endometrial stem cells or de novo from metaplasia and displaced embry-

onic pluripotent Müllerian remnants [76, 93, 94]. This Müllerian metaplasia theory is supported by case reports of adenomyosis in hypoplastic myometrium of patients with Mayer-Rokitansky-Kuster-Hauser syndrome (absence of functional endometrium).

The other origin of metaplasia may lie in small populations of adult epithelial and stromal stem cells that have been reported in the uterus and are thought to differentiate [95]. These cells reside in the endometrial basalis within niches and have a clonogenic and progenitor activity responsible for the remarkable regenerative activity of the endometrium [93]. They may also have enhanced capacity to regenerate, leading to a dysregulation of endometrial stem cells, which could represent a mechanism for seeding ectopic endometrium into the myometrium. Endometrial stem cells may be deposited in the muscular wall due to retrograde menstruation containing endometrial fragments and then differentiate into endometrial tissue. Moreover, it has been suggested that adult stem cells could be activated by tissue injury promoting the disruption of stem cell niches in the junctional zone [93, 96]. Recently, Ibrahim et al. described a population of epithelial stem-like cells called "pale cells" in the basal endometrial glands [97]. These cells have motile properties and may represent the population that migrates actively into the myometrium, fostered by microscopic injury at the endometrial junctional zone.

## *3.3 Treatment*

Several therapeutic options are available, from medical hormonal or nonhormonal treatments to nonconservative surgery, but to date there are no international guidelines. The choice depends on the woman's age, reproductive status, and clinical symptoms [98].

### 3.3.1 Steroidal Treatments

Adenomyosis is an estrogen-dependent condition that responds to hormonal treatment. The aim of medical treatment is to induce amenorrhea and inhibit ovulation, based on the theory that the responses of the eutopic and ectopic endometrium are substantially similar, leading to an improvement of the symptoms and a potential increase of fertility.

Oral estrogen-progestin contraceptives commonly used to treat adolescents cause decidualization and subsequent atrophy of the uterus, enabling long-term pain control and reducing menstruation.

GnRH agonists present antiproliferative and anti-inflammatory effects, reducing the uterine size and improving symptoms [99]. However, the use of GnRH agonists has hypoestrogenic side effects such as vasomotor syndrome, genital atrophy, mood instability, and reduced bone mineral density. To limit these side effects, an "add-

back" therapy is recommended. Nonetheless, specific studies on this therapeutic regimen for the treatment of adenomyosis are lacking.

Progestins such as danazol, norethisterone acetate (NETA), and dienogest (DNG) have the same mechanism of actions as GnRHa and also induce a hypoestrogenism, having consequently the same effects. Unfortunately, there are limited data regarding the use of progestins in women with adenomyosis. Few retrospective and prospective studies showed a significant improvement in pelvic pain and bleeding [100–107].

Levonorgestrel-releasing intrauterine device (LNG-IUD) seems to be an effective long-term treatment. It leads to a reduction of menstruation and pain through a decidualization and an atrophy of the uterine wall and a reduction of uterine volume [108–110]. It acts directly on adenomyotic lesions by downregulating estrogen receptors [111]. Ozdegirmenci et al. compared the LNG-IUD with hysterectomy in adenomyosis patients, in a randomized controlled trial. After 6 months, the hemoglobin levels in both groups were similar and increased with LNG-IUD; this treatment has a superior effect on the quality of life compared to hysterectomy [112].

Selective estrogen receptor modulators (SERMs), selective progesterone receptor modulators (SPRMs), and aromatase inhibitors (AIs) are emerging drugs that show promising results [69], but supporting evidence for their clinical use is still necessary.

### 3.3.2 Nonsteroidal Medical Treatments

Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually used to treat adenomyosis-related symptoms. Some systemic reviews showed that they are effective in treating menstrual pain and reducing menstrual blood loss [47, 113]; however, there are no studies investigating the use of NSAIDs in adenomyosis. Medical approaches can be ineffective and symptoms often relapse.

### 3.3.3 Interventional Procedures

Conservative treatment is required for women who wish to preserve their fertility. Uterine artery embolization (UAE) and MRI-guided focused ultrasound (MRgFUS) are conservative interventional procedures [114–116]. UAE has shown to be effective in the treatment of women with ULs and with both ULs and adenomyosis [117]. Several studies investigated the use of MRgFUS in women with symptomatic adenomyosis; this procedure appears to be effective and safe, but more clinical data is required [117].

### 3.3.4 Surgical Treatment

Minimally invasive surgical procedures are an alternative option when medical treatment is insufficient. Hysteroscopic excision of adenomyosis foci has been suggested before treatment for fertility. Results of studies on endometrial ablation of adenomyosis are conflicting [117]. This technique should not be used when foci of adenomyosis are deep, a major cause of treatment failure.

Surgical excision by laparoscopy of localized lesions sparing the uterus seemed to be safe. Hysterectomy is a definitive surgery and represents the gold standard treatment for women who have no desire for future fertility. Total hysterectomy should be favored over subtotal hysterectomy since there were few case reports of recurrence of the disease in the cervical stump or in the rectovaginal septum [118].

## 4 Endometrial Polyps

### *4.1 Definition, Epidemiology, Clinical Features*

Endometrial polyps (EPs) are localized exophytic biphasic growths of endometrial glands and stroma with blood vessels protruding into the uterine cavity. They can arise at any age in about 13–17% of women but are more frequent shortly after menopause [119]. They can be single or multiple, measuring a few millimeters up to several centimeters, and can be sessile or pedunculated in shape (see Fig. 1). They can develop anywhere in the uterine cavity and can regress spontaneously [120]. EPs are in a large majority benign (Fig. 6), but atypical hyperplasia and adenocarcinoma, generally of the endometrioid type, may occur [121].

EPs are usually asymptomatic. They can be a cause of abnormal bleeding with no correlation with the polyp's size or growth rate [122].

### *4.2 Etiopathogenesis*

Several hypotheses have been suggested regarding their pathogenesis. They may arise as monoclonal overgrowths of genetically altered stromal cells promoting proliferation of adjacent epithelial cells [123, 124]. Rearrangements in a high mobility group (HMG) family of transcription factors have been identified in EP [124–126]. It has been suggested that they can develop through a mechanism involving an aromatase-dependent focal hyperestrogenism [127, 128]. Ovarian hyperthecosis, a source of estrogen, may participate to the development of EPs in postmenopausal women [129]. EPs are related to hormonal imbalances; they can be functional show-

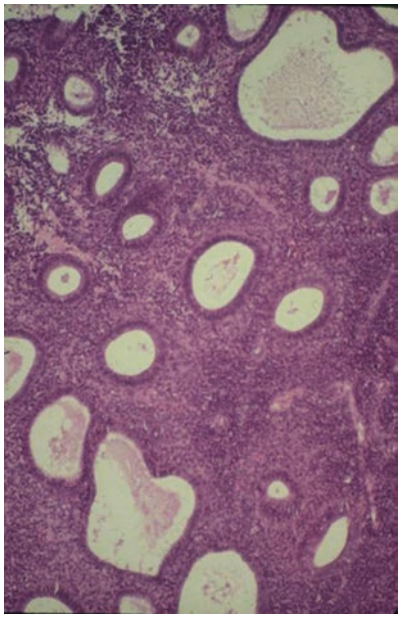

**Fig. 6** Benign endometrial polyp with non-atypical glandular hyperplasia. H&E ×100

ing cycling changes in synchrony with those seen in the adjacent normal endometrium but more often are nonfunctional with no proliferative or secretory activity.

In recent years, the increasing age and the use of tamoxifen were the two most significant risk factors for the development of EPs (Fig. 7) [122]. Women on tamoxifen are more likely to present much larger, more fibrotic EPs, with mucinous metaplasia, and these EPs are more likely to contain hyperplasia or carcinoma [130].

Other risk factors have been reported in the pathogenesis of EPs, such as obesity, hypertension, and diabetes, but none of them is significant when women's age is taken into consideration [131].

EPs are associated with an increased risk of endometrial malignancy. Primary malignancy degeneration of a polyp occurs in 0.5–4.8% [132, 133]. EPs can also spontaneously regress over time, especially smaller ones (mean diameter 10.7 mm) compared to larger ones (mean diameters 15.1 mm), more frequently in premenopausal women [122].

## *4.3 Treatment*

Current management of EPs depends on whether the patient is asymptomatic or not [134]. Some studies reported no correlation between polyp's growth rate, monitored by ultrasound scans, and symptoms. These findings suggest that routine ultrasound

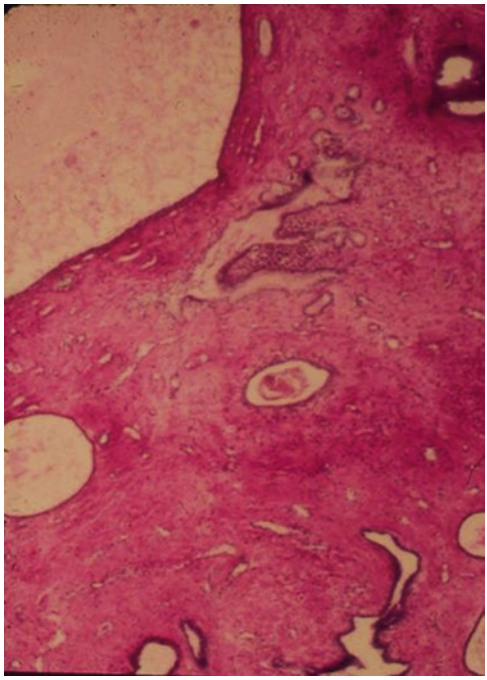

**Fig. 7** Tamoxifen-treated patient with endometrial polyp showing cystic glands, mucinous metaplasia, and fibro-hyalinized stroma. H&E ×25

scans should not be used to predict the onset of symptoms and that patients with asymptomatic EP should report symptoms if they appear rather than having routine ultrasound scans [122].

EPs are generally removed by transcervical resection (TCRP) under hysteroscopy, a minimally invasive effective method, or by curettage or other sampling techniques such as pipelle [135]. When endometrial hyperplasia or adenocarcinoma is present on the specimen, the patient should be managed in the same way as if these premalignant and malignant lesions were found in a non-polypoid area.

Few studies have investigated the use of hormone therapy in the treatment of EPs after resection or the use of levonorgestrel-releasing intrauterine device, but significant clinical evidence supporting their use is needed [136, 137]. Currently, there is no recommended medical hormone therapy for the treatment of EPs.

## 5 Conclusions

Leiomyoma, adenomyosis, and endometrial polyps are common endometrial diseases. They share some common risk factors and symptoms such as heavy menstrual bleeding, pelvic pain, and a negative impact on women's quality of life. They also represent a significant health cost, particularly leiomyoma.

They seem to arise in a context of hormonal imbalances due to steroid hormones, estrogen and progesterone. A growing body of evidence suggests that those hormones and their receptors are key modulators in the genesis and the growth of those pathologic entities. Further studies are required to understand their involvement in the pathogenesis of those lesions and their link to other factors such as extracellular matrix components, growth factors, chemokines, cytokines, and tissue repair mechanisms. This will allow the identification of potential targets and co-targets for medical intervention.

Currently, medical therapies of leiomyoma and adenomyosis are focused on estrogen and progesterone receptors, showing significant results in decreasing symptoms and improving the quality of life of patients. Selective progesterone receptor modulators such as ulipristal acetate in the treatment of symptomatic leiomyoma demonstrated their efficacy in numerous studies and are currently available. Gonadotropin-releasing hormone agonists are used in preoperative treatment of leiomyoma. Steroidal treatment in adenomyosis showed consistent results, although, to date, there are no specific steroid therapy. For the treatment of endometrial polyp, transcervical resection remains the gold standard since these entities are easily resectable. In addition, most of them are nonfunctional, raising the possibility that hormonal treatment will not have any effect on their growth or their related symptoms.

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