The Pathophysiology of Adenomyosis

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Abstract

Our understanding of adenomyosis remains hampered because of the lack of clarity of the clinical significance of the finding of aberrant endometrial glands and stoma within the myometrium. Despite the growing number of publications and the renewed interest generated by advances in vaginal ultrasounds and magnetic resonance imaging as non-invasive diagnostic techniques, many basic questions remain. Some of the theories of the pathogenesis stem from observations made in early writings with little supporting evidence. More recent research has highlighted a possible role for the myometrium.

Keywords

Organoid tumour • Histoid tumour • Wolffian duct • Müllerian theory • Endo-Myometrial Junctional Zone • α-SMA and desmin • Ultrasound • Invasion • Estrogen • Estrogen receptor • Progestogen • Progesterone receptor • Tamoxifen • Epithelial-mesenchymal transition

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M. Habiba, G. Benagiano (eds.), *Uterine Adenomyosis*, DOI 10.1007/978-3-319-13012-5_3

Introduction

Uterine adenomyosis was recognised more than a century and a half ago. Rokitansky described the condition as cystosarcoma adenoids uterinum [1]. The first theories on the pathogenesis of adenomyosis date back to the end of the nineteenth century. Von Recklinghausen in a well recognised book published in 1896 described two classes of adenomyomas: (1) those situated at the periphery of the uterus and in the tubes and, (2) those arising centrally in the uterus. He viewed the first type to be derived from a numerical increase of the Wolffian tubules and the second type to originate from the uterine mucosa. Von Recklinghausen believed central adenomyosis to be rare and, because of the identification of three cases with malignancy, he concluded that they are prone to malignant change. Von Recklinghausen described cystadenoma as resembling an infiltrating fibroid that has diffused itself in the muscle wall and regarded these masses as 'organoid tumours' arising from a whole organ as distinct from 'histoid tumours' that arise from a particular tissue [2]. Much of the decline of the Wolffian and embryonic origin theories are attributable to the work of Cullen who first published his observations in 1896 [3]. Cullen emphasised the mucosal origin of the glandular component of adenomyosis and demonstrated extension of the endometrium within adenomyosis [4]. The Wolffian duct theory had many advocates who viewed it as established by fundamental proof [5].

The importance of the smooth muscle component of adenomyosis can be seen from earlier controversy about the theories of origin of adenomyosis. One of the arguments made by Von Recklinghausen against the Müllerian theory is that the spread of adenomyoma did not occur along the whole length of Müllerian ducts, but stopped at the internal os. Thus it was argued that the Müllerian component present in the cervix did not cause adenomyosis. Kossmann (1897) proposed that the reason for the rarity of adenomyosis in the cervix is not the lack of mucosal invasion, which is commonly evident, but the lack of myomas in the cervix [6]. The importance of mucosal continuity with the eutopic endometrium was emphasised by Cullen, but even instances where continuity cannot be demonstrated can be explained by the downward growth becoming cut-off from the eutopic mucosa or by the presence of accessory Müllerian glands. Another argument put forward in support of the Wolffian origin of adenomyosis is that adenomyosis is (perhaps) more common in the posterior uterine wall. But whether the incidence is higher in the posterior compared to the anterior uterine wall has long been a matter for debate including in more recent literature. Nevertheless, Kossmann (1897) argued that a higher incidence of adenomyomas in the posterior wall may be a reflection of the observation that fibroids may also be more common in the posterior uterine wall [6]. Based on the work of Kossmann and others, the theory subsequently emerged that adenomyomas are formed from Müllerian duct epithelium and 'inflammation' was suggested as a mechanism relevant to the process. Links to inflammation were mainly hypothesised with reference to tuberculosis. Meyer (1903) described adenomyosis as originating from uterine mucous membrane which sends hyperplastic and hypertrophic glands into the muscle even when the endometrium is not hyperplastic [7]. Meyer described these as arising from different points and spreading mostly to involve the inner and middle muscle layers and the fundus. He thus described 'invading masses of mucosa and branching complex glands that rarely become malignant' [7].

Although adenomyosis is basically a disease of adult women, the process may start during adolescence and become manifest during the third decade of life [8–12]. Meyer examined 100 uteri from foetuses, newborn children and girls up to the age of 14 years. He reported that mucosal invasion was seldom seen and concluded that the disease is one of adult life. Among the observations that favoured 'epithelial invasion' is the well recognised absence of a uterine submucosa. Thus it is hypothesised that a breach in the muscle

interstitial substance or mechanical stress acting on interfascicular connective tissue would facilitate such invasion [13].

Cullen (1908) described cases of diffuse adenomyomas, all of which had no evidence of inflammation [14]. This added support to the view that mucosal invasion is not necessarily linked to inflammation. Another theory advanced in early writings to explain adenomyosis is an origin from the uterine serosa by in-growth of epithelium into the outer layers of the uterus. This was also proposed as a mechanism for adenomyosis of the rectovaginal septum. Erich Opitz proposed that peripheral growth arose from the serosa and that deeper growth arose from the mucous membrane [13].

Forms of mucosal invasion into the myometrium, termed '*adenomyomata*', were thought to represent "a new formation composed of gland-elements, hyperplastic cellular connective tissue, and smooth muscle" [13]. The origin of these "mucosal invasions" was debated for decades and it took half a century before their "endometrial" nature became fully accepted [15]. Typically, focal adenomyosis has poorly defined margins merging with the surrounding normal myometrium, and – in contrast to leiomyomata – cannot be enucleated. 'Focal' lesions can resemble leiomyomata; hence the term adenomyoma which was criticised as it implies neoplasia which is not relevant to the condition [16].

When, in 1925, Frankl coined the term '*adenomyosis*' (alternatively called '*endometriosis interna*') to distinguish it from the forms of endometrial colonization within the peritoneum (also termed 'endometriosis externa') he specified that "*the direct connection of the endometrium with the islands of mucosa located in the musculature can be established in serial sections*". He defended the use of the term adenomyosis because it "does not suggest any inflammatory genesis" [17]. At this point adenomyosis came to be identified as an entity separate from endometriosis.

The link to stromal invasion is maintained in more recent writings. Bird recognises that the lesion is benign, yet he defines adenomyosis in terms of *invasion* of the endometrium into the myometrium [18]. Vercellini et al. (2006) describes stages in the process starting with disruption of the normal boundary between the basal layer and the myometrium and invasion of endometrial glands into the myometrium as a consequence of this disruption. The resulting ectopic intramyometrial glands then cause myometrial hypertrophy and hyperplasia [19].

Until the 1980s, adenomyosis could only be detected by histological examination of hysterectomy specimens. This changed following the introduction of non-invasive diagnosis using Magnetic Resonance (MRI) [20–22], Ultrasound imaging [23], transvaginal ultrasound (TVS) [24, 25] and, more recently, three dimensional transvaginal ultrasound scan (3D-TVS) [26]. The lack of non-invasive diagnostic tests and doubts about the reliability of imaging based diagnostics have for a very long time impeded research and our understanding of the condition. The lack of reliable preoperative diagnostic meant that, in the past, the condition came to clinical attention only as a finding in hysterectomy specimens and consequently, less emphasis was placed on its importance and clinical impact.

Some advances were made following the recognition of the diagnostic value of MRI and TVS, yet at an elemental level, there is still a lack of congruity between the diagnostic criteria for adenomyosis. Histological diagnosis is based on the presence of endometrium beyond the junction of endometrium and myometrium, whilst imaging techniques mostly measure thickness and/or irregularity of the inner portion of the myometrium. Thus imaging diagnoses utilise techniques based on differences in the appearance of smooth muscle, particularly the inner myometrium (the *myosis* component), whereas histology relies on the presence of ectopic endometrial glands within the myometrium (the *adeno* component). The relative contribution of each component varies considerably, and this can account for the discrepancies observed between the diagnostic modalities.

The Endo-myometrial Junctional Zone

The inner myometrial layer immediately underlying the endometrium appears on MRI as a distinct area, named the Junctional Zone (JZ). Despite the absence of distinctive histological features on light microscopy, the distinct features seen on imaging emphasised or perhaps overemphasised the importance of this zone. Some characterisations view this zone as having distinct embryological origin and this seems to generate an impression of anatomical distinction. This portion of the myometrium has been variously labelled '*archimyometrium*', inner myometrium, endometrial-myometrial interphase, transitional zone or subendometrial myometrium and is often distinguished on T2-weighted MR images of the uterus [20]. One important limitation of MRI, however, is the absence of a definable JZ in 20 % of premenopausal women [27] and in a bigger proportion of postmenopausal women. When seen on MRI, the JZ appears as a distinct and regular inner layer of the myometrium, measuring 5 mm or less in thickness. But the reasons for the distinct zonation are unclear [28, 29]. It is still unclear whether the JZ undergoes cyclical changes in thickness mimicking those of the endometrium [30]. Kunz et al. (2000) argued that, like the endometrium, the inner myometrium is of Müllerian origin, while the outer myometrium is of non-Müllerian, mesenchymal derivation and that it has structural and functional differences compared to the outer myometrium [31]. Both EMI components have a common embryological origin from the paramesonephric duct. Konishi et al. (1984) examined autopsy material obtained from human abortuses and stillborn fetuses [32]. At 12 weeks of gestation, the mesenchymal cells were distributed sparsely in the uterine mesenchyme and were mostly round in shape, with high nucleo-cytoplasmic ratios but there were no smooth muscle cells. By 14 weeks, mesenchymal cells formed two layers: the cells near the serosa were the most abundant and elongate, whereas the cells toward the lumen were sparse and round in shape. From 14 to 20 weeks the spindle shaped cells of the outer layer gradually increased in number and at 20 weeks this layer formed the bulk of the uterine thickness. Mitotic figures of the mesenchymal cells were most frequent in the inner layer between 14 and 20 weeks. At 26 weeks the thickness of the outer layer increased markedly and at 31 or 40 weeks bundles of cells resembling smooth muscles became obvious. These observations imply that the outer mesenchymal layer of the body of the fetal uterus gives rise to the myometrium and that the inner layer corresponds to endometrial stroma of the adult uterus [32]. Using electron microscopy, Konishi et al. (1984) were able to demonstrate the stages in smooth muscle differentiations and development of intracellular organelles and myofilaments [32]. The process starts around 16 week gestation with the appearance of cytoplasmic filaments with dense bodies which are characteristic of smooth muscle cells at 16 weeks of gestation. Spindle shaped cells containing a few myofilaments scattered in the cytoplasm and well developed organelles such as mitochondria, free ribosomes, granular endoplasmic reticulum and Golgi membranes appear in the outer layer of the uterus at 18 weeks. These cells resemble immature smooth muscle cells. Other ultrastructural characteristics of smooth muscle cells develop later; surface vesicles of the cell membrane begin to increase at about 20 weeks, dense plaques along the cell membrane appear by 26 weeks and an external lamina is almost complete by 31 weeks. These observations imply that undifferentiated mesenchymal cells which develop into smooth muscle cells may exist in the inner layer of the fetal uterus and that smooth muscle differentiation may occur at the junctional area between the myometrial and endometrial stromal layers [32]. Thus it is possible that disruption of the process can result in loss of orientation leading to the observed presence of stroma within the myometrium. In addition, the developmental sequence resembles that observed in rodents. It casts doubts on theories that view the inner and the outer myometrium as embryologically distinct. The research by Fujii et al. (1989), shows that stromal and myometrial cells in the adult uterus exhibit plasticity as the cells at the stromal-myometrial interface

morphologically resemble myofibroblasts in the follicular phase and differentiate into cells morphologically resembling smooth muscle cells in the luteal phase and early pregnancy. This is perhaps not surprising given the shared enbryological origin. It further opens the possibility that disruption of the mechanisms that control the process can result in the disorganisation noted in adenomyosis [33].

The Müllerian origin of the outer myometrium is also supported by Robboy et al. (1982) who implanted human reproductive track obtained from early embryos into BALB/C athymic nude nice and used the model to describe the normal development of the human female reproductive tract and the alterations resulting from experimental exposure to diethylstilbestrol [34].

In the presence or absence of adenomyosis, JZ thickness is reduced in post-menopausal women and in premenopausal women taking oral contraceptives or gonadotrophin-releasing hormone analogues. This effect results because of the suppression of ovarian activity and is reversed by the administration of hormone replacement therapy which may cause the reappearance of the typical JZ [35]. In women with normal menstruation, variations in myometrial contractility waves suggest that uterine peristaltic activity originates exclusively from the JZ, while the outer myometrium remains quiescent [36, 37]. It appears that uterine peristalsis is hormone dependent, and that it is affected by both estrogen and progesterone. It is possible that inner myometrial peristalsis plays a role in sperm transport, as well as in stabilization of the blastocyst prior to nidation and there is evidence that the "zonal-endometrial" complex may play a role in uterine receptivity in relation to the outcomes of assisted conception. On the other hand, the use of oral contraceptive and intrauterine contraceptive device [38] or sterilization by tubal ligation [39] do not appear to be associated with a risk of adenomyosis.

While MRI may identify the uterine JZ as a distinct hypodense layer [29, 40], the reason(s) for this demarcation is unclear. It may be due to an increase in nuclear area in the inner myometrium [29], to different water content between the inner and outer myometrium [41] or to differences in the distribution of laminin-β2 [42]. Differences in blood flow between the inner and outer myometrium have been proposed as an explanation of the MRI appearance, but against this is the observed zonation in uterine hysterectomy specimens when examined using MRI despite the clear absence of blood flow [29]. MRI features suggestive of adenomyosis are indirect and include increased JZ thickness [40, 43, 44]. Mehasseb et al. (2011) demonstrated that the inner myometrium of normal uteri has higher cell density and total nuclear area compared to the outer myometrium (increased by 1.6–1.8 fold) and importantly in relation to the features seen on MRI, they demonstrated that the change in cell density is gradual throughout the uterine thickness with no distinct point of demarcation [28]. This echoes the finding of gradual increase in elastin expression from the inner to the outer myometrium [30], but contrasts with the notion of a clearly defined JZ as implied by MRI.

The maximum change observed by Mehasseb et al. (2011) in cell density from the inner to the outer myometrium is less than the three-fold change reported by Scoutt et al. (1991) [28, 29]. The difference between the two studies may be related to methodological issues. The study by Mehasseb et al. used true colour image analysis without grey-scale transformation, which allows more accurate definition of cellular structures. Nevertheless, both studies agree on the main findings. It remains possible that the distinct MRI features are due to lower water content in the inner myometrium reflecting a reduction in intercellular space between more tightly packed cells. It has been demonstrated that water content is lower in the subendometrial myometrium compared to the outer myometrium [41]. This implies that the in vivo difference in cell density between the inner myometrium and outer myometrium may in fact be larger than the differences noted in formalin-fixed tissue. It is possible that the subendometrial halo seen on MRI reflects a transitional point of cell count or water content, but it remains unclear why this zone is not seen in all uteri [44]. This also leaves the definition of the JZ dependent on MRI, which raises important question about its very nature. On the other hand, the

finding of similar expression of the intracellular components α-SMA and desmin in the corresponding layers (inner or outer myometrium) in adenomyosis compared to normal myometrium points to a reduced extracellular fluid content in adenomyosis [28], thus the reason for increased JZ thickness in affected uteri remains unclear. The lack of a clear distinction between the inner and outer muscle layers does not rule out a functional distinction as demonstrated in studies using ultrasound [31, 45, 46], because differences may exist in steroid receptors expression [47] or in innervation [48] which can lead to differential functional response.

The extent of adenomyosis varies from simple JZ thickening to more diffuse or nodular lesions involving the entire uterine wall. It can also take the form of an adenomyoma, a focal thickening or a nodular structure arising at the JZ and extending within the myometrium where it is identified with low signal intensity on T2-weighted MRI [35]. A normal JZ is between 5 and 12 mm thick on T2-weighed MRI, and features highly predictive of histological adenomyosis include JZ measuring >12 mm, with hemorrhagic high-signal myometrial spots [36]. Adenomyosis can also be observed utilizing transvaginal sonography where it appears as heterogeneous and hypoechogenic, poorly defined areas in the myometrium [21, 37, 43, 49]. These areas may appear with or without anechoic lacunae or cysts of varying size, and the echo texture of the myometrium may be increased. Moreover, there may be linear striations radiating out from the endometrium into the myometrium and an indistinct endo–myometrial junction with a pseudo-widening of the endometrium. The hypoechogenicity may be caused by the muscular hypertrophy, while the increased echogenicity, the cyst, the linear striations, and the indistinct endo–myometrial junction may be caused by ectopic endometrial tissue. In a meta-analysis of reports published between 1966 and 2007 on the diagnostic accuracy of TVS in women having a hysterectomy, Meredith et al. (2009) reported that TVS has a predictive likelihood ratio of 4.67 (95 % CI: 3.13–6.17) [50]. The overall prevalence of adenomyosis was 27.9 % (95 % CI: 25.5–30.3) and the probability with an abnormal TVS of 66.2 % (95 % CI: 61.6–70.6). The probability of adenomyosis with a normal TVS was 9.1 % (95 % CI: 7.3–11.1). They concluded that TVS is a moderately accurate test for the diagnosis of adenomyosis. The myometrium surrounding the adenomyotic foci, whether diffuse or focal, showed normal immunohistochemical staining for low and high molecular weight cytokeratins, estrogen and progesterone receptors, vimentin, actin and desmin [51].

A recent study compared histopathology to morphological alterations of the myometrium as detected on two-dimensional (2D) and three-dimensional (3D) TVS in 72 premenopausal women. The most specific 2D-TVS feature of adenomyosis (specificity = 98 %; accuracy = 78 %) was the presence of myometrial cysts, whereas the most sensitive feature was the finding of a heterogeneous myometrium (sensitivity = 88 %; accuracy = 75 %). On 3D-TVS the best markers of adenomyosis were related to the JZ myometrium. A difference in its thickness of more than 4 mm and JZ distortion and infiltration had high sensitivity (88 %) and the best accuracy (85 % and 82 %, respectively). Overall, for 2D-TVS and 3D-TVS, respectively, the accuracy was 83 and 89 %; sensitivity was 75 and 91 %; specificity was 90 and 88 %; positive predictive value was 86 and 85 %; and negative predictive value was 82 and 92 % [52]. It seems therefore that a diagnosis of adenomyosis can be made when one or more of the following sonographic findings are present: (1) a globular uterine configuration; (2) poor definition of the endometrial-myometrial interface; (3) sub-endometrial echogenic linear striations; (4) myometrial anterior-posterior asymmetry; (5) myometrial cysts; (6) a heterogeneous myometrial echo texture [53]. Additional preliminary information seems to indicate that diagnosis may be more accurate during the luteal phase [54].

Champaneria et al. (2010) conducted a systematic review with meta-analysis of all published data on test accuracy of ultrasound scans and MRI for the diagnosis of adenomyosis based on studies which also reported histological confirmation of the diagnosis [55]. TVS had a pooled sensitivity of 72 % (95 % CI = 65–79 %),

specificity of 81 % (95 % CI = 77–85 %), positive likelihood ratio of 3.7 (95 % CI = 2.1–6.4) and negative likelihood ratio of 0.3 (95 % CI = 0.1–0.5). MRI had a pooled sensitivity of 77 % (95 % CI = 67–85 %), specificity of 89 % (95 % CI = 84–92 %), positive likelihood ratio of 6.5 (95 % CI = 4.5–9.3), and negative likelihood ratio of 0.2 (95 % CI = 0.1–0.4). The authors concluded that both TVS and MRI showed high levels of accuracy for the non-invasive diagnosis of adenomyosis.

Possible Pathogenetic Mechanisms

Direct Endometrial Invasion

Adenomyosis has been traditionally described in terms of abnormal ingrowths and invagination of the basal endometrium into the subendometrial myometrium [18]. The more widely accepted theory on pathogenesis proposes that during periods of regeneration, healing and re-epithelialisation, the endometrium can invade a predisposed myometrium or a traumatised endometrial–myometrial interface. In support of this theory is the observation of increased incidence following uterine curettage. Parazzini et al. (1997) reported on 707 consecutive women who underwent a hysterectomy. The incidence of adenomyosis was 21.2 % (n = 150) [38]. The risk of adenomyosis was reported to be lower in women who smoked (OR 0.7; 95 % CI 03–1.3) compared to women who never smoked, and the risk decreased in relation to increased number of cigarettes per day. The frequency of adenomyosis was higher in parous women and was higher in women who reported one of more than one spontaneous miscarriage compared to those who did not have a miscarriage (OR = 1.7; 95 % CI, 1.1–2.6). But whether miscarriage is the cause or the result of adenomyosis remains to be ascertained [38, 56–58].

The relation between adenomyosis and parity has also reported in other studies [59, 60] but remains controversial (See Chap. 2). In the study by Parazzini et al. (1997) the odds ratio for adenomyosis in the group who ever had a dilatation and curettage was 2.2 (95 % CI 1.2–4.0) and the authors suggested that the trauma of curettage may favour the inclusion of islands of endometriosis in the myometrium [38]. Levgur et al. (2000) reported on clinical correlations in 111 uteri removed at hysterectomy [58]. All samples weighed less than 280 g. There were 17 uteri with adenomyosis alone, 19 with adenomyosis and fibroids, 39 with fibroids only and 36 samples with no fibroids or adenomyosis. The incidence of pregnancy termination in the group with adenomyosis alone was 58.8 %, and in the group with adenomyosis and fibroids was 47.4 %. This compares to an incidence of 20.5 % in the group with fibroids alone and of 22.2 % in the group with neither. Adenomyosis was assessed based on 5–10 sections per specimen and using a cut-off point for endometrial glands within the myometrium of at least 2.5 mm. Perhaps uncharacteristically in relation to the diagnosis of adenomyosis, they reported that there was no inter-observer variability. Interestingly, during the study period the incidence of adenomyosis in the 111 women in whom the uterine specimens weighed <280 g as 32.4 % compared to an incidence of 6 % amongst the group (n = 132) whose uterus weighed >280 g. The group with larger uteri were excluded from the analysis. The reasons given were uterine distortion and the lack of full-thickness sections which they believed would preclude accurate histological evaluation. However, the indications for the hysterectomy are not provided and the rationale for excluding larger uteri from this analysis is debatable as it should be possible to examine the subendometrial myometrium even in large uteri. Nevertheless, the authors argued that their study provided evidence of a link between adenomyosis and pregnancy termination. Ostrzenski (1998) reported a case which resembled adenomyosis that was identified with endometrial tissue within the myometrium following laparoscopic myomectomy, suggesting a link to myometrial disruption [61]. However, this case does not describe the classic disease, and the presence of inclusion cysts is well recognised in other parts and tissues of the body. The link to pregnancy and pregnancy termination is weakened by evidence that about

20 % of women with adenomyosis have never had a pregnancy [62]. Interestingly, sharp curettage in the non-pregnant status does not seem to increase the risk of adenomyosis [58, 63–65]. The differential effect might be related to the disruption of the EMI by the invading trophoblast. Focal disruption of the EMI in early pregnancy can be observed using MRI, which reverts to normal 2–24 weeks after delivery [66]. It cannot be ruled out that changes occurring in the JZ during pregnancy, such as angiogenesis and trophoblast invasion, may aggravate existing adenomyosis. Parazzini et al. (1997) reported on the risk factors for adenomysis in a series of 707 consecutive women who underwent a hysterectomy [38]. Women reporting one or more spontaneous abortions had an odds ratio of 1.7 (95 % CI 1.1–2.6) for adenomyosis. Women who had a dilatation and curettage for a gynaecological indication (n = 58) had an adjusted odds ratio for adenomyosis of 2.2 (95 % CI: 1.2–4.0). Curtis et al. (2002) examined the relation between pregnancy-related and non-pregnancy-related curettage and the development of adenomyosis in a series of 1850 women [65]. Adenomyosis was diagnosed after hysterectomy in 368 (19.9 %) of the cohort although the diagnostic criteria are not provided. The investigators obtained self reported history of abortion or curettage from participants. Women with adenomyosis reported a history of induced abortion more frequently than did women without adenomyosis (17.1 % and 12.6 %, respectively; $p = 0.02$). The prevalence of caesarean delivery and D&C were similar between the two groups. No association was found between caesarean section or dilatation and curettage and adenomyosis, but induced abortion was associated with a non-significant increased risk.

The process of "invasion" of endometrial glands within the myometrium is said to develop in stages as referred to above [19]. A number of hormonal, genetic, immunological and growth factors were hypothesised to play a role in this sequence of events. Familial predisposition may have a role as documented in one series, of seven cases in which mothers and daughters were affected [67].

In a retrospective study including 200 women who underwent hysterectomy for benign disease, Whitted et al. (2000) observed a higher incidence of caesarean delivery in patients with adenomyosis compared to the group without adenomyosis (30 % vs. 23 %) [68]. But some studies found no statistically significant association between adenomyosis and previous caesarean section, endometrial curettage, or evacuation of the uterus [58, 63, 64, 69]

The hypothesis originally proposed by Cullen centres on an origin of adenomyosis from basalis endometrium invaginating deep within the myometrium. The hypothesis is built on the observed histological continuity between the basal endometrium and underlying inner myometrium and also because of the absence of a separating basal membrane. The hypothesis can be seen as being supported on two further counts: the first is the proven relationship of the disease to factors that favour increased 'invasiveness', either because of external or mechanical forces or as innate properties of the endometrium in adenomyosis; and the second is the presence of similarities between the basalis glands and adenomyosis nodules. But histological continuity is not always demonstrable or present.

There is evidence of increased invasiveness of endometrial cells in adenomyosis, as well as in endometriosis [70, 71] and, at least in some subgroups, the two conditions often coexist. Research has shown differences between the eutopic endometrium of women with both diseases when compared to controls. This suggests an immune dysfunction and alterations of adhesion molecules, cell proliferation and apoptosis. An increase in cytokines and inflammatory mediators has also been observed. Finally, the presence of oxidative stress and anomalies in free-radicals metabolism may alter uterine receptivity. When the two conditions were compared, dissimilarities were also observed in the extent of apoptosis inhibition and in the expression of some inflammatory mediators. It is not clear if differences are primarily related to the presenting symptoms. Finally, both conditions are steroid–dependent and research suggests a role for epigenetic mechanisms.

Gaetje et al. (1995) reported that endometrial cells obtained from endometriosis nodules, but not from normal endometrium, grown on a collagen invasion assay, had invasive potential similar to metastatic bladder carcinoma cell line (EJ28) and exceed those of non-metastatic bladder cell line (RT112) [72]. This needs further corroborative evidence. In a subsequent publication, the same group identified the invasive cells in endometriosis as E-Cadherin negative epithelial cells [73]. Such invasion could be facilitated by the loss of cohesion of myometrial bundles influenced by enzymes such as matrix metalloproteinases [74, 75]. Endometrial stromal fibroblasts produce tenascin, a fibronectin inhibitor that in turn facilitates epithelial migration. Tenascin mediates epithelial-mesenchymal interactions by inhibiting cell attachment to fibronectin, an action stimulated by hormonally regulated epidermal growth factors. But whether this interaction plays a role in the development of uterine adenomyosis is unknown [76].

Thus whilst abnormal stromal cell differentiation and invasion has been proposed in the aetiology of adenomyosis, the features in the microenvironment that limit myometrial penetration by the overlying endometrium and the changes that precede or trigger the development of uterine adenomyosis are unknown. Mehasseb et al. (2010) examined the migration of human endometrial stromal cells in a three-dimensional co-culture in plain collagen or in collagen in which myometrial cells were grown. The in-vitro experiment included crossover between cells from uteri with and without adenomyosis. Stromal cells from adenomyosis exhibited greater invasiveness when grown on a plain collagen matrix or in double culture with myocytes from normal or adenomyosis affected uteri compared to normal stromal cells [77]. Also myocytes from adenomyosis were shown to enhance invasion of stromal cells when compared to normal myocytes. This suggests that both the stromal and the myometrial component have a role in the aetiology of the disease. In a subsequent study the same group reported the effect of estradiol, progestogen and tamoxifen alone or in combination on stromal cell invasion in three dimensional co-cultures [78]. The addition of estradiol or tamoxifen, but not of the estradiol and progesterone combination, increased the depth of invasion of both adenomyotic stromal cells and control stromal cells in all cell combinations. When grown on plain collagen, the depth of invasion for control stromal cells and adenomyotic stromal cells increased by 126 and 93 % with the use of tamoxifen, and by 71 and 50 %, with the use of estradiol. The depth of invasion for adenomyotic stromal cells was statistically significantly higher compared to the control stromal cells whether grown on plain collagen, on collagen containing control or on adenomyotic muscle cells. The addition of estradiol or tamoxifen, but not of the estradiol and progesterone combination, increased the depth of invasion of both adenomyotic stromal cells and control stromal cells in all cell combinations. When grown on plain collagen, the depth of invasion for control stromal cells and for adenomyotic stromal cells increased by 126 and 93 % with the use of tamoxifen, and by 71 and 50 %, with the use of estradiol. Thus both estradiol and tamoxifen enhance stromal cell invasion and the addition of progesterone to estrogen inhibits estrogen effect. This would appear to support a role for estrogen in stromal invasion and in the pathophysiology of adenomyosis. But the greater depth of invasion of adenomyotic stromal cells and the enhancing effect of adenomyotic muscle were maintained under all experimental conditions which suggest an inherent predisposition that is related to the origin of stromal cells rather than an effect of estrogen on the ability of cells to invade within the matrix.

Derivation from Multipotential Perivascular Cells

An alternative theory suggests that the basalis endometrium invagination occurs along the intra-myometrial lymphatic system, rather than by disruption and “invasion” of the muscle bundles. This possibility is supported by the occasional finding of endometrial tissue in the intra-myometrial lymphatics in hysterectomy

specimens. Sahin et al. (1989) identified endometrial tissue in 14 cases that had extensive adenomyosis [79]. They speculated that the intimate relationship between endometrial tissue and the vessels may be explained by an origin of the endometrial tissue from uncommitted or multi-potential perivascular cells. They also reported on the absence of a connection between adenomyosis foci and the eutopic endometrium. In their study, they emphasised that the phenomena is distinct from neoplasia. Intravascular proliferation of adenomyotic stroma was found in 17.5 % of cases in another study involving 200 cases with adenomyosis [80]. A more recent study seems to confirm the phenomenon [81]. Vascular involvement in adenomyosis was noted in 54 (12.4 %) cases out of a large series (n = 434) of uteri affected by adenomyosis. The degree of vascular involvement varied. A single vessel was involved in 19 of 54 cases (35 %), 2–3 vessels were involved in 16 cases (30 %), and multiple vessels were involved in 19 cases (35 %). The intravascular component comprised endometrial stroma only in 34 cases (63 %) and contained glands and stroma in 20 cases (37 %). In most cases, the intravascular component was covered by intact endothelial lining.

Mai et al. (1997) examined cases of adenomyosis and endometriosis using immunohistochemistry for estrogen receptor, vimentin, Ber-EP-4 (Epithelial specific antibody to EpCAM: Epithelial cell adhesion molecule) and cytokeratin [82]. They identified nodes of stromal cells without endometrial glands, located along blood and lymphatic vessels. They termed these type 1 nodules. Stromal cells were positive for vimentin and negative for cytokeratin and were not connected to adjacent adenomyosis. These nodules were often seen at the periphery of adenomyosis and appeared fusiform or satellite, tapering in the myometrium or in the adventitia of blood vessels or in contact with other type 1 nodules. Occasionally, these nodules had projections as polypoid structures into the vessel lumen. The term *type 1 nodules* was used to distinguish these lesions for *type 2 nodules* which also contained mesothelial cysts and *type 3 nodules* which describes nodules containing endometrial glands. Type 2 and 3 nodules were present in endometriosis, but not in adenomyosis. In adenomyosis, there were foci of adenomyosis with sparse glands, characterised by low gland/stromal ratio. Around blood vessels within type 1 nodules, there were cells with embryonic features with hyperchromatic nuclei. Many of the type 1 nodules had no connection with adjacent endometrium. Mai et al. (1997) viewed these as precursors or early stages of adenomyosis [82]. Interestingly, they also identified regions were endometrial glands were present where the surrounding stroma was undergoing fibrosis with replacement of stromal cells by fibromuscular tissue in what they considered to be end stage disease. The proposition put forward is that these nodules develop from perivascular pericytes and that hormonal, immunological or other growth factors induce the transformation into endometrial stromal nodules. These stromal nodules are assumed to later incorporate endometrial epithelial cells either through growth from adjacent nodules or through 'transformation' of the stromal and smooth muscle cells into endometrial stromal cells. Thus, the newly enlarged area of stroma serves as "new soil", facilitating further downward growth of the endometrial glands [82]. An important differential diagnosis is stromatosis or endometrial stromal sarcoma (endolymphatic stromal myosis), both of which are characterized by endometrial stroma without endometrial glands (as opposed to adenomyosis that consists of both endometrial stroma and glands). Goldblum et al. (1995) described the features that can help differentiate adenomyosis with sparse glands from low-grade endometrial stromal sarcoma [83]. These include the small size of the lesions in the absence of grossly evident tumour nodules and the presence of typical adenomyosis with glands elsewhere in the myometrium. Also relevant is the patient's age and menopausal status.

Adenomyosis as a Uterine Disorder

Smooth muscle cells from uteri with adenomyosis are ultra-structurally different from smooth muscle cells of normal uteri [84]. In adenomyosis, myocytes exhibit cellular hypertrophy and

the intermediate filaments are abundant and form cytoplasmic aggregates. The nuclei have a smooth outline with a clear ground substance, prominent nucleoli and peripherally arranged nuclear chromatin. There is an occasional infolding of the nuclear envelope with entrapment of cytoplasmic organelles. The sarcolemmal bands are significantly longer and there are fewer caveolae. The perinuclear cell organelles are more distinct. The rough endoplasmic reticulum and Golgi apparatus are more prominent, denoting active protein synthesis, this is consistent with the observed cellular hypertrophy [84]. The transition from the inner to the outer myometrium is reported to be gradual with no clear demarcation between the two components [28, 30]. The identification of differences between myocytes in the outer myometrium remote from adenomyotic lesions suggests that the changes are not a reaction to the presence of ectopic endometrium. Myocytes obtained from women with adenomyosis and added to the co-cultures resulted in enhanced stromal cell invasion within the matrix when compared to the effect of myocytes obtained from unaffected women. In the same study, Mehasseb et al. (2010) reported the presence of differences in secretory proteins in the culture supernatant of cells depending on their source of origin (adenomyosis or control) [77]. Allowing a 0.1 % margin of error in estimating the m/z ratio for protein clusters, there were 28 common peak clusters among the peaks differentially expressed in culture supernatant between stromal cells from uteri not affected by adenomyosis and stromal cells from uteri affected by adenomyosis. These differences were noted in experiments were stromal cells were grown on plain collagen as well as in experiments were stromal cells were grown on cultures of collagen containing control, or adenomyotic myocytes. There were nine common peak clusters among the peaks differentially expressed when comparing cultures in which muscle cells from controls and adenomyosis when grown on plain collagen, or when co-cultured with control or adenomyotic stromal cells. Interestingly, there were six distinct peaks that were common to both "adenomyotic stromal cells" and "adenomyotic myometrial cells."[77]. This suggests that: (1) both stromal and muscle cells have a role in the aetiology of adenomyosis, (2) that the disease may be a reflection of a pan-uterine abnormality [77, 85]. Steroids have been shown to affect the migration of stromal cells derived from uteri with or without adenomyosis. The observation that myocytes from adenomyosis enhance stromal cell invasion and the presence of similar peak cluster patterns for secreted proteins when adenomyosis stromal and muscle cells grown in culture are compared to normal stromal and muscle cells respectively suggests that both stromal and muscle cells have a role and reflect a pan-uterine abnormality.

Studies that used the neonatal mouse model [86] and the prolactin induced adenomyosis mouse model [87] suggested that disruption and/or "permissiveness" of the inner myometrium could play a role in the development of uterine adenomyosis. Mehasseb et al. (2009) reported the effects on uterine development and myometrial differentiation of the administration of tamoxifen and estradiol to neonatal mice [88]. Female CD1 pups were administered tamoxifen or estradiol from age 1 to 5 days and compared to controls. Uteri were examined on days 2, 5, 10, 15, and 42 of age using image analysis and immunohistochemistry for α-smooth muscle actin (α-SMA), desmin, and estrogen receptor-α (ER-α). Following tamoxifen exposure, all uteri showed adenomyosis by 6 weeks of age. The inner myometrium showed thinning, lack of continuity, disorganization, and bundling but α-SMA expression was comparable to normal controls. In untreated neonatal uteri, desmin expression showed a wave of maturation that was absent in tamoxifen-treated mice. In the group administered estradiol, uterine layers were normally developed but hypertrophied and there was no development of adenomyosis. The inner myometrium retained its circular arrangement. This suggested that the development of the inner myometrium is sensitive to estrogen antagonism and that disruption of the inner myometrium may play a role in the development of uterine adenomyosis.

However, administration of tamoxifen to the neonatal C57/BL6J mice, whilst associated with similar disruption of the inner myometrium, did

not result in the development of adenomyosis [89]. Following tamoxifen exposure, all uteri showed inner myometrial thinning, lack of continuity, disorganisation and bundling. αSMA immunostaining was reduced in the circular muscle layer of tamoxifen treated mice. The temporal pattern of desmin immunostaining found in control mice was absent in tamoxifen-treated mice. Tamoxifen induced similar inner myometrial changes in C57/BL6J and CD-1 neonatal mice. Thus, disruption of the development and differentiation of the inner myometrium cannot be the sole explanation of the development of tamoxifen-associated adenomyosis and adenomyosis must be dependent upon interactions that are strain-dependent.

This supports the hypothesis that adenomyosis is a disease of both the myometrium and the endometrial stroma which is perhaps not surprising given the common paramesonephric duct embryologic origin of the endometrial stroma and the inner myometrium. The research by Fujii et al. (1989) shows that stromal and myometrial cells exhibit some level of plasticity [33]. Fujii et al. (1989) examined the ultrastructure of mesenchymal cells at the endometrial-myometrial junction during the menstrual cycle and early pregnancy and identified cells with features of smooth muscle among the usual endometrial stromal cells in every specimen [33]. In the follicular phase of the menstrual cycle, such cells resembled myofibroblasts, but in the luteal phase and during early pregnancy they had more distinct cytoplasmic filaments with dense bodies and dense plaques and other fairly well developed characteristics of smooth muscle. The identification of smooth muscle-like cells amongst stromal cells in the adult uterus and the finding that their morphology changes into cells having many of the characteristics of smooth muscle cells during the luteal phase and early pregnancy, suggests that smooth muscle differentiation possibly occurs from multi-potential mesenchymal cells in the endometrial stroma. It could be envisaged that disruption of the process can result in the genesis of adenomyosis. Studies in rodents are indicative of a role for neurotrophins such as nerve growth factor (NGF) which was significantly upregulated in endometrial luminal epithelium in the CD-1 mouse model of adenomyosis [90]. Thus neurotrophins may affect myogenic differentiation through paracrine mechanisms. The pattern of neurotrophin (NGF, BDNF) and neurotrophin receptor (trkB, trkC and $p75^{NTR}$) expression in the human myometrium also points to a possible role [85].

Epithelial-Mesenchymal Transition

Whilst the derivation of stromal cells could be explained by derivation from perivascular cells, through mechanisms involved in stromal to smooth muscle differentiation, these do not explain the derivation of the epithelial component. One possibility is that the epithelium develops through direct extension from the basalis or from adjacent adenomyosis foci. Alternatively, this may arise through mechanisms involving epithelial-mesenchymal transition [91]. Epithelial-mesenchymal transition (EMT) is believed to be estrogen dependent and may be important to the acquisition by epithelial cells of invasive properties. Chen et al. (2010) reported increased vimentin and reduced E-Cadherin in ectopic endometrium, but not in eutopic endometrium from women with adenomyosis [91]. This provides evidence for EMT. They also reported that serum estradiol was negatively correlated with E-cadherin expression in the epithelial components of the eutopic endometrium and in adenomyotic lesions suggesting a role of estradiol in the process. Chen et al. (2010) also reported that Ishikawa endometrial epithelial cells undergo morphological changes acquiring a fibroblast-like phenotype in response to estrogen and that these cells also exhibit a shift from epithelial to mesenchymal marker expression, increased migration and invasion, and up-regulation of the EMT regulator Slug [91]. Slug is a zinc finger transcriptional factor and has been recognized as a major EMT inducer through repressing E-cadherin expression. These effects were inhibited by raloxifene, a selective estrogen receptor modulator (SERM). Zhou et al. (2012) utilized a two-dimensional polyacrylamide gel

electrophoresis and Mass Spectrometry based proteomics analysis to compare and identify differentially expressed proteins in matched ectopic and eutopic endometrium of adenomyosis [92]. They identified 93 significantly altered proteins. These included 22 estrogen responsive proteins, estrogen responsive genes, genes involved in cell proliferation, apoptosis, cell adhesion, cell motility, angiogenesis, cell signalling and redox homeostasis.

These included annexin A2, which was upregulated most significantly in the ectopic endometrium of adenomyosis. Over-expression of ANXA2 was tightly correlated with markers of epithelial to mesenchymal transition. Expression of ANXA2 enhanced the proangiogenic capacity of adenomyotic endometrial cells through HIF-1/VEGF-A pathway. ANXA2 inhibition abrogated endometrial tissue growth, metastasis, and angiogenesis in the adenomyosis nude mice model and significantly alleviated hyperalgesia. This suggested a role for ANXA2 in the pathogenesis of human adenomyosis through conferring endometrial cells both metastatic potential and proangiogenic capacity. Angiogenesis is required for the invasion of ectopic endometrial implants and their subsequent proliferation. VEGF, a major angiogenic factor, is an important protein for angiogenesis and thus the development of adenomyosis [92].

Chen et al. (2010) isolated mesenchymal like stem cells from the endometrium (EMSC) and from adenomyosis (AMSC) and demonstrated increased COX-2 expression in AMSC compared to EMSC and that the addition of COX-2 inhibitor suppressed migration and invasion and induced apoptosis in AMSC but not in EMSC [93]. The findings suggested a role for COX-2 in adenomyosis. Cyclooxygenase-2 (COX-2), the enzyme that converts arachidonic acid into prostaglandins (PGs), is over expressed in adenomyotic and endometriotic lesions compared with eutopic endometrium. Also importantly, the isolation of AMSC raises the possibility of a role in the pathophysiology of adenomyosis. The same group (Huang et al. 2014) demonstrated that estradiol elicited a Slug-VEGF axis in endometrial epithelial cells, and also induced proangiogenic activity in vascular endothelial cells [94]. The antagonizing agents against estradiol or VEGF suppressed endothelial cells migration and tubal formation. The authors suggested that these results highlight the importance of estrogen induced angiogenesis in adenomyosis development and provide a potential strategy for treating adenomyosis through intercepting the estradiol-Slug-VEGF pathway.

Tissue Injury and Repair

Adenomyosis and endometriosis have long been argued to share a common pathogenesis [95–97]. Endometrial stroma is in direct contact with the underlying myometrium allowing communication and interaction. This may facilitate endometrial invagination or invasion of either a normal or structurally weakened myometrium During periods of regeneration, healing and re-epithelialisation, the endometrium could invade a normal or a predisposed myometrium possibly as a result of trauma to the epithelio-myometrial interface (EMI) [51]. Mechanical damage or physical disruption of the EMI by dysfunctional uterine hyperperistalsis or by dysfunctional contractility of the sub-endometrial myometrium [31, 95] or by sharp curettage especially if done during pregnancy in relation to pregnancy termination [65] may allow for the dislocation of basal endometrium into the myometrial wall and subsequently leads to the development of adenomyosis. An altered immune response has also been proposed as a mechanism for disturbance of the junctional zone resistance to invasion [98].

Most of the literature describing immunological changes associated with adenomyosis is attributed to Ota and coworkers [98–108]. In these studies, changes in both cellular and humoral immunity were described (e.g. a strong expression of cell surface antigens or adhesion molecules, an increased number of macrophages or immune cells, and deposition of immunoglobulins and complements components). Using immunohistochemistry, increased expression of the major histocompatibility complex class II antigen (HLA-DR) in the gland cells of eutopic

and adenomyotic endometrium has been described [108]. Macrophages in the myometrium of adenomyotic uteri seem to increase, possibly activating helper T-cells and B-cells to produce antibodies [98]. Peripheral blood concentrations of autoantibodies are increased in adenomyosis [101]. The deposition of complement components C3 or C4 in adenomyosis is increased in 74 % and 89 % of patients respectively. The expression of E-cadherin in the endometrial tissue of adenomyosis was found to be significantly higher [98].

Using immunohistochemistry, adenomyotic uteri showed excessive expression of superoxide dismutase throughout the menstrual cycle [107]. Similarly, glandular tissue in adenomyosis showed increased expression of glutathione peroxidase [105], cyclo-oxygenase-2 [104] and xanthine oxidase [103] when compared to eutopic endometrium. The exact significance of these immune phenomena in adenomyosis remains to be elucidated. On occasions there has been a problem with reproducibility of results between laboratories and the statistical analysis presented often does not enable clear comparisons between the various layers or clinical conditions [71]. It is not known whether these immunological changes and biochemical derangements are a consequence or a cause of adenomyosis.

Increased expression of basic fibroblast growth factor (bFGF) and its receptor (FGF-R) are found in the epithelium of adenomyosis compared with eutopic endometrial epithelium in menopausal women. The authors suggested that bFGF might contribute to the pathogenesis of abnormal uterine bleeding associated with adenomyosis [109].

Intraepithelial leukocytes (IEL) are an immunological component of most mucosal surfaces although the function and significance of their presence is not known. IEL in eutopic endometrium of patients with adenomyosis varied during the menstrual cycle, with *CD45+, CD43+ and CD56+* cells increasing from the proliferative to the late secretory phase. IEL were elevated in surface compared with glandular epithelium in the proliferative and early secretory phases. Throughout the menstrual cycle there was no significant differences in IEL between eutopic and ectopic endometrium in adenomyosis [110].

Endometrial stromal fibroblasts produce tenascin, a fibronectin inhibitor which in turn facilitates epithelial migration. Tenascin mediates epithelial-mesenchymal interactions by inhibiting cell attachment to fibronectin, an action stimulated by hormonally regulated epidermal growth factors. Whether this interaction plays a role in the development of uterine adenomyosis or endometriosis is unclear [76].

The EMI is also disturbed by the penetration of trophoblast into the myometrium during early pregnancy and this may underlie the higher incidence of adenomyosis in parous women. This putative mechanism may be supported by the finding that the administration of tamoxifen to neonatal CD1 mice is associated with disruption of the inner myometrial circular layer and the development of adenomyosis. However, as mentioned above, neonatal exposure of C57/BL6J mice to tamoxifen resulted in disruption of the inner circular layer, but not to the development of adenomyosis which suggests that disruption of the myometrium is not sufficient for the development of the disease [88, 89].

Expression of the motility-related molecule Cdc42 in eutopic endometrium was higher in patients with ovarian endometriotic cysts compared with patients with adenomyosis [111], suggesting that Cdc42 may not be involved in the pathogenesis of adenomyosis, but may play a role in the process of endometrial cell migration; this could contribute to the pathogenesis of ovarian endometriosis by supporting the process of adhesion of endometriotic cells on the ovarian surface followed by invagination and pseudocyst formation [111, 112]. On the other hand, Fibroblast Growth Factor (FGF-1) polymorphism has been linked to risk of endometriosis but not to adenomyosis, whilst FGF-2 754C/G polymorphism was associated with a decreased susceptibility to developing endometriosis [OR = 0.575, 95 % confidence interval (CI) = 0.387–0.854] and adenomyosis [OR = 0.577, 95 % CI = 0.367–0.906]. This shows some differences in the risk factors of both diseases [113].

Leyendecker et al. (2009) presented what they described as a unifying concept linking the pathogenesis of adenomyosis to that of endometriosis [114]. According to this theory, circumstantial evidence suggests that these two conditions are caused by trauma, since chronic uterine peristaltic activity added to possible phases of hyperperistalsis may induce micro-traumatisations that, in turn, can activate a mechanism identified as 'tissue injury and repair' with a local production of estrogen. With time, the number of sites affected might increase and, in turn, increase the production of estrogens that, in a paracrine fashion, begin to interfere with the ovarian control over uterine peristaltic activity, resulting in permanent hyperperistalsis and a self-perpetuation of the disease process. The result is an auto-traumatisation of the uterus causing, in the case of endometriosis, the dislocation of fragments of basal endometrium into the peritoneal cavity and in the case of adenomyosis the infiltration of the basal endometrium into the inner myometrial wall. The hypothesis, postulates the existence in most cases of endometriosis and/or adenomyosis, of a causal event rapidly leading to uterine hyperperistalsis. Even if such an event does occur it is postulated that unavoidably, with time, even normoperistalsis will lead to some extent of micro-traumatisation. According to this hypothesis, endometriosis in young women and adenomyosis in premenopausal women, share the same pathogenetic mechanism. Both result from the physiological mechanism of 'tissue injury and repair' which respond to the local estrogens outside the control of the ovary.

The Role of Steroids and Steroid Receptors

It is not surprising that adenomyosis is influenced by steroids and a link between adenomyosis and estrogen has been proposed for almost a century. The role of steroids is supported by the identification of adenomyosis in women receiving tamoxifen as well as by the experimental animal model [115]. If hyperestrogenism is involved in the pathogenesis, it is proposed to operate through local production rather than through systemic hyperestrogenism [116]. Increased local estorgen may also account for the hypertrophy or hyperplasia in the surrounding myometrium and overlying endometrial hyperplasia. Experimental data in rodent models have shown that *in utero* or neonatal exposure to tamoxifen or to diethylstilboestrol can induce adenomyosis and induce marked myometrial disruption [86, 117]. The critical stage for neonatal exposure in rodents is because of the significant uterine development that takes place in the early neonatal period. These experiments raise the hypothetical possibility that the corresponding developmental stages in the humans which occur *in utero* will be sensitive to steroids and that *in utero* exposure may lead to adenomyosis. Studies in animal models also support a role for hyperprolactinemia (either induced by pituitary transplantation or by drug therapy), although it is unclear if a similar mechanism is involved in humans [87].

Whilst adenomyosis occurs spontaneously in many animal species, the first reported experimental animal model was by Lacassagne in 1935 who administered estrogen to mice for more than 6 months [118]. Subsequently, it was demonstrated that prolonged estrogen treatment resulting in adenomyosis, is also associated with elevated serum prolactin in intact animals [119]. Prolonged administration of progesterone either alone or in combination with estrogen also result in the development of adenomyosis [120, 121]. The effect of progesterone may be direct or may be enhanced by elevated levels of prolactin [122]. It has also been proposed that elevated level of progesterone may have a role in the induction of adenomyosis in the pituitary implant model. The observation that the development of adenomyosis was completely eliminated by ovariectomy immediately after pituitary transplantation and that the effect of ovariectomy was reversed by the administration of estrogen and progesterone combination but not by either estrogen or progesterone alone [123] suggested that the development of adenomyosis results from chronic hormonal imbalance involving the three hormones [122]. Spontaneous adenomyosis develops in SHN mice with advancing age, but this is

inhibited by the administration during the critical development window of bromocriptine-mesilate for more than 4 weeks [124, 125]. But whilst this supports the role of prolactin, is it also possible that bromocriptin-mesilate exerts an effect through inhibition of estrogen binding to its receptor.

There is considerable literature on the distribution of estrogen (ER) and progesterone (PR) receptors and their isoforms in the endometrium. Most of these studies have documented fluctuation in steroid receptor expression during the menstrual cycle. Some studies have reported on receptor distribution in the inner but did not examine the outer myometrium [126–128]. The cyclical changes in the uterine junctional zone as seen by magnetic resonance imaging, together with the peristaltic waves seen by videosonography, support the hypothesis that this layer is influenced by steroid hormones [129, 130]. Steroid hormones have also been implicated in the pathogenesis of uterine adenomyosis [116], and local rather than systemic hyperestrogenism may be implicated [131].

Takahashi et al. (1989) [132] [quoted from [116]], demonstrated no significant differences in estradiol levels in peripheral blood in women with adenomyosis. But women with adenomyosis had the highest estrogen level in menstrual blood compared to women with endometriosis who, in turn, had higher levels compared to unaffected women. This suggests that these higher estrogen concentrations are generated locally within the uterus. The mechanism for higher local estrogen production may be through the action of aromatase on androgen precursor [133], or the action of estrone sulphatase which converts estrone-3-sulphate to estrone [134]. Kitawaki et al. (1997) performed immunohistochemistry and examined the catalytic activity, and mRNA expression for aromatase cytochrome P450 ($P450_{arom}$) in tissue specimens [135]. $P450_{arom}$ was immunohistochemically localized in the cytoplasm of glandular cells of endometriotic and adenomyotic tissues and mRNA for aromatase cytochrome P450 was identified in adenomyotic tissue homogenate. However, neither $P450_{arom}$ protein activity nor mRNA was detected in endometrial specimens obtained from normal menstruating women. There is also evidence of altered 17β-hydroxysteroid dehydrogenase type-2 expression in the endometrium in women with adenomyosis and this results in increased conversion of estradiol to estrone during the secretory phase of the cycle [136]. Estrogen receptor alpha (ER-α) isoform expression is reduced in a CD-1 neonatal mouse model fo*r* adenomyosis, but a similar reduction is noted after tamoxifen administration to C57/BL6J mice that did not develop the disease.

Aromatase and estrone sulfatase activities were detected in adenomyosis foci using anion-exchange resin column chromatography, thin-layer chromatography, cocrystallization, and immunohistochemistry [137]. This may also account for the hypertrophy/hyperplasia in the surrounding myometrium. Interestingly, endometrial hyperplasia is often found in women with adenomyosis [51]. In the model proposed by Leyendecker and colleagues for the development of adenomyosis, a key modulator may be an increase in the local production of estrogen secondary to a pathological expression of the P450 aromatase enzyme [114, 138]. The starting event may be hyperactivity of the endometrial inflammatory response or hyperactivity in the endometrial oxytocin receptor system or in the pathological expression of the P450 aromatase system itself. This leads to uterine hyperperistalsis and endometrial hyperproliferation.

Endometrial glands in adenomyotic tissue selectively express more *human chorionic gonadotropin (HCG) – luteinizing hormone (LH) receptor mRNA* and immunoreactive protein than the non-invaginating eutopic glandular epithelium. This increased expression was also found in endometrial carcinoma and in invasive trophoblasts of choriocarcinoma [139]. The increased receptor expression in the invaginating endometrial epithelium may be related to the potential to invaginate into the myometrium and to form adenomyotic foci.

There are also several animal models that support a role for hormonal disturbance in the pathogenesis of adenomyosis. A high rate of uterine adenomyosis in mice was induced by intrauterine

or ectopic anterior pituitary isografts [140, 141]. Fluoxetine (a serotonin uptake inhibitor) was used to induce hyperprolactinaemia in castrated and non-castrated rats. Adenomyosis uteri developed in the non-castrated group, suggesting that high prolactin concentrations can cause myometrial degeneration/weakness and subsequent endometrial invasion, in the presence of ovarian steroids [87]. It is not known if hyperprolactinaemia plays a role in the development of adenomyosis in humans.

Adenomyosis has also been reported in postmenopausal breast cancer patients treated with the selective estrogen receptor modulator (SERM) tamoxifen [142]. The associated risk of adenomyosis with conventional postmenopausal hormone replacement therapy (HRT) is not known. Adenomyosis was incidentally found in some HRT users having endometrial ablation for postmenopausal bleeding [143]. The use of oral contraceptives does not appear to be associated with a risk of adenomyosis [38].

Mehasseb et al. (2011) reported on the distribution of estrogen and progesterone receptor isoforms in adenomyosis [144]. In the adenomyotic functionalis glands and stroma, there was a statistically significant ($p<0.001$) decrease in ER-α expression during the mid-secretory phase of the menstrual cycle, but the expression of ER-α in the inner and outer myometrium was not statistically significantly different. The ER-β expression was statistically significantly elevated in the adenomyotic functionalis gland during the proliferative phase and throughout the myometrium across the entire menstrual cycle. Expression of PR-A was similar to that of PR-B, with reduced expression in the basalis stroma, and the inner and outer myometrium in adenomyosis. The pattern of ER-β, PR-A, and PR-B expression was similar in the endometrial basalis and adenomyotic foci [144]. Higher ER-β expression and the lack of PR expression may be related to the development and/or progression of adenomyosis and might explain the poor response of adenomyosis to progestational agents.

Tamoxifen has been linked to postmenopausal adenomyosis and to an endometrioma in one case report [145] and to adenomyosis and an adenomyomatous endometrial polyp in another [145]. In a small series of eight women with endometrial pathology during tamoxifen therapy; one had adenomyosis [147]. Cohen et al. (1995) reported adenomyosis in 8 (57.1 %) out of 14 women who had a hysterectomy whilst receiving tamoxifen [142]. Seven of these women had small microscopic foci, and one had a large fundal adenomyotic lump. Cohen et al. (1997) reported adenomyosis in 15 (53.6 %) out of 28 postmenopausal women with breast cancer receiving tamoxifen who underwent hysterectomy compared to only 2 (18.2 %) out of 11 postmenopausal women with breast cancer not receiving tamoxifen [148]. This suggested an association between tamoxifen use and adenomyosis, but differences in the incidence of adenomyosis may be related to the indications for hysterectomy in the two groups. A comparative histopathologic evaluation concluded that tamoxifen-associated cases of adenomyosis were more likely to feature cystic dilated glands, stromal fibrosis and various epithelial metaplasias and higher epithelial proliferation [149]. Tamoxifen also induces distinct MRI patterns in the postmenopausal uterus on tamoxifen and the majority have heterogeneous endometrial signal intensity on T2-weighted images (mean = 1.8 cm) with enhanced endometrial-myometrial interface, coexisting sub-endometrial cysts, nabothian cysts, leiomyoma, and adenomyosis [150].

Familial and Genetic Factors

Whether hereditary or familial factors for adenomyosis exist is unknown. We only identified one case series by Emge, who operated on seven cases of adenomyosis in which mothers of the patients were operated upon for the same reason, raising the possibility of a hereditary factor [151]. The same article refers to a description of adenomyosis in a fetus at term. We are not aware of any studies on adenomyosis in twins.

Experimental observations in animals suggest that hereditary factors may be involved in the pathogenesis of adenomyosis. The uteri of recombinant inbred SMXA mice spontaneously

develop histological changes similar to adenomyosis [152]. The uteri of F1 mice strain contain more prominent changes resembling human adenomyosis.

Pandis et al. (1995) reported the finding of *del [7] [q21.2q31.2]* in three short term cultures from human mesenchymal cells of adenomyosis [153]. The deletion was found in myometrial cells of adenomyotic lesions. The karyotypic anomaly was previously reported in uterine leiomyomas. This led the authors to suggest that adenomyosis may be similar to fibroids in that it arises through a neoplastic process.

Goumenou et al. (2000) used 17 microsatellite markers, in four tetraplex and one single PCR assay, to determine the incidence of loss of heterozygosity in 31 cases of adenomyosis [154]. The markers used are located close to tumor suppressor genes, DNA repair genes, and genes which are thought to be involved in endometriosis. The markers were involved in regions on chromosomal arms 1p, 1q, 2p, 2q, 3p, 9p, 9q, 17p and 17q. Nine samples (29.0 %) showed loss of heterozygosity in at least one locus. Loci 2p22.3-p16.1, 3p24.2-p22 and 9p21 exhibited imbalance (19.4 %, 9.7 % and 6.5 % respectively). The study suggested a link between hMSH2, hMLH1, p16Ink4 and GALT genes and the pathogenesis of adenomyosis. Using comparative genomic hybridisation, Wang et al. (2002) were not able to identify positive recurrent gene copy number alterations in 25 cases of pathologically proven adenomyosis [155]. Which suggests that genetic alterations in adenomyosis are either rare of that the technique used was insufficiently sensitive.

Aberrant expression of ERα might be partly involved in the onset or growth of adenomyosis and its poor response to anti-estrogen therapy. Using PCR/single strand conformation polymorphism analysis, Oehler et al. (2004) identified somatic estrogen receptor ERα gene mutations in three out of 55 samples from adenomyosis uteri [156]. Two of the mutant ERα proteins display severely impaired DNA-binding and transactivation properties secondary to an altered response to estrogens or changes in epidermal growth factor-mediated ligand-independent activation. They suggested that such mutations may account for the apparent resistance of endometriotic cells to hypoestrogenic conditions and poor response to estrogen-ablative therapy in adenomyosis [156].

Gene expression profile demonstrated differences between mRNA expression in the inner and the outer myometrium in women with adenomyosis and the corresponding layers in unaffected uteri. WNT5A mRNA was consistently down-regulated in adenomyosis, both in the secretory and the proliferative phases [157]. WNT5A is a conserved homolog of Wingless, a key regulator of *Drosophila melanogaster* embryonic segmentation and patterning. The WNT gene family are critical regulators of cell polarity, motility, differentiation, apoptosis, and carcinogenesis.

The Role of Endometrial Stromal Cells in the Development of Adenomyosis

The development and differentiation of myometrial smooth muscle is affected and directed by the uterine epithelial and stromal cells. Using uteri from BALB/c mice 1–60 days postpartum, uterine mesenchyme produced larger amounts of smooth muscle when co-cultured with epithelium. This suggests that uterine epithelium plays a promotional role in the differentiation and spatial organization of the myometrium [158, 159].

To determine whether myometrial smooth muscle is newly produced at the EMI of the adult uterus, Fujii et al. (1989) examined the ultrastructure of the mesenchymal components of the EMI during the menstrual cycle and early pregnancy [33]. They identified cells that morphologically resembled myofibroblasts in the follicular phase and which differentiated into cells that morphologically resembled smooth muscle cells in the luteal phase and early pregnancy. This adds to the evidence that smooth muscle differentiation may occur from mesenchymal cells in the endometrial stroma.

In neonatal rodents models, the use of tamoxifen produces abnormal and aberrant endometrial tissue growth leading to adenomyosis. This is the

result of the disruption of the mesenchymal layers surrounding the endometrium in the neonatal period, triggering a disordered development of the uterine stroma, smooth muscle, blood vessels and possibly innervation [160]. Decidual stromal cells express α-smooth muscle actin and show ultrastructural similarities with myofibroblasts, supporting the view that metaplasia can occur in the endometrium [161]. Using immunohistochemical staining, isolated nodules of endometrial stromal cells without glands were characterized along blood or lymphatic vessels in the myometrium [82]. Multipotent pericytes are thought to be the origin of these stromal nodules. Due to the proliferative nature of the endometrial glands, the newly enlarged area of stroma could serve as "new soil", facilitating further downward growth of the endometrial glands. Hormonal, genetic, immunological and growth factors possibly play a role in this sequence of events [82].

Adenomyosis and Endometriosis

Whether adenomyosis and endometriosis share a common aetiology has long been debated in literature. Many hypotheses exist that propose common mechanisms including the link to hyperestrogenism, hyperperistalsis and microtraumatisation and the development from multipotential perivascular cells. The advent of MRI has renewed interest in this link because of the possibility of non-invasive diagnosis. Some studies have indicated a possible link. Bazot et al. (2004), for example, found that 27 % of the women with endometriosis concomitantly had adenomyosis [162]. Kunz et al. (2005) reported an even higher association of 70 % in a highly selected subpopulation [163]. Larsen et al. (2011) performed MRI of the uterus in 153 women with suspected deeply infiltrating endometriosis and a reference group of 29 women with cervical cancer and another 100 women without endometriosis who underwent a hysterectomy for other indications [36]. They reported that 53 (34.6 %) of the women in the endometriosis group had adenomyosis, compared to 6 (20.7 %) in the cervical cancer group and 19 (19.4 %) in the hysterectomy group. The difference between the groups was statistically significant ($p<0.05$). Sixty one (39.9 %) of the women in the endometriosis group had an irregular JZ (JZ-dif>2) compared to 6 women (20.75 %) in the cervical cancer group and 23 women (23 %) in the hysterectomy group. The difference was statistically significant ($p<0.01$). In a subgroup analysis, 4 (26.7 %) of women (n=15) with AFS stage I endometriosis had adenomyosis compared to 13 (35.1 %) in women with AFS stage II (n=37), 8 (24.2 %) of women with AFS stage III (n=33) and 24 (42.8 %) of women with AFS stage IV (n=56) endometriosis. The difference was not statistically significant. But more women with AFS stage IV endometriosis had deeper wall invasion with adenomyosis. The presence of deep infiltrating rectovaginal endometriosis and the size of infiltration did not correlate with the presence or the depth of adenomyosis. Thus they concluded that there was only limited correspondence between the invasive potential of endometrial cells in the uterus and in the peritoneum. It is also important to note that there were significant differences between the groups in factors of age and parity which are both relevant to the incidence of adenomyosis.

The mechanism by which endometrial cells might migrate within the myometrium is not known. Factors may involve local imbalance or, as mentioned earlier, factors that are innate to the cells in question. Goteri et al. (2006) evaluated the motility-related molecule Cdc42 expression in eutopic and ectopic endometrial tissue in patients with adenomyosis (n=24) and ovarian endometriotic cysts (n=19) compared with patients without endometriosis (n=9) [111]. In eutopic endometrium of patients with adenomyosis and with fibroids or benign ovarian cysts, the intensity of Cdc42 immunostaining was weaker, especially in the specialised stromal cells, compared with cases with ovarian endometriosis. Expression of Cdc42 in eutopic endometrium showed a trend to be higher in the secretory than in the proliferative phase and in patients with ovarian endometriotic cysts compared to patients with adenomyosis (unpaired t test, $p=0.005$),

especially in the proliferative phase. Cdc42 is a key molecule in intracellular signalling pathways that lead to changes in cellular morphology, cell polarity, motility and migration, gene transcription, cell cycle progression, and programmed cell death, both in normal conditions and in tumours. Cdc42 induces the formation of actin-rich finger-like membrane extensions (filopodia) and regulates anchorage independent cell growth. The differential expression in ovarian endometriosis and adenomyosis let Goteri et al. (2006) to speculate on a role for Cdc42 in endometrial cell migration in ovarian endometriosis but not in adenomyosis, implying that the mechanisms of the two conditions may be different [111].

The question therefore arises whether the pathogenesis of adenomyosis is more associated with deep recto-vaginal endometriosis than cystic ovarian endometriosis. Yang et al. (2009) examined the invasiveness into matrigel matrix of endometrial stromal cells obtained from eutopic endometrium from women with and without adenomyosis and measured the concentration of the matrix metalloproteinases (MMP-2, MMP-9) and the tissue inhibitors of metalloproteinases (TIMPP-1, TIMP-2) in culture supernatants [164]. Using migration assay, they reported that migration of endometrial stromal cell from adenomyosis was not different from that of the control group of endometrial stromal cells cultured alone or with the addition of IL-6, anti-IL-6 or the GM6001 (a synthetic inhibitor of MMP). Furthermore, these agents did not significantly alter cell migration compared to controls. Yet, the concentration of MMP-2, but not of MMP-9, produced by ESCs from women with adenomyosis was higher compared to women without adenomyosis. The level of TIMP-1, but not of TIMP-2 in culture media was also higher in women with adenomyosis compared to controls. This suggests that the concomitant elevation of MMP-2 and TIMP-1 may explain why invasiveness was not increased.

A marked increase in vascularization of the endometrium in adenomyosis was reported with the total surface area of capillaries up to 11.6 times that of the controls in the proliferative phase [165]. This has not been confirmed in a subsequent study, although microvessel density in adenomyotic tissue was increased compared to the endometrium of the same patient [166]. A recent molecular study found an elevation of matrix metalloproteinase (MMP-2 and −9) expressions in eutopic and ectopic endometria with a good correlation with increased microvessel density [167]. The role of the MMPs and TIMPs in the development of adenomyosis was further investigated through genetic studies; there was an association between adenomyosis and MMP-2 -1306C/T polymorphism in North Chinese women [168]. The same investigators also suggested that the presence of the −2578*A* or −1154*A* allele of the vascular endothelial growth factor (*VEGF*) gene might be protective [169], and that polymorphisms of two angiogenic factors, fibroblast growth factor 1 and 2 might play a role in the initiation of angiogenesis in endometriosis or adenomyosis [113]. Caution, however, is needed when interpreting these gene association studies [71].

Benagiano et al. (2014) reviewed studies that involved comparison between the eutopic endometrium in women with endometriosis or with adenomyosis [71]. Many similarities and also some differences were identified between the eutopic endometrium in both conditions. Much of published research in this area may have been influenced by bias consequent to the method of diagnosis. Compared to control endometrium, both endometriosis and adenomyosis exhibited immune dysfunction and there were alterations in adhesion molecules, cell proliferation and apoptosis. There was also an increase in cytokines, inflammatory mediators and in oxidative stress and free-radical metabolism. Dissimilarities were reported in the extent of apoptosis and in the expression of some inflammatory mediators.

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