The Incidence and Clinical Significance of Adenomyosis

2

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Abstract

For more than a century the diagnosis of adenomyosis was only possible through pathological examination of hysterectomy specimens but this has changes with the introduction of transvaginal ultrasound and MRI. Despite the large number of published studies reporting on the incidence and the clinical correlates of adenomyosis, there is no agreement on the definition and cut-off between adenomyosis and normal uteri and most reports still rely on case series of women undergoing hysterectomy. This poses considerable challenge to our understanding of the disease, its impact and of the accuracy of imaging diagnosis.

Keywords

Incidence • Adenomyosis • Adenomyosis sub-basalis • Endometrial myometrial interphase • Transvaginal ultrasound • Magnetic resonance imaging • Junctional zone • Subendometrial myometrium • Abnormal uterine bleeding • Parity • Infertility • Peristalsis • Utero-tubal transport

The Incidence and Clinical Significance of Adenomyosis

For more than a century after adenomyosis was first described, the diagnosis was only possible through pathological examination of hysterectomy specimens. This changed following the advent of high definition transvaginal ultrasound and MRI which enabled non-invasive diagnosis. There are a large number of published studies reporting on the incidence and the clinical correlates of adenomyosis. Mostly, these still rely on case series of women undergoing hysterectomy. The reported incidence in different studies

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varies from 5 to 70 % [7]. The very wide variation is more likely to be related to differences in diagnostic criteria and to methodological issues in case ascertainment. But there are also differences between the study populations.

It is well recognised that the endometrial-myometrial interface in normal uteri is irregular [37]. Classically, pathologists made the diagnosis of adenomyosis based on their subjective assessment of the degree of deviation from what they regarded as normal. More than a century on, there remains lack of agreement on the definition of the appropriate cut-off point.

Defining Adenomyosis

Classically, adenomyosis is defined by the presence of heterotopic endometrial glands and stroma within the myometrium. Relevant diagnostic features are the depth of stromal and glandular presence within the muscle and the presence of myometrial hypertrophy or hyperplasia around adenomyotic glands. Hendrickson and Kempson [37] described myometrial changes as a collar of hypertrophic smooth muscle around adenomyotic foci [37]. But there are no objective definitions for the reported changes in smooth muscles. Irregularity at the endometrial myometrial interface is almost universal [37], thus the identification of adenomyosis has relied on an assessment of the degree of deviation of mucosal presence compared to uteri judged to be normal. Inevitably, this will remain subjective unless defined features can be linked to the genesis of symptoms. In one study the reported incidence of adenomyosis varied almost fivefolds (from 12 to 58 %) between hospitals and by almost ninefolds (from 10 to 88 %) between pathologists. There were also important differences amongst pathologists working at the same hospital [96]. Because of the perceived risk of over diagnosis, many pathologists argued for the adoption of conservative cut-off points [32, 112]. But as mentioned above, this approach remains arbitrary [12] and can clearly result in overlooking early stages of the conditions. Consequently, any possible contribution of less extensive disease to symptoms will not be recognised. Indeed, it likely that in most cases, it is the presence of symptoms that necessitated the hysterectomy in the first instance. Thus it remains unclear how a conservative approach to histological diagnosis can be scientifically justified. The few studies that addressed this point, did find a link between symptoms and minimal depth lesions [12, 94]. The term "adenomyosis sub-basalis" was introduced to denote lesions within one low power field (LPF) [94] or <1 high power field (HPF) [112] below the basal endometrium. Despite this, these uteri would be classified as "normal" using the more prevalent definition of adenomyosis.

It is also unfortunate that definitions used to describe adenomyosis utilise expressions that convey a particular conception of the pathophysiology of the disease especially given the current limitation of our understanding of the condition. It is now common for the term 'invasion' to be used when describing the observation of the mere presence of glands within the myometrium. Vercellini et al. (2006), for example, states that: "it is generally agreed that adenomyosis occurs when the normal boundary between the endometrial basal layer and the myometrium is disrupted" [113]. They add that "as a consequence of this disruption, the endometrial glands *invade* the myometrium". The sequence is thus set as disruption leading to invasion. Uduwela et al. (2000) propose the inverse sequence when they write: "adenomyosis is a disease characterized by deep invasion of the inner myometrium by endometrial glands and stroma thereby disrupting the EMI (Endometrial Myometrial Interphase)" [107]. Whilst both invasion and disruption may have a role in the disease, it is important to consider the framing bias entailed in utilising these terms.

Beside the question of defining the cut-off for identifying adenomyosis, the reported incidence of adenomyosis after hysterectomy is also necessarily affected by the degree of diligence in case ascertainment. The extent of sampling becomes important because uterine affection is not uniform. Yet, some studies have relied on as few as two random sections of the uterus [120]. In this respect, it seems that the rate of diagnosis

increased overtime. In the early series by Dreyfuss (1940), 1807 surgically removed uteri were examined. He reported a combined incidence of "adenomyosis and endometriosis" in 224 instances (12.4 %) and that in 152 cases (8.4 % of the total) the lesion was localised within the myometrium representing cases of adenomyosis [25]. Three decades later, Bird et al. (1972) reported on the incidence of adenomyosis in 200 consecutive hysterectomies [12]. When these cases were examined routinely, adenomyosis was identified in 31 % of instances. The figure rose to 38.5 % when 6 additional blocks were examined and to 61.5 % when sub-basal lesions (within one LPF below the basal endometrium) were included. There is controversy over which of the uterine walls is most affected. Some studies reported more affection in the posterior wall [120], but others disagreed. In a study involving 88 samples, Sammour et al. (2002) reported affection of both the anterior and posterior walls in 76 % of cases, affection in the anterior wall only in 6.8 % of cases and of the posterior wall only in 17 % of cases [94].

The cut-off point for the diagnosis of adenomyosis remains open to interpretation and also to miscommunication. It is sometimes expressed with reference to the microscope optical field but this varies according to microscope design and objective lens used. Attempts at standardisation included the use of cut-off points reported in terms of millimetres below the EMI. But this method may require calibration, or in terms of the percentage of myometrial wall affected. The latter can also be fraught with difficulty because full thickness myometrial biopsy may not be part of routine processing especially for benign disease and also because of the practical difficulty of processing full thickness hypertrophied muscle wall. In this regards it is to be reiterated that there is no objective definition of myometrial hypertrophy and hyperplasia which are often stated as characteristic features of adenomyosis. Whether myometrial hyperplasia is considered essential to the diagnosis or not can also affect the reported incidence. In one study the incidence varied from 18.2 % using 1 mm cut-off to 11.5 % using 5 mm cut-off and the authors reported that the incidence will be lower if myometrial hyperplasia was considered an essential diagnostic requirement [11].

Table 2.1 The depth for endometrium presence within the myometrium that was used as a cut-off point for the histological diagnosis of adenomyosis in various studies

Diagnostic cut off point	References
>1 HPF	[84]
>0.5 LPF (1 mm)	[89, 112, 120]
>1 medium-power field (×100)	[32]
>1 LPF	[85]
>1/4 of total uterine wall thickness	[37]
2.5 mm or more	[56]
3 mm or more	[11]

LPF low power field, *HPF* high power field

Table 2.2 The classification of adenomyosis as proposed by Bird et al. [12] based on depth and extent of involvement

Depth of "invasion"	
Grade I	Sub-basal lesions within one LPF
Grade II	Up to mid myometrium
Grade III	Beyond mid-myometrium
Degree of involvement	
Slight	1–3 glands/LPF
Moderate	4–9 glands/LPF
Marked	10 or more glands/LPF

The classification does not however take into account the overall uterine size or the extent of uterine affection. *LPF* low power field [12]

In terms of the depth at which endometrial gland and stroma should be present within the myometrium for the diagnosis to be made, the adopted cut-off points vary (Table 2.1). Bird et al. (1972) proposed a classification into: Sub-basal lesions which are lesion present within one LPF (grade I); presence to mid myometrium (grade II); presence beyond mid-myometrium (grade III). They also classified the degree of involvement into three degrees: slight (1–3 glands/LPF), moderate (4–9 glands /LPF), and marked (10 or more glands/LPF) disease (Table 2.2) [12].

In the study by Bird et al. (1972), adenomyosis (including sub-basal disease) was the sole pathology (termed 'essential' adenomyosis) in 92 (46 %) out of the study population of 200 cases and was the sole pathology in 75 % of cases of adenomyosis [12]. There were 47 women who had sub-basal (grade I) adenomyosis and no other

pathology. Out of this subgroup, 60 % had significant menorrhagia. The incidence of menorrhagia was higher in women with sub-basal disease when compared to women with grade II and grade III lesions (n = 45) where the incidence of menorrhagia was 42 %. Thus this finding does not support definitions that exclude sub-basal lesions. Dysmenorrhoea, on the other hand, was related to the depth and the degree of involvement. The degree of involvement has rarely been the focus of research and even if reported it has seldom been included in statistical analysis. One possible explanation is that most published studies have relied on routine histology which does not regard the degree of involvement as prognostically relevant. The uncertainty linked to the appropriate cut off point lends considerable support to the suggestion made by McCausland and McCausland (1998) that histopathology should report on the actual depth of glandular presence rather than attempt a dichotomous diagnosis into normal and adenomyosis using arbitrary cut-off points [71].

Imaging Diagnosis

There are no symptoms or physical signs that are specific to adenomyosis. Classically, the uterus with adenomyosis is described as tender and symmetrically enlarged. It is interesting to note that the debate about whether adenomyosis has any characteristic symptoms is longstanding. Cullen, among other early investigators, believed that in contrast with early stage disease which is difficult to detect, fairly advanced disease could be diagnosed with great ease including by the 'hospital assistant'. Lockyer (1918) on the other hand observed that: "it is, however, clear that in many cases, if not in most, the diagnosis is made at the operation or by the microscope" [59]. This led Lockyer (1918) to conclude that "we are therefore obliged to accept the view that an opinion expressed before operation only amounts to a probability" [59]. There is agreement in more recent literature that the specificity of preoperative diagnosis based on clinical features is poor [12], with a reported range of 2–26 % [7, 78, 85].

The introduction of transvaginal ultrasound offered an opportunity to improving the diagnostic accuracy. But earlier attempts at preoperative diagnosis using ultrasound were hampered because of the inability to reliably distinguish these lesions form fibroids [4]. The advent of transvaginal ultrasound provided a breakthrough as it was linked to improved sensitivity and specificity of >80 % (Table 2.3). The ultrasound features linked to adenomyosis include uterine enlargement in the absence of fibroids, asymmetric thickening of the anterior or posterior uterine wall, lack of contour abnormality, lack of mass effect, heterogeneous poorly circumscribed areas within the myometrium, anechoic myometrial blood-filled cysts, increased echogenecity of the endometrium, and subendometrial linear striations. Ultrasound could also detect adenomyosis as localised non-homogenous lesions within the myometrium. There is disagreement in published literature on the diagnostic value of each of these features. Meredith et al. (2009) analysed data from 14 selected published studies on the use of preoperative ultrasound and compared the findings to histological diagnosis [74]. They reported

Table 2.3 The diagnostic accuracy of Transvaginal Ultrasound (TVU) and Magnetic Resonance Imaging (MRI) in various studies

Study	Sensitivity (%)	Specificity (%)
Accuracy of TVU in diagnosis of adenomyosis		
Fedele et al. (1992) [28]	87	99
Ascher et al. (1994) [2]	53	67
Brosens et al. (1995) [15]	86	50
Reinhold et al. (1995) [90]	86	86
Atzori et al. (1996) [5]	87	96
Koçak et al. (1998) [47]	89	88
Bromley et al. (2000) [14]	84	84
Bazot et al. (2001) [8]	65	98
Dueholm et al. (2001) [26]	63	65
Accuracy of MRI in the diagnosis of adenomyosis		
Mark et al. (1987) [65]	61	100
Ascher et al. (1994) [2]	88	66
Reinhold et al. (1996) [91]	89	89
Bazot et al. (2001) [8]	78	93
Dueholm et al. (2001) [26]	70	86

that adenomyosis was more common in women with heavy bleeding (31.9 %) compared to all hysterectomies (25.9 %). The probability of adenomyosis in a woman with heavy bleeding and positive ultrasound features was 68.1 %, compared to 65.1 % probability in a woman with positive ultrasound undergoing a hysterectomy for any symptom. But the probability of adenomyosis after a normal transvaginal ultrasound scan was 10 % in symptomatic patients compared to 8.7 % probability for women undergoing hysterectomy for any reason. The sensitivity and specificity for symptomatic women was 84.3 and 82.3 %, and for all women undergoing hysterectomy was 81.1 and 85.1 % (Table 2.4). The figures lend support to the conclusion that transvaginal ultrasound scan is an accurate test for adenomyosis, but this is necessarily weakened because of the lack of uniform histopathological or ultrasound based diagnostic criteria. This is particularly important given that most studies have used histopathology as the gold standard.

Champaneria et al. (2010) published a systematic review including a meta-analysis of published articles that compared the diagnostic accuracy of transvaginal ultrasound (TVU) or MRI and that used histological diagnosis as the gold standard comparator [17]. The selection criteria for the systematic review were studies that involved premenopausal women (although studies often included both pre- and post- menopausal women) and that used the same individuals for the test and subsequently had a hysterectomy which enabled histological diagnosis. Initially, the systematic search identified 23 articles that met these selection criteria. However, 17 of identified studies were excluded because they were judged to be of poor quality, were partially duplicated with other published research or because published details were insufficient for the construction of comparison 2x2 table. This left only 3 studies that reported on the use of MRI [8, 26, 91] and 6 studies that reported on the use of TVU [8, 9, 26, 42, 91, 111]. In these studies, the pooled sensitivity and specificity of TVU was 72 % (95 % CI 65–79 %) and 81 % (95 % CI 77–85 %) respectively. TVU had a positive likelihood ratio of 3.7 (95 % CI 2.1–6.4) and a negative likelihood ratio of 0.3 (95 % CI 0.1–0.5). The pooled sensitivity and specificity for MRI were 77 % (95 % CI 67–85 %) and 89 % (95 % CI 84–92 %) respectively. MRI had a positive likelihood ratio of 6.5 (95 % CI 4.5–9.3), and a negative likelihood ratio of 0.2 (95 % CI 0.1–0.4) [17].

Despite the apparent favorable diagnostic statistics, there are many important differences between these studies. The first difficulty concerns the point discussed earlier about the cut-off point for histological diagnosis. Histological diagnosis was critical to the inclusion criteria as it was used as the reference point, but it is difficult to establish whether the cut-off points were equivalent. Bazot et al. (2001, 2002) used 2.5 mm as their cut-off point [8, 9], Dueholm et al. (2001) used a medium power field (×100) or 2 mm [26], Vercellini et al. (1998) used half a low power field (or 2.5 mm) [111], and Reinhold et al. (1996) described using one high power field [91]. The number of sections examined also varied between the studies and whilst some studies described assessment of uterine weight and

Table 2.4 The diagnostic accuracy of preoperative ultrasound in women undergoing hysterectomy in relation to presenting symptoms [74]

Variable	All studies, n (95 % CI)	Hysterectomy in symptomatic patients, n (95 % CI)	Hysterectomy for any reason, n (95 % CI)
Sensitivity	82.5 (77.5–87.9)	84.3 (76.3–93.2)	81.1 (74.5–88.2)
Specificity	84.6 (79.8–89.8)	82.3 (72.5–93.5)	85.1 (79.3–91.4)
Likelihood ratio of positive results	4.7 (3.1–7.0)	4.1 (2.0–8.2)	5.1 (2.3–8.7)
Likelihood ratio of negative results	0.26 (0.18–0.39)	0.25 (0.14–0.43)	0.28 (0.17–0.45)

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morphological descriptors such as uterine wall thickness, no account is provided as to whether or how this was taken into consideration. Histological criteria recorded in a number of studies include the grade of lesions based on the depth of presence of glands and stoma within the myometrium, and lesion density [8, 9, 42]. But again, where these were mentioned as part of the methodology, they were not taken into account in the analysis. Also, those studies that made a histological distinction between focal and diffuse adenomyosis [8, 9, 26, 42] did not take this factor into account when the results were analyzed. All the studies included in the meta-analysis by Champaneria et al. (2010) included women who were scheduled for hysterectomy, but there are indicators of differences between the study populations [17]. It should be considered that the threshold for hysterectomy varies based on the population and the health care system and this may have been a factor why the incidence of adenomyosis varied between the studies ranging from 21 [26] to 37.1 % [42]. All of the 6 studies reported positive and negative predictive values which can be affected by the incidence in the population considered. It is notable that the positive predictive value of ultrasound was low (below 55 %) in all three studies included in the meta-analysis [26, 42, 111].

Also, despite the strict exclusion criteria, the two studies by Bazot et al. (2001, 2002) included 120 and 129 women respectively and described different patient profile [8, 9]. Yet both studies reported that they recruited consecutive women from the same hospital during the same time interval. This suggests significant overlap. Bazot et al. (2001) reported that 61 of the 120 patient had menorrhagia and 32 had endometrial cancer compared to the report by Bazot et al. [9] where 92 out of 129 women had menorrhagia and 13 had endometrial cancer [8, 9]. Reinhold et al. (1996) included 26 women with endometrial cancer into the study despite the fact that this can affect the appearance of the subendometrial myometrium [91]. In the study by Kepkep et al. (2007) only 8 out of 70 women had hysterectomies because of premenopausal abnormal uterine bleeding [42]. In the study by Reinhold et al. (1996) almost half the participants were postmenopausal [91]. In the study by Vercellini et al. (1998) the indication for hysterectomy was menorrhagia and/or worsening dysmenorrhoea, but the study excluded women with fibroids that distort the uterus or that were more than 12 weeks size [111]. All of the other studies included women with fibroids without stipulation of any cut off points related to the size of fibroids. A concern is that both Vercellini et al. (1998) and Reinhold et al. (1996) excluded women after investigation if the uterus could not be assessed because of fibroids although this can affect quoted sensitivity and specificity [91, 111].

With regards to image based diagnostic criteria, there was agreement on three of the features used to diagnose adenomyosis: the presence of myometrial cysts, heterogeneous myometrium and focal abnormal echotexture. In addition all studies except Dueholm et al. (2001) and Reinhold et al. (1996) included the presence of globular or asymmetrical uterus [26, 91]. Kepkep et al. (2007) and Bazot et al. (2002) but not the other studies emphasised the diagnostic value of subendometrial linear striations [9, 42]. Only Bazot et al. (2002) utilised colour Doppler [9]. Bazot et al. (2002) reported on the diagnostic value of the individual features used for ultrasound identification of adenomyosis [9]. But here again, it is interesting to note that some of these individual features had a higher sensitivity than the overall ultrasound assessment. Thus it remains unclear what relative weight was assigned by the investigators to each of the identified features. In the earlier study report by Bazot et al. (2001), the combined assessment had a higher sensitivity than the individual features [8]. The reported sensitivity, specificity, positive and negative predictive value for TVU in the study by Kepkep et al. (2007) are identical to those reported for the sonographic feature or "heterogeneous myometrium" [42]. Here again it becomes unclear what impact, if any, the other features had on the final classification.

In contrast to histopathological classification which focuses on the presence of glands and stroma within the myometrium, ultrasound diagnosis seems focussed on the appearance of the

myometrium, the overall shape and size of the uterus or the presence of asymmetry. Ultrasound also emphasises the role of myometrial cysts not all of which can be histologically linked to adenomyosis. There is disagreement between the studies on whether ultrasound correctly identified the grade or degree of adenomyosis. No correlation was found between ultrasound and histopathology in the study by Bazot et al. (2001) where sonography and histopathology concurred in only 57 % of cases when assessing the depth of presence of endometrium within the myometrium and in only 23 % of cases when assessing the degree of involvement and lesion density [8]. On the other hand, Reinhold et al. (1996) reported a Kappa statistic of 0.69 indicating good agreement between TVU and histology in depicting the location of adenomyosis and a Kappa statistic of 0.81 in relation to the maximum depth of involvement [91].

Thus whilst Champaneria et al. (2010) concluded that TVU has a high level of accuracy for the diagnosis of adenomyosis, it should be borne in mind that the studies included in their review were focused on a subset of patients scheduled for hysterectomy [17]. There is lack of clarity as to the exact diagnostic criteria and the relative weight of the various features linked to the condition. In addition, the choice of histological cut off points, and the choice regarding inclusion and exclusion criteria e.g. the inclusion of women with endometrial cancer may have affected the overall assessment and ultimately the judgment in favour of TVU.

A more recent development is the advent of three dimensional ultrasound and its use in relation to adenomyosis. Little research has been published so far. Naftalin et al. (2012) reported on the use of 3D-TVU in 985 consecutive women who attended a general gynaecology clinic in a large teaching hospital in the UK [81]. They reported the prevalence of adenomyosis in the whole group as 20.9 % (95 % CI: 18.5–23.6 %). It was possible to compare histological findings with 3D-TVU in the subgroup of women (n = 45) who subsequently underwent a hysterectomy. After excluding women with cancer (n = 14) and with large fibroids (n = 4), the investigators reported a fair level of agreement between 3D-TVU and histological diagnosis of adenomyosis [$\kappa = 0.62$ ($p = 0.001$), 95 % CI (0.324, 0.912)]. They reported a positive correlation between age and the finding of adenomyosis, but the incidence is not provided divided by age groups or by clinical presentation. Thus although the study population may provide a range of diverse presentations, it will necessarily be affected by specialisation within the clinic and referral criteria therefore caution should be exercised when extrapolating the figures to different populations. Luciano et al. (2013) prospectively evaluated the accuracy of 3D-TVU in 54 symptomatic premenopausal women undergoing hysterectomy for benign conditions [61]. Of these, there were 32 patients who had no previous treatment, 26 of whom had adenomyosis. Features linked to adenomyosis were: (1) Maximum Junctional Zone thickness (JZmax) ≥ 8 mm, (2) myometrial asymmetry and (3) hypoechoic myometrial striations. They reported that when at least 2 of these features were present, 3D-TVU was 90 % accurate (sensitivity = 92 %; specificity = 83 %; PPV = 99 %; and NPV = 71 %). Interestingly the accuracy reduced to 50 % in the subgroup who had undergone endometrial ablation (n = 12), and was 60 % in the group receiving medical treatment (n = 10).

Thus – despite much promise – studies assessing the role of ultrasound and MRI in diagnosing adenomyosis all suffer methodological weaknesses some of which are due to the constraints inherent in the study population. The need for histology as the gold standard means that only a particular cohort could be assessed. Still, a major difficulty has been in the use of retrospective cohorts which suffer from lack of standardisation and incomplete assessment. The indications for hysterectomy are becoming increasingly narrow which add to the need for reliable non-invasive diagnostics.

Biomarkers in Adenomyosis

Despite the breakthrough achieved with the use of MRI and transvaginal ultrasound, reliable diagnosis of adenomyosis remains difficult and

expensive. Thus, the identification of a non-invasive reliable marker for the disease will have significant clinical value. Such a marker may also help monitor disease progression or response to treatment.

CA125 is perhaps one of the earliest biomarkers to be studies in relation to endometriosis and adenomyosis. CA125 is produced by most non-mucinous epithelial ovarian tumours. More research has been directed to assessing its use in endometriosis than to adenomyosis, but meta-analysis of published results concluded that it is of limited utility [77]. More recent research has again demonstrated the limited utility of CA125 in endometriosis without endometrioma, but that accuracy could be improved by using a lower combined cut-off values for CA-125 at 20 and 30 U/mL [46]. Concomitant use of CA125, CA19-9 and IL-6 did not add significantly to the value of CA125 alone [99].

In relation to adenomyosis, Takahasi et al. (1985) examined 11 patients with fibroids, 7 with adenomyosis and 1 with adenomyosis and fibroids and reported that the mean CA125 level (± SD) was 18.3 (±6.1) U/ml in patients with fibroids and 93.3 (±49.4) U/ml in those with adenomyosis [100]. The difference was statistically significant. Seven out of the 8 women with adenomyosis but none of those with fibroids had serum CA125 > 35 U/ml. Following surgery, CA125 level in patients with adenomyosis gradually decreased and returned to normal 1 month postoperatively. But the diagnostic value was disputed by others. Halila et al. (1987) measured serum CA125 in 22 women undergoing a hysterectomy for adenomyosis or fibroids but reported normal CA125 levels (<35 U/ml) in 20 patients including in all those with histologically proven adenomyosis [35]. One complicating factor is the observation that serum levels of CA125 varies with the menstrual cycle. Masahashi et al. (1988) reported a transient rise during menstruation. They also reported that serum levels are higher in patients with adenomyosis and with advanced endometriosis compared to normal controls [67]. Takahashi et al. (1988) reported that after control for cycle phase, CA125 was elevated in patients with adenomyosis (as well as in endometriosis) [101]. Interestingly, Bischof et al. (1992) reported elevated CA125 levels in women with fibroids. They attributed this to increased peritoneal distension secondary to uterine enlargement by the fibroid [13].

Agic et al. (2008) measured chemokine (C-C motif) receptor 1 mRNA (CCR1 mRNA) in peripheral blood leukocytes together with monocyte chemotactic protein-1 (MCP-1) and CA125 protein in serum of women with endometriosis and adenomyosis. The ratio of CCR1/HPRT mRNA (Hypoxanthine-guanine phospho-ribosyltransferase) in peripheral blood of patients with endometriosis was significantly elevated compared to women without endometriosis. No significant difference in CCR1/HPRT mRNA levels was found between women with adenomyosis and the control group. Serum levels of MCP-1 and CA125 were significantly higher in patients with endometriosis. The combined test using the three markers was considered positive if at least one of the markers was above the set threshold. When used to detect endometriosis, this combined test showed sensitivity, specificity, NPV, PPV of 92.2 %, 81.6 %, 83.3 % and 92.3 % respectively. The combined test predicted the presence or absence of adenomyosis to a lesser extent: sensitivity, specificity, NPV, and PPV were 72.7 %, 81.6 %, 93.0 %, 47.1 % respectively [1].

Another approach is the use of proteomic analysis of serum samples. Long et al. (2013) compared serum samples from women with adenomyosis, endometriosis and controls using MALDI-TOF-MS proteomic analysis. They identified 13 protein peaks that were abnormally expressed in endometriosis and 12 in adenomyosis compared with control groups. Five-peak masses were significantly down regulated both in the women with endometriosis and adenomyosis. Two protein peaks with m/z of 2.748 and 5.759 kDa were reported to be of high value in the diagnosis of adenomyosis [60]. However, this approach is fraught with difficulty. Previous studies using this technique in endometriosis have led to the identification of different putative protein markers. Jing et al. (2009) identified two marker proteins with m/z of 5.83 and 8.865 kDa [40]. Kyama et al. (2011) reported that endometriosis was diagnosed with high sensitivity (89.5 %) and specificity (90 %) with use of five down-regulated

mass peaks (1.949, 5.183, 8.650, 8.659, and 13.910 kDa), and minimal-mild endometriosis was diagnosed with four mass peaks (two up-regulated: 35.956 and 90.675 kDa and two down-regulated: 1.924 and 2.504 kDa) with maximal sensitivity (100 %) and specificity (100 %). The 90.675 and 35.956-kDa mass peaks were identified as T-plastin and annexin V [52]. Ding et al. (2010) detected 3 mitochondrial protein peaks as potential biomarkers for endometriosis with m/z of 15.334, 15.128 and 16.069 kDa [24]. The differences may be due to different experimental conditions, different protein chips or technologies used, or to patient related factors.

Xiaoyu et al. (2013) used iTRAQ (isobaric tags for relative and absolute quantitation) technology to compare serum samples from women with and without adenomyosis. They reported that 21 proteins were significantly up-regulated and 4 proteins were significantly down regulated in women with adenomyosis (Table 2.5) [119]. They thus raised the possibility of using the identified proteins as biomarkers for adenomyosis.

Dechaud et al. (2014) performed gene expression array in adenomyosis and reported that the most up regulated genes in the endometrium in adenomyosis were SH2D3A, KLHL31 and ADAMTS16 whilst the most down regulated genes were FOXP2, F2RL2 and DGKB and raised the possibility of these being useful as markers of adenomyosis [23].

Table 2.5 Proteins differentially expressed when comparing serum samples from women with adenomyosis and controls using iTRAQ analysis [119]

Up-regulated proteins	
Fibrinogen α	Fibrinogen β
Fibrinogen γ	CD44
Fibronectin 1	Complement C1r
Apolipoprotein B-100	Complement factor B
Hemoglobin subunit δ	Complement C1s
Complement C3	Complement C5
Antithrombin-III	Vitamin K-dependent protein S
Ceruloplasmin	Serum amyloid P-component
Leucine-rich α-2-glycoprotein	α-1-antichymotrypsin
Inter-α-trypsin inhibitor heavy chain H4 isoform 1	Vitamin D-binding protein
Apolipoprotein C-II	
Down-regulated proteins	
Gelsolin isoforms-a	Apolipoprotein A-IV
Transthyretin	Keratin, type I cytoskeletal 9

Clinical Manifestations of Adenomyosis

As mentioned above, the preoperative diagnosis of adenomyosis is poor. In one study, the diagnosis was suspected preoperatively in only 10 % of cases and recognized at surgery in 35 % of patients [85]. It is perhaps well recognized that there are no symptom or symptoms that are individually or collectively pathognomonic of uterine adenomyosis. Traditionally adenomyosis has been linked to a variety of common gynaecological presentations, most prominently abnormal bleeding, dysmenorrohea and although it is more common in parous women, it has been linked to infertility. It is also recognised that many cases are identified in asymptomatic women. This will be explored further, but it is important to point out that a variety of other gynaecological conditions such as endometriosis and fibroids have also been linked to these presentations as well as being diagnosed in asymptomatic women. Both endometriosis and fibroids are commonly present in association with adenomyosis. The significance of the finding of adenomyosis needs to be considered against the knowledge that the threshold at which women seek medical care for any of these presentations varies and at the same time, the clinical threshold for defining normality is not always clear or agreed.

Symptoms Linked to Adenomyosis (Box)

Abnormal Uterine Bleeding

Heavy menstrual bleeding is one of the more common indications for hysterectomy, and as adenomyosis has been reported in a sizable percentage of surgically removed uteri, it is not surprising that heavy menstrual bleeding has come

to be linked to adenomyosis. In the study by Bird et al. (1972) 200 hysterectomy specimens were assessed for the presence of adenomyosis. Lesions were classified into three grades: Grade (I), sub-basal adenomyosis where the lesions were found within one low power field below the basal endometrium, but no further; Grade (II), where adenomyosis was found up to the mid-myomstrium; and Grade (III) where adenomyosis extended beyond the mid-myometrium [12]. Adenomyosis was identified histologically in 31 % of the 200 specimens examined using routine histopathology, but when additional sections were taken, 38.5 % were identified as having adenomyosis and the figure rose to 61.5 % when Grade I (sub-basal) adenomyosis was included. Adenomyosis was the only uterine lesion in 16.5 % of cases and was the major pathology found in 32.5 % of cases. In 46 % of all cases (92 out of the 200 women included in the study) adenomyosis was either present alone or together with other non-significant pathology, this included 47 Grade I, 33 Grade II, and 12 Grade III cases. Thus all the 47 cases of sub-basal adenomyosis belonged to the group where adenomyosis was the sole significant pathology. Ninety (83.5 %) of the women identified with adenomyosis (n = 123) had associated pathology. These included fibroids (n = 68), endometrial hyperplasia (n = 9), endometriosis (n = 8), or polyps (n = 5). The presence of pathology associated with adenomyosis is well recognised in literature. Of the 92 women who had adenomyosis alone or with no other significant pathology in the report by Bird et al. (1972), 51.2 % had menorrhagia, 10.9 % had metrorrhagia, 28.3 % had dysmenorrhoea, 2.2 % had postmenopausal bleeding and 23.9 % were asymptomatic [12]. Only 18.7 % had both menorrhagia and dysmenorrohea. Of the 47 patients who had adenomyosis sub-basalis, 60 % had significant menorrhagia compared to 19 (42 %) of the 45 women who had grade II or III adenomyosis. Thus the difference between the two is not statistically significant. Two of the 47 patients with Grade I disease had dysmenorrhea, compared to 14 of 33 with Grade II, and 10 of the 12 women with grade III. In terms of the degree of involvement, dysmenorrhea was present in 13.3, 26.7, and 58.8 % of women with slight, moderate, or marked disease. The difference was statistically significant. Although Bird et al. (1972) did not provide information about how symptoms or symptom severity were assessed or a definition of what constituted metrorrhagia, they concluded that adenomyosis "may cause hypermenorrohea and increasingly severe, acquired dysmenorrhea" [12].

Box Symptoms Linked to Adenomyosis

Menorrhagia	Increased
Dysmenorrhoea	Increased
Chronic pelvic pain	Increased
Dyspareunia	Limited data
Infertility	Increased
Spontaneous abortion	Increased

Owolabi and Strickler (1977) used one LPF as a cut-off point and used two random tissue blocks in routine histopathology to diagnose adenomyosis and identified adenomyosis in 161 out of 1619 (10 %) consecutive hysterectomies [85]. In 97 (60.2 %) cases, there was coexistent pathology, mostly fibroids, endometrial hyperplasia and carcinoma, and endometriosis. They reported that 65 % of the group who had adenomyosis as the sole pathology (n = 64) had abnormal bleeding and that there were also symptoms of dysmenorrhea, non-menstrual pelvic pain and/or dyspareunia. It is not possible to understand these figures further as the exact number of patients affected is not provided and the article reports individual symptoms rather than patients affected. None of this group was asymptomatic, but two of those with abnormal bleeding were postmenopausal with atrophic endometrium and their symptoms are thus unlikely to be related to adenomyosis. In addition, there were five asymptomatic women who had associated pathology (three had CIN and two had adnexal masses) and thus no symptoms attributable to the presence of adenomyosis. It remains speculative if non-menstrual pain or dyspareunia that was present in 12 and 6 % of the adenomyosis only group can in fact be attributable to adenomyosis. Although

the study concludes that the presence of adenomyosis is always associated with symptoms it should be considered that the group as a whole were symptomatic, hence the hysterectomy, but also that the study does not provide a comparison with patients who underwent hysterectomy but did not have adenomyosis. Furthermore, it is possible that a significant number of cases with adenomyosis were missed because of the sampling protocol that was followed.

Levgur et al. (2000) assessed 111 uteri all of which were below 280 g for the presence of adenomyosis [56]. When present, the lesions were classed as superficial if they were at a depth of less than 40 % of the uterine wall, intermediate if they were found at a depth between 40 and 80 % of uterine wall and were classed as deep if they were present at more than 80 % of uterine thickness. The authors reported an association between the number of foci and the depth of endometrial presence within the myometrium. The median number of foci was higher in women with dysmenorrhoea compared to those without dysmenorrhoea, but there was no difference in the number of foci in women with or without menorrhagia. In this study, superficial-depth-adenomyosis was not associated with menorrhagia or with dysmenorrhea. However, Levgur et al. (2000) excluded from the definition of adenomyosis lesions that were less than 2.5 mm below the endometrium [56]. Also excluded were 132 women who had a uterus >280 g in weight. The given reason for the exclusion was the difficulty obtaining full thickness myometrial biopsies (this group included 6 women with adenomyosis). In the 111 women included in the study, 17 had adenomyosis alone, 19 had adenomyosis and fibroids and 39 had fibroids but no adenomyosis. No information is provided on other associated pathology, or on the indications for hysterectomy. The authors state that menorrhoagia and dysmenorrhoea were associated with 'degree of myometrial depth' and that menorrhagia occurred in 36.8 % of women with deep foci and 13.3 % with intermediate foci. The corresponding figures for dysmenorrohea were 77.8 % and 12.5 % respectively. However, it is difficult to assess the significance of the findings as the figures were only provided as percentages and it is not stated whether the denominator included all women with adenomyosis or whether that was restricted to the subgroup without fibroids. Also, while the study objective was to correlate symptoms of uterine adenomyosis with histopathologic findings, the number of women with menorrhagia, dysmenorrohea or both and the indications for hysterectomy are not provided. The age ranges suggest that a large percentage were postmenopausal. Other methodological problems include the relatively small number of slides examined per patient, and that lesions were reported as number per sections examined rather than as lesion density.

Sammour et al. (2002) examined 94 uteri from women who underwent a hysterectomy and who were diagnosed with adenomyosis. Twenty five of these women also had fibroids [94]. The indications for hysterectomy are not provided, but the mean ages suggest that a good proportion may have been postmenopausal. The specimens were classified into four groups each corresponding to 25 % of myometrial thickness. Foci less than 2 mm below the endometrium were not included in the definition. The four groups were compared in relation to the symptoms of menorrhagia, dysmenorrhea, dyspareunia or pelvic pain, put no difference was found between the groups. The 'spread' of adenomyosis was assessed by examining the number of foci per slide and the number of slides varied according to the presence or absence of gross disease. The symptoms were not defined beyond the title, thus the distinction between pelvic pain and other pain symptoms is not clear. Comparisons were made based on the main complaints, yet more than one complaint was recorded per patient. The main finding of this study was a lack of correlation between symptoms and the depth of adenomyosis and that there was a significant correlation between pelvic pain or dysmenorrhea but not between menorrhagia or dyspareunia and the 'spread' of adenomyosis. These findings should be interpreted with caution because of lack of standardization in defining disease 'spread' and because the indications for the surgery is not provided. In addition, only three tissue blocks were examined per specimen

leaving the possibility of under diagnosis of adenomyosis.

Ozkan et al. (2011) reviewed the records of 1680 patients who underwent a hysterectomy [86]. Amongst this group, 98 patients were identified with adenomyosis and 106 had fibroids. Most (61 %) of the group with adenomyosis and 48 % of the group with fibroids were >50 years old. The diagnostic cut-off point and the number of tissue blocks assessed is not stated, but the overall incidence of adenomyosis in this group (12 %) was lower than reported in most other recent series. No indication is provided about associated pathology or about the number of patients with concomitant fibroids and adenomyosis. Ozkan et al. (2011) made a distinction between the frequency of dilatation and curettage – which was not statistically significantly different between the two groups – and endometrial sampling and the incidence of adenomyosis [86]. There was a higher incidence of endometrial sampling in the adenomyosis group. Therefore, Ozkan et al. (2011) argued that intrauterine sampling may trigger adenomyosis through deterioration of the endomyometrial junction [86]. But whist it is possible to speculate that deep endometrial sampling through overzealous curettage may disrupt the endomyometrial junction, modern alternative endometrial sampling techniques are designed to obtain more superficial samples of the functionalis endometrium and are unlikely to result in direct injury to deeper tissue. The more frequent resort to endometrial sampling in this group may reflect clinical practice in response to clinical presentation. In support of this is the observation that there was a statistically significant difference between the number of women undergoing hysterectomy for endometrial hyperplasia in the adenomyosis group (n = 32) and in the group with fibroids (n = 20), and a statistically significantly higher number of postmenopausal women in the adenomyosis group (n = 48) compared to the group with fibroids (n = 36). Interestingly, more than half of the patients in both groups were diagnosed with 'tubal inflammation', between 35 and 49 % had ovarian cysts and between 91 and 93 % had 'chronic cervicitis' as coexisting pathology. But there was no mention of other pathologies known to be associated with adenomyosis such as polyps or endometriosis. In their binary logistic regression Ozkan et al. (2011) identified age, menometrorrhagia and endometrial sampling as important covariant associated with adenomyosis [86]. However, the incidence of menometrorrhagia in the adenomyosis group (35 %) was lower than the incidence in the group with fibroids (43 %) and examination of menstrual bleeding was limited to a classification into 4 groups: regular, oligomenorrhea, menometrorrhagia and menopause which may be a reflection of clinical practice where menstrual bleeding patterns and/or quantity are poorly explored.

In a retrospective case control study from the United States, Taran et al. (2010) compared women undergoing hysterectomy with adenomyosis or with fibroids as the sole pathology [102]. They identified 76 cases with adenomyosis which were matched 2:1 by surgeon and by year of surgery to 152 women with fibroids only. The rationale for matching by surgeon is stated as the elimination of confounders of referral patterns and the elimination of bias based on the effect of concomitant procedures on practice style. However, no indication is provided as to what these confounders might be, or of how matching was undertaken within the practice of each surgeon beyond the given time frame (±1 year). Of the patients identified as having had a hysterectomy during the study period (n = 1871), 582 had fibroids, 133 had adenomyosis and 53 had both. This gives a relatively low overall incidence of adenomyosis of 186 (10 %), but the diagnostic criteria used for adenomyosis are not provided. The exact ethnic distribution is not provided, but it is stated that 95.1 % of both study populations were Caucasian. The indications for hysterectomy in 92.1 % of the adenomyosis group and in 94 % of the hysterectomy group were the presence of adenomyosis or leiomyomas or the presence of one or more disease-specific symptoms. The remaining hysterectomies were performed for indications of uterine prolapse, grade II cervical intraepithelial neoplasia, endometriosis and permanent sterilization. Taran et al. (2010) identified differences in the age distribution, the

group with adenomyosis being relatively younger (41 ± 6.4 years) compared to the group with fibroids (44.4 ± 4.8 years) [102]. There were no differences between the groups in the number of children, miscarriages or abortions the women had. The duration of menstrual bleeding was also similar in both groups (7.9 ± 3.6 days in the adenomyosis group and 7.9 ± 4.2 days in the group with fibroids). There was a higher incidence of depression (55.3 % vs. 26.3 %) and of the use of antidepressant in the adenomyosis group (35.5 %) compared to the group with fibroids (19.1 %). The authors put forward the suggestion of a possible aetiological link to antidepressants through an effect on raised prolactin secretion secondary to their use. There was a higher incidence of dysmenorrhea (60.5 % vs. 39.7 %), dyspareunia (17.1 % vs. 6 %) and of the use of NSAID (67.1 % vs. 42.1 %) in the adenomyosis group compared to the group with fibroids. There was also a higher proportion of women with abnormal cervical smears (30.3 % vs. 16.5 %) and of procedures for cervical dysplasia (9.2 % vs. 2 %) in the group with adenomyosis. However, the symptom complex of the two groups is necessarily affected by the indication for hysterectomy. Adenomyosis *per se* is not, and rarely are fibroids, an indication for hysterectomy in the absence of associated symptoms. As such, much of the quoted outcomes including abnormal smears, pain symptoms, abnormal bleeding, surgical intervention for cervical dysplasia, and endometriosis were not independent of the reason why surgery was performed. It is also possible that the presence of chronic pain was associated with the need for antidepressants. As mentioned above, the reliability of the outcome data of this and other retrospective studies will necessarily be affected by the thoroughness by which clinical detail was collected. This is not restricted to random errors, but there can be systematic points emanating from the way diseases are viewed. Whilst documentation in prospective research can be standardized between comparison arms, information available for retrospective research relies on available documentation which may vary from the most thorough to what individual clinicians may regard as sufficient. Thus the absence of documentation of any particular symptom can be open to various interpretations. In addition, the severity of documented symptoms and their clinical impact can vary considerably for a variety of reasons. It is also possible that the threshold for surgery may be lower in the presence of anatomical lesions such as fibroids. Taran et al. (2010) identified a history of infertility to be significantly linked to adenomyosis (14.1 % vs. 4.6 %) mainly because of associated endometriosis [102]. However, endometriosis was one of the quoted indications for surgery. Still, there was no difference between the adenomyosis and the fibroid groups in gravidity (2.7 ± 2.2 vs. 2.4 ± 1.8), parity (1.9 ± 1.4 vs. 1.9 ± 1.3), the number of spontaneous miscarriages (0.7 ± 1.4 vs. 0.4 ± 0.9) or of therapeutic abortions (0.1 ± 0.4 vs. 0.02 ± 0.2). It is notable that Taran et al. (2010) restricted their multivariable regression analysis to patients with symptoms of abnormal bleeding and/or pain which they believed to be 'disease-specific symptoms' [102]. This assumption limits the utility of this study towards addressing the basic question of whether adenomyosis is in fact relevant to these symptoms or whether it is incidental.

A different view-point was presented by Weiss et al. (2009), who reported on the findings of a study involving women who underwent a hysterectomy whilst under follow-up as part of a trial primarily concerned with the health of women during their middle years [118]. There were 3302 eligible women identified from seven centers in the US, but 200 women never completed a follow-up. At the time of recruitment women had to be aged between 42 and 52 years and to have an intact uterus. After 9 years of follow-up, 239 women underwent a hysterectomy (8 %). It was possible to obtain consent and the medical records of 137 women for the purpose of the report by Weiss et al. [118]. These were divided into two groups; one group comprised women reported as having adenomyosis on histological examination (n = 66), the other group comprised all other patients (n = 71). Case notes were obtained retrospectively and examined to compare the characteristics of both groups. The diagnosis of adenomyosis was obtained from the

clinical records based on local hospital practice, but the criteria are not defined. It is notable the while adenomyosis was present in 48 % of all samples, only one patient had adenomyosis with no associated pathology. Women with adenomyosis were more likely to have been pregnant (95 %) compared to those with no adenomyosis (85 %) and the difference was statistically significant. The two groups were not statistically significantly different in factors of ethnicity, educational attainment, income category, smoking, number of pregnancies, BMI, age at hysterectomy or uterine weight. There were no differences between the two groups with regards to their symptoms at the time of hysterectomy. The most common presentations in the adenomyosis group were problems with vaginal bleeding (n = 35), fibroids (n = 34), chronic pelvic pain (n = 15), prolapse (n = 6), stress urinary incontinence (n = 5), acute pelvic pain (n = 3). The most common presentations for the group with no adenomyosis were fibroids (n = 46), problems with vaginal bleeding (n = 43), chronic pelvic pain (n = 19), prolapse (n = 7), stress urinary incontinence (n = 6) and acute pelvic pain (n = 3). As there were no statistically significant differences in the presenting diagnosis for women with or without adenomyosis, Weiss et al. (2009) argued that despite a woman's presenting symptom or indication for hysterectomy, she is equally likely to have or not to have adenomyosis [118]. Weiss et al. (2009) identified three 'associations' with adenomyosis: fibroids, endometriosis and abnormal bleeding [118]. These were present in 51 (37 %), 4 (3 %) and 35 (27 %) of cases with adenomyosis, and in 59 (43 %), 7 (5 %), and 43 (33 %) of the group that did not have adenomyosis. The authors therefore argued that there was no association between the presence of abnormal bleeding or endometriosis and the presence or absence of adenomyosis. The authors also undertook a multivariate logistic regression analysis with fibroids, endometriosis, abnormal bleeding or chronic pain as independent variables to assess whether these conditions were associated with adenomyosis independent of other factors and found no association. Yet again, this study shares many of the weaknesses of the other retrospective studies published to date. There is no indication about how adenomyosis was defined and the symptoms prior to hysterectomy were only superficially described. All uterine bleeding is included under the heading of abnormal bleeding thus overlooking basic distinctions such as that between pre- and post- the menopause. In addition, fundamental problems become apparent when assessing the study design against the hypotheses being tested. Weiss et al. (2009) wrote that their study tested four hypotheses: (1) adenomyosis is associated with the presence of fibroids; (2) adenomyosis is more common in the presence of endometriosis; (3) adenomyosis is associated with abnormal uterine bleeding; (4) symptoms of chronic pain are more likely in uteri with fibroids if adenomyosis is present [118]. They concluded the data generated is their study did not provide evidence in support of these hypotheses. Testing the association with fibroids requires the assessment of uteri identified with adenomyosis for the presence of fibroids compared to a group without adenomyosis. The difficulty here is that fibroids were present as a reason for hysterectomy in the majority (n = 80 or 58 %) of the study population, yet it is included as an outcome measure. In relation to the second hypothesis, the research design does not inform what associated pathology exists in women with endometriosis. In addition endometriosis is not a disease of the fifth or sixth decades. Neither can this study design inform the debate about the symptoms that may be linked to adenomyosis or to uteri with both fibroids and adenomyosis. Thus a main flow in the study is the inclusion of entry criteria (fibroids, bleeding, and pain) as outcome variables in the analysis.

Vercellini et al. (1995) compared the incidence of adenomyosis in 1334 hysterectomy specimens in relation to the indication for hysterectomy. Adenomyosis was identified in 332 (24.9 %) of all cases [112]. The incidence of adenomyosis was 23.3 % in women with fibroids and menorrhagia compared to 25.7 % in women with prolapse, 21.4 % in women with ovarian cysts, 19 % in women with cervical cancer, 28.2 % in women with endometrial cancer, 28.1 % in women with ovarian cancer and in

24.7 % of women with other miscellaneous indications. The difference between the groups was not statistically significant. These findings, if confirmed, suggest a weaker link between adenomyosis and menstrual symptoms. The study by Vercellini et al. (1995) relied on routine histological assessment of removed samples, and used a cut-off point of half a LPF for adenomyosis (estimated to be about 2.5 mm) [112]. But again it has a number of significant weaknesses. For example, the study included some cases with malignancy which may undergo more rigorous sampling; in addition the analysis included fibroids and menorrhagia within the same analysis group without a clear rationale. The retrospective design did not allow adequate assessment of the menstrual history, or an assessment of dysmenorrhea or pelvic pain which are important outcome measures. No definition is provided of what is grouped under the heading 'menorrhagia', and no indication is given of the menstrual history of patients who underwent hysterectomy for other reasons. The study also suffers from incomplete ascertainment of data. For example, information about spontaneous or induced abortion is provided on 134 (40 %) and 105 (32 %) women respectively in the adenomyosis group. The corresponding figures for the group without adenomyosis were 343 (34 %), and 262 (26 %). Some of the two patient groups may have been misclassified in relation to the presence or absence of adenomyosis and the indication for surgery. It is clearly possible that adenomyosis may account for menstrual symptoms in some but not all those affected, or that some women with menstrual symptoms respond to conservative or medical treatment but undergo hysterectomies for other indications later in life.

In a subsequent study, the same group published a report on a group of women (n = 707) who underwent a hysterectomy and who had clinical information collected in advance of the operation [89]. The indications for hysterectomy were fibroids and/or menorrhagia (n = 140, 19.8 %), prolapse (n = 100, 14.1 %), ovarian cyst (n = 81, 11.5 %) or cancer (n = 14, 2 %). About a fifth of the cohort (n = 150, 21.2 %) were identified with adenomyosis using the same cut-off point as per their previous study; half a LPF or about 2.5 mm below the endometrial-myometrial junction. But no indication is provided of the incidence or the type of associated pathology in the group with adenomyosis or of the findings in the control group. Parazzini et al. (1997) reported that women who smoked were at lower risk of adenomyosis, and that the risk seemed inversely related to the number of cigarettes smoked [89]. But the age-adjusted trend in risk was of borderline statistical significance (χ^2 trend 3.57, $p = 0.06$). Adenomyosis was higher in parous women and in relation to number of children compared to nulliparous women (χ^2 trend 20.71, $p < 0.01$) and in those who had spontaneous abortions (odds ratio = 1.7; 95 % CI 1.1–2.6). There was no difference in relation to the use of oral contraception, IUCD or a history of induced abortion. Parazzini et al. (1997) stated that the risk of adenomyosis tended to be lower in more educated women but that the finding was not statistically significant [89]. The study found no difference between the two groups in the incidence of dysmenorrhea, intermenstrual pelvic pain or dyspareunia.

One of the main difficulties with the study is the challenge of controlling for confounders. There is a complex interaction between socioeconomic and demographic factors including factors such as age and parity and symptoms in decisions for hysterectomy. Much of this is now well documented. Indeed the authors attempted to control for these through the use of age and multivariate adjusted models. One analysis included controlling for age and intensity of flow in a comparison involving the menopausal status. This concluded that there was no relation between the menopausal status and the incidence of adenomyosis, although a significantly higher proportion of the group with adenomyosis were postmenopausal (48 % vs. 33.5 %, $p = 0.0016$). There was no difference in the incidence of heavy flow based on the presence (39.7 %) or the absence (35.4 %) of adenomyosis when the two groups were compared, but the difference was statistically significant in the age adjusted (odds ratio 1.7; 95 % CI 1.1–2.6) but not in the multivariate (odds ratio 1.4; 95 % CI 0.9–2.2) model. Indeed it is arguable

that age is relevant to a number of other factors included in the analysis such as a history of dilatation and curettage which used to be a very common procedure in the past but that has now been largely abandoned. Induced abortion is far more common now compared to former years. Because of the more focused effort at recoding the menstrual history, Parazzini et al. (1997) were able to perform a more detailed analysis than was possible in older literature [89]. Despite this, it is difficult to see how the information included in the analysis could be a reflection of patients' presentation. The main categories included in the study are described as: (1) categories based on the 'lifelong menstrual pattern'. Menstrual history is used to categorize women into three categories based on the length of the menstrual cycle (<25, 26–30, and >31 days); (2) categories based on duration of bleeding. Here, 'flow days per month' was used to categorize women into two groups depending on whether their loss lasted 5 or fewer days, or >5 days; (3) categories based on amount of loss. Here, 'intensity of flow' was used to categorize women into two categories as being either regular or heavy. Whilst recognizing the difficulties inherent in providing an accurate description of menstrual cycles, information collected retrospectively but prior to hysterectomy could hardly provide an accurate account of lifelong menstrual patterns. Menstrual patterns are known to change overtime including in women who have no menstrual complaints. In their conclusion, Parazzini et al. (1997) stated that no relationship was found in their study between adenomyosis and several menstrual characteristics including polymenorrhea and pain and that the relationship with heavy cycles disappeared in the analysis after adjustment for potential covariate [89]. They add that the presence of endometriosis was not associated with adenomyosis. But as explored above, the design of this study is not suited to addressing the question of whether there is a relationship between adenomyosis and the symptoms described.

Bergholt et al. (2001) reported on a series of 549 consecutive hysterectomies. The indications for hysterectomy were bleeding disorders in 50.6 % of cases, malignancy in 33.7 %, pelvic pain in 26.6 % and pelvic relaxation in 142 (25.9 %), 22.8 % had both bleeding and pain as indications for surgery [11]. The vast majority had abdominal hysterectomy and only 11 (2 %) had vaginal hysterectomy. When histopathological sections were examined, the incidence of adenomyosis varied depending on the chosen criteria. In the absence of myometrial hyperplasia, the reported incidence was 18.2 % when the cut-off point for adenomyosis was set at >1 mm, 15.8 % when using >3 mm depth as the cut-off point and was lower at 11.5 % when >5 mm was used as a cut-off point. The corresponding figures when myometrial hyperplasia was considered as a prerequisite for diagnosis were 14.3 %, 12.5 % and 10 %, respectively. It is notable that the reported incidence of adenomyosis in this cohort is low. This may be related to the particular patient profile or to local clinical practice. The authors used >3 mm cut-off point for subsequent analysis and reported that the only variable significantly associated with adenomyosis was endometrial hyperplasia, but that other factors included in the analysis (previous caesarean section, endometrial curettage, or surgical evacuation of the uterus) were not linked to adenomyosis. The study did not find a link between adenomyosis and pain-related symptoms (dyspareunia, dysmenorrhea or chronic pelvic pain), the indication for hysterectomy, age, parity or the number of myometrial samples examined [11]. The incidence of caesarean section in this cohort was low at 5.8, 18 % of women were nulliparous and only 25.5 % were <45 years old. The investigators reported that there was no association between the four indication groups: bleeding disorders, pelvic relaxation, pelvic pain and neoplasia of the genital tract and the incidence of adenomyosis. But it remains unclear what is classified under each of the given headings as the age distribution suggests that a large proportion were in fact postmenopausal. On histological examination, only 204 (37 %) had cycling endometrium and out of a total of 185 women with genital cancer, 41 (7.5 % of the whole group) had endometrial cancer. The proportion of women with bleeding disorders who had postmenopausal bleeding is unclear. There is a discrepancy between the

number of cases with pelvic relaxation (n = 142) and the number who had vaginal hysterectomies (n = 11). One interesting observation from that study is that the adjusted odds ratio for adenomyosis in those with neoplasia was 0.6 (95 % CI 0.2–1.4). Whilst it is unclear whether adenomyosis and cancer risks are independent, the figure suggests a tendency to lower adenomyosis compared to the rest of the cohort. This, however, did not reach statistical significance. Firm conclusions will inevitably be hampered because of the difficulty inherent in making a diagnosis of adenomyosis in cases with endometrial cancer because of the possible effect of cancer invasion and also in women with ovarian cancer who are often older with atrophic endometrium and where adenomyosis can be more difficult to detect. In addition, it is questionable if the chosen (>3 mm) cut off point for the diagnosis of adenomyosis is the appropriate diagnostic threshold for this group.

Benson and Sneeden (1958) reported on 2536 abdominal and 740 vaginal hysterectomies from premenopausal women aged <50 years old (age range 18–50 years) [10]. Using a cut-off point of >2 low power fields, they identified 701 cases of adenomyosis in this cohort. Uteri were grouped into four groups according to uterine weight: those >100 g were considered not enlarged; 100–150 g were classed as slightly enlarged; 150–200 g were classed as moderately enlarged; and <250 g were classed as markedly enlarged. Cases were classified by the investigators according to the likelihood that adenomyosis was the cause of symptoms. In the absence of any other lesion, the question of causation was classed a 'likely' (n = 112); in the presence of other conditions (examples given are hypertension, myomas and salipingitis), adenomyosis was considered 'contributory' (n = 344); and in cases where adenomyosis was discovered incidentally such as in cases of prolapse, adenomyosis was considered as 'no cause' (n = 245). Fibroids were present as an associated finding in 56.6 % of cases of adenomyosis, and pelvic endometriosis was present in 13.3 % of cases. In this series the investigators reported that there was no association between adenomyosis and endometrial hyperplasia. Benson and Sneeden (1958) observed that ectopic glands resemble the basalis and that they only occasionally respond to progesterone and that blood is rarely seen within these glands suggesting that bleeding in these lesions is rare [10]. The most frequent menstrual complaint in this group was menorrhagia occurring as a sole complaint in 43/112 (38.4 %) of women who had no associated pathology, and in 98/344 (28.5 %) of those who had pathology associated with adenomyosis. Menorrhagia was also the most frequent complaint amongst women who had multiple presentations. Menometrorrhagia was less common, whilst metrorrhagia was rare. This study may have adopted a higher cut-off point for the diagnosis of adenomyosis which was diagnosed as the only pathology in 3.4 % of the group, and was discovered as an incidental finding in 7.5 % of the cases. A complete list of associated pathology is not provided but it would appear that some of the provided diagnoses may not be relevant to abnormal bleeding. However the incidence of adenomyosis as an associated pathology is 10.5 %. The research methodology cannot provide convincing evidence of a relation between symptoms of adenomyosis.

Given the lack of clarity and the diagnostic difficulties linked to adenomyosis, it is hardly surprising that the incidence of adenomyosis in asymptomatic women is even less known. Lewinski (1931) reported an incidence of 54 % in 54 autopsies [57]. In one series, seven cases were reported in which mothers and daughters were affected [27]. Using MRI criteria Hauth et al. (2007) identified adenomyosis in 12 out of 100 healthy women [36]. In another study, the diagnosis of adenomyosis was suggested by MRI in 19 of 204 (9.1 %) women following term deliveries and in 16 of 104 (15.4 %) women following preterm delivery; the overall incidence was 11.3 % [41].

Fraser et al. (1986) assessed menstrual blood loss in 55 women presenting with subjective menorrhagia including 40 women with 'recognizable' pelvic disease and 15 women with confirmed coagulation disorder [30]. Menstrual blood loss was measured using the alkaline haematin method. They concluded that women with

fibroids always had large volumes of menstrual blood loss and that women with other pathologies such as endometriosis, adenomyosis and myometrial hypertrophy also often exhibited genuine menorrhagia. The study group comprised 18 women with fibroids, 5 with adenomyosis, 11 with endometriosis, 2 with pelvic inflammatory disease, 1 with endometrial polyp, one with myometrial hyperplasia and two women who had a bicornuate uterus. It is not clear how adenomyosis was diagnosed but 3 out of the 5 women with the condition had objective menorrhagia compared to 4 out of the 11 with endometriosis and 15 out of the 18 with fibroids. The measured blood loss in the adenomyosis group was 84.7 ml (SEM = 22.6) and was comparable to the group with endometriosis (83.8 ± 21.5 ml) but lower than the group with fibroids (171.7 ± 31.2 ml). Of interest, is that there was one woman (age 24 years) who was diagnosed with pure myometrial hyperplasia and who had an enlarged uterus to 14 weeks size. The finding was confirmed on full thickness biopsy. She had severed bleeding leading to anaemia.

Idiopathic myometrial hypertrophy has been described in the literature under various names including fibrosis uteri and chronic subinvolution. Uterine size is recognized to vary with age and parity, and is also increased as a result of myometrial hypertrophy in adenomyosis. The question of uterine size can be compounded in the presence of fibroids. Molitor (1971) reported on uterine weight in their series of women with adenomyosis with no fibroids, the largest of these uteri weighed 705 g [78]. However, interpreting these findings require better definition of the size of the normal uterus which is perhaps very surprisingly little reported in literature and remains uncertain. One frequently quoted study in historical literature is that by Langlois (1970) who reported that parity was the primary determinant of uterine weight in women <49 years of age [53]. He suggested the upper limit of normal to be 130 g in nulliparous women, 210 g in women with parity 1–3, and 250 g in women of parity 4 or above. Verguts et al. (2013) reviewed uterine measurements obtained by ultrasound in 5466 non-pregnant uteri with no identifiable pathology on ultrasound [114]. Those with adenomyosis or fibroids were excluded. Increased gravidity was associated with increased uterine length, anterioposterior diameter and width and also with a lower mean length-to-width ratio. Maximum uterine dimensions were recorded between age 35–40. Exact figures are not provided, but the plots suggest a range of variability. Determination of the size of the normal uterus is relevant to discussions about what constitutes myometrial hyperplasia. One other consideration in relation to myometrial hyperplasia and the presence of glands within the myometrium is whether a causative like exists between these features.

Molitor (1971) reported the finding of adenomyosis in 281 (8.8 %) of hysterectomy specimens removed over a 10 year period (Table 2.6) [78]. He stated that 71 % of these patients had symptoms that were due to or contributed to by the presence of adenomyosis; he also argued that functionally active ectopic endometrium does not always produce symptoms. In cases where there was coexistent disease, symptoms where considered to be due to either adenomyosis or the co-existent pathology depending on clinicians' evaluation of the merits of both, e.g. a small fibroid or minimal endometriosis were considered less important than bigger or more extensive diseases. In this series the most common symptom was menorrhagia, followed by metrorrhagia followed by pain and dysmenorrhoea alone and, less frequently, in combination. There were 28.8 % (n = 81) asymptomatic women in this series including 38 women with minimal involvement (confined to the inner third of the myometrium), 33 women with moderate involvement (confined to the inner two thirds of the myometrium) and 10 women with extensive disease involving whole myometrial thickness. Fibroids coexisted in 108 (38.5 %) of

Table 2.6 The size of the uterus in cases of adenomyosis

Size of the uterus (gm)	No (%)
>80	9 (5.2)
81–120	36 (20.8)
121–150	35 (20.3)
151–200	54 (31.2)
<200	39 (22.5)

Data from Molitor [78]

cases, but symptoms were attributable to adenomyosis in 116 (41.3 %) patients. The majority of these had moderate to extensive involvement. Adenomyosis was believed to have contributed to symptoms in 84 women (30 %) who had adenomyosis in association with other pathology. A greater proportion of these cases had minimal and moderate involvement (Table 2.7). The difference between the groups was statistically significant $p<0.001$ (Contingency table X^2). The most common associated pathology was uterine fibroids in 38.4 %, endometriosis in 14.2 % followed by polyps in 1.7 % of cases. The infrequent association with endometrial hyperplasia was considered as evidence of lack of association with hyperestrogenism.

Like most studies of the subject, the report by Molitor (1971) in necessarily influenced by the indications for hysterectomy, which are not provided [78]. The classification adopted in the study was based on the presence or absence of symptoms and associated pathology is interesting, but the study did not include a group where adenomyosis was the sole diagnosis. Overall 181 cases had associated pathology, but no breakdown is provided as to the distribution of these between the three analysis groups. The presenting symptoms comprised abnormal bleeding (menorrhagia or metrorrhagia) and/or pain (pain or dysmenorrhoea). No further description is provided, and there is no break-down of the symptom complex in relation to age groups.

In order to ascertain their symptoms, Kilkku et al. (1984) interviewed 212 women who were scheduled for hysterectomy for benign disorders prior to surgery [43]. All women were below age 60, 28 (13.2 %) women were later diagnosed with adenomyosis and 157 had neither adenomyosis nor endometriosis. The authors found no difference between the two groups in the presenting symptoms including: urinary symptoms, pain and duration of menstrual bleeding. The final diagnosis in the control group was uterine fibroids (n = 131), dysfunctional uterine bleeding (n = 10), endometrial hyperplasia (n = 8), ovarian cyst (n = 4), endometrial polyp (n = 2) and chronic cervicitis (n = 2). But no indication is provided of the presence or type of associated pathology in the adenomyosis group. Kilkku et al. (1984) concluded that there is no symptom profile that is specific to adenomyosis [43]. But no detail is provided about the reasons for the hysterectomy or how patients were selected or of the criteria used for to diagnose adenomyosis.

Vavilis et al. (1997) set to estimate the frequency and risk factors for adenomyosis by studying the clinical records of 594 women undergoing hysterectomy [110]. They identified adenomyosis in 116 (19.4 %) of the cases. Adenomyosis was diagnosed by the presence of glands and stroma one or more low power field below the endometrial myometrial junction. The indication for surgery were fibroids (n = 308), genital prolapse (n = 43), benign ovarian tumors (n = 62), endometrial hyperplasia (n = 44) cervical cancer (n = 11) endometrial cancer (n = 62), ovarian cancer (n = 13) and three cases had leiomyosarcoma (Table 2.8). The incidence of adenomyosis was 20.4 % in the group with fibroids, compared to 25.55 % in the group with prolapse, but there was not statistically significantly different in the incidence of adenomyosis between the groups. Examining the figures provided demonstrates that 63/116 (54.3 %) of the group with adenomyosis are among the group where fibroids is provided as the indication for

Table 2.7 The number and percentage of symptomatic women who had adenomyosis in relation to the depth of adenomyosis within the myometrium compared to asymptomatic women

The depth of endometrium present within the myometrium	Symptomatic		Asymptomatic
	Adenomyosis sole or main pathology (n = 116)	Adenomyosis contributes to symptoms (n = 84)	(n = 81)
Up to the inner third	6 (5.2 %)	24 (28.6 %)	38 (13 %)
Up to the inner two thirds	62 (53.4 %)	41 (48.8 %)	33 (40.7 %)
All thickness	48 (41.3 %)	19 (22.6 %)	10 (12.3 %)

Data from Molitor [78]

Table 2.8 The indications for hysterectomy in the group with and without adenomyosis

Indication for hysterectomy	Adenomyosis	No adenomyosis
1. Fibroids	63	245
2. Prolpase	11	32
3. Benign ovarian cysts	11	51
4. Cervical cancer	2	9
5. Ovarian cancer	13	48
6. Leiomyosarcoma	0	3
All 2–6	37	143
7. Endometrial hyperplasia	6	38
8. Endometrial cancer	10	52
All 2–8	53	233

There was no statistically significant difference in the incidence of adenomyosis when the group with fibroids was compared to group 2–6 ($p=1$), or to groups 2–8 ($p=0.6$). Fisher's exact test, from Vavilis et al. (1996, [110])

hysterectomy. The list of associated pathology in the group with adenomyosis is not provided, but as mentioned above, more than half had fibroids and 25 (21.5 %) women had cancer. It is notable that the traditional indications for hysterectomy e.g. abnormal uterine bleeding and/or pain were absent from the list of surgical indications although it is possible that these indications were subsumed under the title 'fibroids' which is itself more likely to indicate hysterectomy if symptomatic. Comparing the incidence of adenomyosis in the group with fibroids as an indication for hysterectomy against those whose indication is unlikely to be linked to adenomyosis (genital prolapse, benign ovarian tumors, cervical cancer, ovarian cancer, leiomyosarcoma) suggests that adenomyosis may not be linked to symptoms. However, firm conclusions cannot be drawn because of the uncertainty as to the way the indications for surgery were classified and the lack of clarity as to whether additional or overlapping symptoms existed.

In a study from Pakistan, Shaikh and Khan (1990) published a retrospective review of 419 hysterectomy specimens and identified 237 (56.5 %) cases with adenomyosis [97]. The apparent high percentage was noted despite the apparent use of the strict criteria for diagnosis based on the presence of endometrial glands and stroma within at least a third or a fourth of the myometrium, and the use of routine histological sections (at least 3 per specimen). They argued that the high percentage (97.9 %) of parous women and women in the fourth and fifth decade of life (82.8 %) amongst the subset with adenomyosis was significant. The incidence of adenomyosis was at least twice as high in parous compared to nulliparous women. However, it must be kept in mind that nulliparous women were a small minority in this study ($n=18$, 4.3 %) and that the indications for hysterectomy are likely to be different in nulliparous women. The authors provide a list of associated pathology in both groups. They state that there were 54 (22.7 %) cases with adenomyosis but no associated pathology and 48 women (26.3 %) in the group without adenomyosis who did not have any associated pathology. The most common associated findings in women with adenomyosis were fibroids which were present in 32.9 % of cases, cervicitis which was present in 31.6 % of case and endometrial hyperplasia which was present in 12.2 % of cases ($n=29$), but endometrial hyperplasia was the only statistically significant association. The list of "associated pathology" of which more than one may be present in any specimen include cervicitis which is currently seen as an insignificant finding and, curiously, uterovaginal prolapase. Whilst it is not possible to assess the significance of the associated pathologies, it is to be considered that some such as endometrial hyperplasia may not have been independent from the indications for hysterectomy. Indeed the reasons why these women underwent a hysterectomy are not provided or considered and there is no exploration of any of the symptoms traditionally linked

to adenomyosis or fibroids such as abnormal bleeding and pain.

Naftalin et al. (2014) analyzed their series which included women attending a gynecology clinic, the majority of whom had a pelvic ultrasound. In this analysis, they reported on the relation of ultrasound diagnosed adenomyosis and menorrhagia [80]. The study population was women before the menopause (n = 892) who were attending the clinic for a variety of indications including menorrhagia (16.7 %), menorrhagia and dysmenorrhoea (4.3 %), intermenstrual or postcoital bleeding (9.5 %), mild or moderate oligomenorrhoea (9.2 %), pelvic pain (18.1), dysmenorrhoea (2.5 %), dyspareunia (1.7 %), infertility (16.1 %), recurrent miscarriage (1.3 %) and other indications in 20.1 %. Menorrhagia was diagnose subjectively (binary response: yes or no) for all participants and using pictoral charts [38] for the month following the ultrasound assessment. The response rate for those who were given menstrual charts was 57.5 %. Using multivariable analysis, there was no significant association between adenomyosis and menorrhagia when adenomyosis was assessed as a binary outcome. But when severity of adenomyosis was assessed by counting the number of morphological features of adenomyosis as seen by ultrasound in each woman, there was a significant (22 %) increase in menstrual loss for each additional feature of adenomyosis [OR 1.21 (95 % CI: 1.04–1.40)]

The study by Naftalin et al. [80] attempted to assess the association between menorrhagia and adenomyosis in women who are not undergoing a hysterectomy. However, the findings need to be interpreted with caution. First, the definition of menorrhagia in the study is not provided beyond either a subjective binary response or using the semi-quantitative charts but with no attempt at standardisation or to consider bleeding patterns. There was only a moderate level of agreement between the methods of assessment. It is also to be considered that the level of agreement between ultrasound and histology in the diagnosis of adenomyosis in this group was only moderate. Future studies should consider the impact of study population, multiple pathologies and the possibility that adenomyosis can contribute to the other presentations in the study population including pain and infertility.

Table 2.9 The basic classification of the causes of abnormal uterine bleeding (PALM-COIEN) as proposed by FIGO [79]

P	Polyp
A	Adenomyosis
L	Leiomyoma (submucosal or other)
M	Malignancy & hyperplasia
C	Coagulopathys
O	Ovulatory dysfunction
E	Endometrial
I	Iatrogenic
N	Not yet classified

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Recently, FIGO proposed a classification system (PALM-COEIN) for the causes of abnormal uterine bleeding [79]. The expert group, whilst acknowledging that the relationship between adenomyosis and abnormal uterine bleeding (AUB) is unclear, included a category for adenomyosis in the classification (AUB-A) (Table 2.9). The FIGO protocol included adenomyosis in the classification because of the existence of sonographic and MRI based diagnostic criteria. The minimal requirement being the performance of ultrasound to include the minimum sonographic criteria needed for diagnosis as well as ultrasound based distinction between diffuse and focal (or multifocal) disease. The group proposed the inclusion of a metric indicating the volume or extent of the disease. Munro et al. (2011) point out that the investigation into the aetiology of abnormal uterine bleeding (AUB) has been hampered by confusing and inconsistent use of nomenclature and by the lack of standardization for investigation and categorization of the various potential etiologies [79]. They also add that these deficiencies have hampered research and comparisons between studies and metanalysis to the point that some have been made counterproductive because of inaccurate conclusions. As such the FIGO classification can be seen as a step in the right direction, but its utility for addressing the difficulties highlighted is questionable. The difficulty for research addressing

AUB is threefold: (1) there is the question of defining normality and deviations there from, (2) the need for a classification of abnormal bleeding that has relevance to aetiology, (3) the need to explore the link between abnormal bleeding with possible aetiology and pathophysiolgy.

The classification adopted by the FIGO provides for nine main categories arranged according to the acronym PALM-COEIN: polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified. As such, the classification does not address the inconsistent use of nomenclature referred to in the article by Munro et al. (2011), but leaves the definition of what is abnormal open to interpretation with no attempt to introduce the desired consistency [79]. The proposed linkage of 'abnormal' bleeding with the identified or assumed aetiological factors does not take into account the significant uncertainties in current knowledge. It is interesting to note that older publications have attempted to classify bleeding abnormalities according to severity and pattern. Molitor (1971) for example described bleeding in terms of menorrhagia, metrorrhagia or menorrhagia and metrorrhagia [78] and Graves WK (1971) [33] in his discussion of the same article suggested the possibility of a link between adenomyosis and the occurrence of postmenstrual abnormal scant and dark flow and intermenstrual bleeding. These contrast with more recent articles detailed in this chapter which have not made distinctions based on patterns of bleeding and which have often included postmenopausal bleeding and bleeding related to endometrial malignancy in the same analysis.

Lessons from Endometrial Ablation

McCausland and McCausland (1996) studies 50 women who underwent rollerball endometrial ablation for heavy menstrual bleeding that did not respond to medical treatment including cyclical progestogen [70]. A 5 mm biopsy was obtained prior to ablation and assessed histologically for the presence and depth of adenomyosis. They reported that the depth of myometrial involvement correlated with the severity of menorrhagia and also with the likelihood of ablation failure. The majority of patients with no or with minimal endometrial presence within the myometrium had good outcome following rollaball ablation which is assumed to destroy 2–3 mm of the superficial myometrium. McCausland and McCausland (1996) thus proposed the plausible hypothesis that bleeding from adenomyosis is not only due to the additional endometrial glands present but also from dysfunctional hypertrophic smooth muscle that lacks the physiological contractility required for the control of bleeding [70]. Indeed Benson and Sneeden (1958) quoted Meyer R [75] as the first to suggest altered uterine contractility as a mechanism of bleeding in adenomyosis [10].

In an earlier publication McCausland (1992) studied the depth of endometrial presence within the myometrium using hysteroscopic biopsy in 50 women [69]. All patients had no intrauterine lesions (fibroids or polyps) and had menorrhagia that did not respond to non-steroidal anti-inflammatory. The study group either had ovulatory cycles as proven by serum progesterone measurements or by luteal phase biopsies or had anovulatory cycles that did not respond to cyclical progestogens. Biopsies were also obtained from a control group who had no menstrual problems. The study involved assessment of menstrual blood loss by quantification of clot size which correlated with the frequency of change of pads and tampons. Clot size was classed as: dime-sized or + (1.5 cm); quarter size or ++ (2.5 cm); 50-cent piece size or +++ (3 cm); and silver dollar egg or fist size or ++++ (4 cm). Myometrial biopsy was obtained from the posterior wall in all cases and an additional sample was taken from the anterior wall in 15 cases for comparison. The depth of adenomyosis was taken from the deepest point below the endometrial myometrial junction. The average depth of adenomyosis in the posterior wall was 0.8 mm and was almost always greater than the depth in the anterior wall (mean 0.46 mm). The average posterior wall adenomyosis in women with menorrhagia was nearly twice the average depth in the control group, and >1 mm depth of adenomyosis was associated with

very heavy (+++ or ++++) bleeding. McCausland (1992) found a statistically significant correlation between the depth of adenomyosis and the severity of menorrhagia ($p=0.05$) and reported that a woman with a grossly normal endometrial cavity who passed clots the size of a quarter or larger is 2.9 times as likely to have adenomyosis >1 mm deep compared to a woman who has not passed such large clots [69]. However, using 1 mm as cut-off point for the diagnosis of adenomyosis would identify the condition in 14/30 of the control group who had no menstrual problems compared to 33/50 of those with menorrhagia. The difference between the two groups with regards to the incidence of adenomyosis is not statistically significant ($p=0.1$, χ^2 test). The tables provided show that there were 18 patients with depth of endometrial presence within the myometrium at ≥2 mm in the menorrhagia group, but none in the control group. Interestingly, 14 women who had gross polyps and 8 with submucous fibroids were identified with deep adenomyosis following removal of the polyps and fibroids. In these two groups, the amount of bleeding did not correlate with the depth of adenomyosis, suggesting that the intra-cavity lesions were the primary cause of the symptoms. The incidence of significant adenomyosis in the group who had a normal cavity was 33 out of 50 (66 %). Based on the distinction between normal and abnormal bleeding, McCausland (1992) went on to propose 1 mm as a cut-off point for the diagnosis of adenomyosis [69]. It is also interesting to note that the depth of endometrial presence within the myometrium in the control group that had normal periods was also deeper in the posterior (mean 0.8 mm) compared to the anterior wall (0.46 mm). McCausland (1992) recognized that clot size is perhaps only a gross measurement of the amount of bleeding, but the study represents an advance in as far as there was an attempt to quantify menstrual blood loss and to give an account of bleeding pattern [69]. The finding of presence at greater depth in the posterior wall compared to the anterior wall is interesting, but the finding was also repeated in the control group, which suggests a possibility of a 'normal' anatomical variation. McCausland (1992) argued that this is in line with previous research that shows the posterior wall to be most affected in diffuse adenomyosis and that a single myometrial biopsy of the posterior wall in both diagnostic and representative of the area most severely involved in adenomyosis [69]. However, studies that included hysterectomy specimens have demonstrated that adenomyosis can be present solely in the anterior wall in a proportion of case.

McCausland and McCausland (1998) argued that it required 1 mm of endometrial presence within the myometrium together with abnormal smooth muscle hypertrophy to cause menorrhagia [71]. Asymptomatic patients had either no glandular presence or up to an average of 0.8 mm. It is to be noted that smooth muscle affection is always deeper than the depth of gland presence in affected women. McCausland and McCausland (1998) argued that histopathology should report on the actual depth of glandular presence rather than attempt a dichotomous diagnosis into normal and adenomyosis using arbitrary cut-off points [71].

Adenomyosis Response to Steroids

It is interesting to note that correlations between the depth or extent of adenomyosis and symptoms assume a relation between symptoms and the phenomena of glands present within the myometrium but seem to miss the possibility of myometrial disease or role in the genesis of symptoms. A frequently overlooked feature of adenomyosis is that it does not uniformly respond to progestogens. This feature has been recognized for a long time [79]. In the study by Molitor (1971), there was agreement between eutopic and ectopic endometrium in 83 % of instances of pseudodecidualisation in response to exogenous progestins and in 44 % of cases of hyperplasia [79]. In addition, the response to progestogens may not always be uniform. It has been suggested that symptoms may be absent in women whose adenomyosis does not respond to steroids [31]. However, in the series by Molitor (1971), some of the cases that exhibited progestogenic response in adenomyosis were asymptomatic [78]. On the

other hand, there is variation in the reported observation of secretory changes in adenomyosis. Novak and de Lima (1948) found no evidence of secretory change in the ectopic endometrium in 99 cases of adenomyosis [83]. Azziz (1989) reviewed available literature and reported that 30–50 % of adenomyotic foci are able to respond to progesterone, but that endometrial dating may be somewhat delayed with respect to the overlying endometrium [7]. There may also be variation in response depending on the depth of adenomyotic foci. Sandberg and Cohn (1962) reported that the response of ectopic endometrium in caesarean hysterectomy specimens (there were 27 uteri with adenomyosis out of 151 uteri examined) varies regionally as deeper glands showed progestogenic response in about a quarter (26 %) of the samples in contrast to adenomyotic glands nearer to the endometrium (at a depth of 1–2 low power fields) which behaved in a manner similar to the basal layer of the endometrium in the vast majority (89 %) of cases [95]. There can also be a patchy response within the same specimen. Azziz (1986) was able to identify 72 cases published in the literature of adenomyosis identified in gravid uteri removed by caesarean hysterectomy [6]. Of these 29 were associated with obstetric complications, the rest were identified in specimen removed electively such as at the time of caesarean sterilization. He concluded that adenomyosis is rarely associated with obstetrical surgical complications, but the cut-off point for defining adenomyosis in the hypertrophied gravid uterus is unclear.

Adenomyosis and Parity

Adenomyosis diagnosed at hysterectomy has traditionally been linked to multiparity [112, 113], pregnancy termination and to uterine curettage, especially after pregnancy. More recent attention has been paid to possible link between adenomyosis and infertility possibly through adverse endometrial factors interfering with implantation or through effects on junctional zone function that results in impairing sperm transport and fertilization [16].

The root of the link between adenomyosis and parity is longstanding but perhaps less firmly established than is often implied. Bird et al. (1972) reported on the parity distribution of women identified with adenomyosis amongst 200 women who underwent hysterectomy [12]. The average parity of the 123 women with adenomyosis was 3.2 compared to 2.5 for all women undergoing hysterectomy. Also, 89.5 % of women with adenomyosis were parous. Of the women with adenomyosis 123 (89.5 %) were parous and 13 (10.5 %) were nulliparous. Bird et al. (1972) concluded that these findings support existing reports which on average indicated that 80 % of women with adenomyosis have borne at least one child [12]. Molitor (1971) identified adenomyosis in 281 uteri out of 3207 hysterectomies [78]. Out of these 281, 263 (93.6 %) were parous and 18 (6.4 %) were nulliparous. Although the parity distribution of the whole group in the study by Molitor [78] is not provided, the author considered the fact that the overwhelming proportion of women with adenomyosis was parous, as evidence to support the notion that childbearing has a role in the aetiology of adenomyosis. Molitor (1971) added that there was no correlation between the number of pregnancies and the degree of uterine involvement in adenomyosis [78]. Thus he predicted that the trend to smaller family sizes is unlikely to reflect in a lower incidence of adenomyosis. In another study, adenomyosis was diagnosed in 5 out of 18 nulliparous women (27.7 %) compared to 150/264 (56.8 %) of women with parity range 1–4, and in 82/137 (59.8 %) of women with parity >4 [97]. The difference between parous and nulliparous women was statistically significant. However, the same study also reported that there were no cases of adenomyosis in the small group of women (n = 7) who were <29 years old, and that the prevalence in the group aged 30–39 was 30.6 % compared to 70.4 % in the 40–49 age group and 74.4 % in the 50–59 age group. Thus the study did not take into consideration the possible interaction between age and parity or the possible difference in the indication of hysterectomy between the nulliparous and multiparous women. This point is particularly important given

that the overwhelming majority (97.9 %) of the whole group were parous.

In another retrospective study involving 1334 women who underwent a hysterectomy, adenomyosis was identified in 332 patients (24.9 %) using one-half of a low-power field below the endometrial-myometrial junction as a diagnostic cut off [112]. The authors reported that in comparison with nulliparous women, the odds ratio (OR) for adenomyosis was higher in women who had one (OR 1.3) or ≥ two (OR 1.5) births ($p < 0.05$) [112]. But the incidence of adenomyosis reported in this study for nulliparous women 25/113 (22.1 %) was not significantly different compared to women who had one (80/322, 24.8 %) or more than one (188/686, 27.4 %) children. The study reported that no relation was found between age at surgery, age at menarche, indications for surgery, menopausal status at intervention and the presence of endometriosis. But there were 147 women in the adenomyosis group who were <50 years old and 184 women >50 years old compared to 508 women and 488 women in the two age brackets respectively who did not have adenomyosis. This indicates a significant difference ($p = 0.038$) between the two groups. It is notable that in contrast to the study by Vavilis et al. (1997) discussed below, the incidence of adenomyosis in the group aged ≥60 years old (22.7 %) was similar to the incidence in the group <50 (22.7 %), but was statistically significantly lower compared to the 50–59 age group ($p = 0.006$) where the incidence of adenomyosis was 32.1 % [110]. Perhaps a clearer link between adenomyosis and parity is provided in the follow-up study by the same group who reported that after adjusting for age, the OR for adenomyosis in primiparous women was 1.8 (95 % CI = 0.9–3.4), and for multiparous women the odds ratio was 3.1 (95 % CI = 1.7–5.5) compared to nulliparous women [89].

In the study by Vavilis et al. (1997), adenomyosis was identified in 116 out of 594 uteri (19.5 %) removed at hysterectomy [110]. Adenomyosis was present in 61/295 (20.6 %) of women <50 years old, 39/136 (28.7 %) of women aged between 50 and 59 years, and in 16/163 (9.8 %) of women ≥60 years old. The difference between the latter group and the other two groups reached statistical significance. There was also a higher incidence of adenomyosis in parous (116/554, 20.9 %) compared to nulliparous (2/40, 5 %) women and the difference was statistically significant ($p = 0.015$). But no analysis is provided that takes account of confounding factors in relation to parity such as age and presenting symptoms. There is a possibility that the low incidence of adenomyosis in older women, may indicate that it contributes to symptoms in younger women leading to early hysterectomy. However, this finding has not been consistently demonstrated.

Bergholt et al. (2001) performed a retrospective study involving 549 women who underwent a hysterectomy [11]. Factors that may be linked to adenomyosis were introduced into a multiple regression model. They reported that the presence of endometrial hyperplasia was the only factor significantly associated with adenomyosis. They did not find an association with age or with parity. In this study, the adjusted OR (95 % CI) for adenomyosis in primiparous women was 1.2 (95 % CI: 0.5–2.8) and for multiparous women was 1 (95 % CI: 0.5–2.0). In comparison to the <45 age group, women between 45 and 54 years old had an adjusted OR (95 % CI) of 1.2 (95 % CI: 0.6–2.4), and those >54 had an adjusted OR of 2.4 (95 % CI: 1.0–5.8).

Panganamamula et al. (2004) reported the findings from a study involving 873 women who underwent hysterectomy for benign conditions [88]. Of these, 412 (47.1 %) were identified with adenomyosis. They reported a statistically significantly higher gravidity (mean 3.5 ± SD = 1.8) and parity (mean 2.7 ± SD = 1.6) in the group with adenomyosis compared to those without adenomyosis (mean gravidity 3.06 ± SD = 1.92, mean parity 2.4 ± SD = 1.5). But there was no difference in age between the group with (mean 47.1 ± SD = 10.7) and without (mean 47.3 ± SD = 11.3) adenomyosis. But no comparison is provided between parous and nulliparous women. In a later study, Panganamamula et al. (2004) identified adenomyosis in 116/594 (19.5 %) uterine hysterectomy specimens; comprising 61/295 (20.6 %) women <50 years old;

39/136 (28.7 %) women aged 50–59 years old; and in 16/163 (9.8 %) women ≥60 years old [88]. The difference between the latter group and the other two was statistically significant. Adenomyosis was more common in parous (116/554, 20.9 %), compared to nulliparous (2/40, 5 %) women. However, the analysis provided does not account for confounding factors in relation to parity, such as age and presenting symptoms.

In the prospective cohort California Teachers Study of female teachers and school administrators, a total of 133,479 women, ranging in age from 22 to over 90 years, completed a self-administered, baseline questionnaire in 1995–1996 [103]. Amongst these 88,273 women were eligible to be included in analysis related to adenomyosis. Members of the cohort provided health related information including the diagnosis of endometriosis, reproductive history, use of hormones, physical activity, diet and alcohol intake, smoking history, and family history of health conditions. Participants were followed up longitudinally and an eligible cohort member was defined as having adenomyosis if the diagnosis was coded within the first three hospital discharge codes of admitted women between the date they joined the cohort and the end of the year 2003. There were 961 women with surgically confirmed adenomyosis. Templeman et al. (2008) reported a higher incidence of adenomyosis in parous (791/56,502, 1.4 %) compared to nulligravid women (116/16,947, 0.68 %) or compared to women who had previous pregnancies but no term pregnancies (50/5015, 0.99 %) [103]. The very low rate of diagnosis of adenomyosis is a factor of the cohort design as only a small proportion of women undergoing surveillance would be expected to undergo a hysterectomy which was the mainstay of histological diagnosis in 96 % of confirmed cases of adenomyosis. In addition, the authors excluded 419 cases from the analysis because adenomyosis was not classed in the top three on the hospital discharge codes. The comparative group comprised 79,329 women. Whilst these findings may indicate a link with parity, it should be considered that adenomyosis was not ruled out in the control group, and the interplay between symptoms and parity and the desire for children is an important driver that influences the choice of hysterectomy as a treatment.

In a retrospective multinominal regression analysis of the risk factors associated with adenomyosis alone or with a combination of adenomyosis and fibroids that involved 206 women, Jean-Baptiste et al. (2013) reported that dysmenorrhea was the only variable significantly associated with adenomyosis (OR 3.34; 95 % CI, 1.14–9.80) [39]. Variables significantly associated with combined adenomyosis and fibroids were age (OR 1.08; 95 % CI, 1.01–1.15), black ethnicity (OR 2.72; 95 % CI, 1.11–6.68) and parity (OR, 1.44; 95 % CI, 1.08–1.92). However, women included in the study either had fibroids only (n = 148), adenomyosis only (n = 21) or a combination of adenomyosis and fibroids (n = 37).

Adenomyosis and Infertility

Since the introduction of non-invasive imaging for the diagnosis of adenomyosis interest was renewed in the hypothesis that there is a strong association between endometriosis and adenomyosis and that coexisting adenomyosis can play a role in the infertility of women with endometriosis and vice versa. Kunz et al. (2005) performed MRI in women with (n = 160) and without (n = 67) endometriosis, taking into account age, disease stage and partners' sperm count [50]. Adenomyosis was present in 90 % of the subset of women with endometriosis who were <36 years and who had fertile partners. It is notable that 81/160 of this group had minimal or mild endometriosis and 79/160 had moderate or severe disease. The prevalence of adenomyosis in the control group which had infertility but no endometriosis was 19/67 (28 %). The authors concluded that adenomyosis causes infertility. The assumed mechanism was adverse effects that impair sperm transport. In the same cohort Kunz et al. (2005) reported on a secondary analysis of 227 patients with infertility and endometriosis [51]. They demonstrated that junctional zone

thickness in the group with endometriosis was higher compared to the control group in all four age groups (17–24, 25–29, 30–34, and >34). The difference was statistically significant only for the two latter groups. The number of women in each age group with junctional zone thickness consistent with adenomyosis is not provided, but the authors proposed that the process of adenomyosis development had already commenced in the third decade of life and that it progressed steadily during the fourth decade in women with endometriosis. Women without endometriosis showed almost no signs of adenomyosis up to the age of 34 years. Kunz et al. (2005, 2007) have not provided in their articles a breakdown of the incidence of the disease taking the 12, 8–12, <8 cut off points and there is a different age based analysis in the two papers [50, 51]. This brings-up the possibility of an alternative explanation for their observation on the differences in junctional zone thickness between the different age groups. Their findings remain consistent with the more widely held view that the incidence of adenomyosis increases with age. This will necessarily make the average thickness higher in older women.

Using MRI and hysterosalpingo-scintigraphy (HSSG), Kissler et al. (2006) linked endometriosis to hyperperistaltic and dysperistaltic utero-tubal transport. They performed HSSG and MRI on 41 infertile women aged 25–39, who had minimal or mild endometriosis (n = 28) or moderate or severe endometriosis (n = 13) [45]. All women had patent fallopian tubes. Adenomyosis was diagnosed in 29/41 (71 %) of participants using a cut-off JZ thickness of 8 mm and was diagnosed in 6 cases who had JZ thickness of <7 mm but who had localised JZ thickness, poor definition of borders or high signal-intensity foci. Taking all these together, the authors considered adenomyosis to be present in 85 % of cases. Based on MRI findings patients were classified into three groups: (1) Group (I), no adenomyosis (n = 6); (2) Group (II), focal adenomyosis (n = 24); (3) Group (III), diffuse adenomyosis (n = 11). Ipsi-lateral (to the dominant follicle) or bilateral tubal transport on HSSG was reported in 4 (67 %) participants in Group (I), compared to 10 (42 %) in Group (II), and 1 (9 %) in Group (III). The proportion of patients who had contra-lateral transport was 33 %, 33 % and 18 % respectively, while the proportion that showed no transport in the three groups was 0 %, 25 %, and 73 % respectively. Interestingly the failure in transport and contra-lateral transport were not significantly dependent on an increase of JZ thickness. The authors considered both endometriosis and adenomyosis to impact utero-tubal transport, but also that much of the reduced fertility in subjects with patent tubes was related to the presence of adenomyosis. However, the study should be interpreted with caution. First, the criteria on which adenomyosis was made is not clear. There was no statistically significant difference in JZ thickness between the group with diffuse (11.2 ± 2.7 mm) and the group with focal (10.3 ± 3.1 mm) adenomyosis compared to 3.2 ± 1.2 mm for the group without adenomyosis. Second, the reason for the very high incidence of adenomyosis amongst participants is unclear. Thirdly – and perhaps most importantly – because of the use of the controversial technique of HSSG as a test for tubal function. Habiba (1994) argued that many of the images produced by HSSG are artefacts [34]. Other authors have demonstrated the inconsistency of radioactive-labelled particle transport [62, 63, 117].

An alternative hypothesis was proposed by Tocci et al. (2008) who argued that because of the different epidemiological features of thickening of the JZ as identified using MRI on the one hand and histologically proven endometriosis on the other, that MRI should be regards as indicative of a "subendometrial myometrial unit disruption disease", as a distinct entity from adenomyosis [105]. Whilst this view point is interesting, it remains highly likely that the difference in epidemiological features reported is a factor of the method of diagnosis. Thus features linked to histological diagnosis are necessarily linked to the older age group who undergo hysterectomy and in whom MRI is often unnecessary, whilst MRI features are largely derived from cohorts of younger women seeking fertility investigation and treatment [51, 121]. It is to be noted that the reason for the distinct echogenic features attributable to adenomyosis on MRI is

unclear. Distinct zonation has been observed in vitro, suggesting that the features may not be linked to differential blood flow. Studies have demonstrated differences in cell density, total nuclear area and in extracellular matrix components, but in contrast to the clear zonation seen on some MRI images, the transition from the innermost to the outermost myometrial layer was shown to be gradual [73].

The effect of adenomyosis on fertility has been assessed through examining its prevalence in infertility clinics or its impact on outcomes of assisted conception. In the study by Kunz et al. (2005) referred to above, adenomyosis was identified in 79 % of cases with endometriosis, rising to 90 % in the subgroup of women <36 years old who had a fertile partner compared to 19/67 (28 %) in the infertile group who did not have endometriosis [50]. Martinez-Conejero et al. (2011) attempted to examine the relation between adenomyosis and implantation by comparing the outcome of donor IVF cycles in their infertility clinic in relation to the presence or absence of adenomyosis and endometriosis [66]. They compared three groups. The first was a group in whom adenomyosis was diagnosed based on ultrasound (n = 152) and who received 328 ovum donation cycles. These included 23 women who also had endometriosis. The second group comprised women with ovarian endometriosis but no adenomyosis (n = 144) and who received 242 ovum donation cycles. The third control group comprised women who had no visual pathology (n = 147) and who received 331 ovum donation cycles. The study reported that implantation rates in ovum donation cycles did not differ among the three groups. There were 88 term pregnancies in the adenomyosis group, 92 term pregnancies in the endometriosis group and 123 term pregnancies in the control group. The corresponding number of miscarriages in the three groups was 43, 15, and 24. Martinez-Conejero et al. (2011) also performed an RNA micro array comparison using endometrial samples obtained 7 days after the LH surge from women with adenomyosis and a control group of health young women with regular cycles and no uterine or endocrine anomalies and who had proven fertility [66]. They reported that there were no differences between the adenomyosis and the control group when comparing the genes known to be relevant to the window of implantation. However, there was a statistically significant higher incidence of miscarriage in the group with adenomyosis compared to the group with endometriosis and to the control group. The reason for the higher clinical miscarriage rate in the group with adenomyosis is unknown. The authors' interpretation is that adenomyosis does not impair implantation but may affect the function of the junctional zone leading to miscarriage. However, it is possible that implantation defects do contribute to increased pregnancy loss [93], or that the mechanisms active in this process involve factors affecting embryo selection [48]. On the other hand, implantation rates in the group with adenomyosis was marginally lower compared to the group with endometriosis, a condition associated with impaired endometrial receptivity [55]. The term pregnancy rate for the control group in the study by Martinez-Conejero et al. [66]. Martinez-Conejero et al. [66] is remarkably high at 84 %, but the indications for donor oocyte are not clear [115]. Martinez-Conejero et al. (2011) did not identify differences in implantation relevant genes in adenomyosis, but in common with other studies in the field, they did not control for the various down-regulation protocols [66].

In a retrospective study involving 74 patients Mijatovic et al. (2010) reported no significant differences when comparing outcomes of women with and without adenomyosis who were undergoing in-vitro fertilisation (IVF) or intracytoplasmic sperm injection cycles (ICSI) [76]. But all women received long-term GnRH-agonist pretreatment and the possibility should be considered that these drugs may have modified the effect of adenomyosis. Mijatovic et al. (2010) also reported the outcome of 74 infertile women with endometriosis who underwent IVF/ICSI [76]. There was a high (90.4 %) proportion with revised American Society for Reproductive Medicine (rASRM) stage III-IV disease. Based on ultrasound criteria adenomyosis was diagnosed in 20/74 of cases. All women received

GnRH-agonist prior to IVF-ICSI. The implantation rate in the adenomyosis group (31 %) was comparable to the rate in the group without adenomyosis (28.2 %). The authors reported that there were no significant differences in any outcomes between women with (n = 20) and without (n = 54) adenomyosis. In contrast to this, in the study by Thalluri and Tremellen (2012) women with ultrasound diagnosed adenomyosis (n = 38) had a statistically significant lower clinical pregnancy rate compared to controls (n = 175) [104]. All women in the study were undergoing IVF and adenomyosis was diagnosed or excluded based on ultrasound. The study reported a significantly lower clinical pregnancy rate in the adenomyosis group (23.6 % vs. 44.6 %). The lower clinical pregnancy rate in the adenomyosis group was maintained after adjustment for maternal age (OR = 0.408, CI = 0.181–0.922, p = 0.031) and when adjusting for the duration of infertility (OR = 0.417, CI = 0.175–0.989, p = 0.047). The same research group linked the outcomes in IVF cycles to differences in stromal leukocyte population, but again they did not control for exogenous steroids [106].

In agreement with the findings of Martínez-Conejero et al. (2011) of a higher miscarriage rate in women with adenomyosis [66]. Chiang et al. (1999) reported a significantly higher miscarriage rate (66.7 % vs. 21 %, p <0.04) in a small group (n = 19) of women who had ultrasound features suggestive of adenomyosis who were undergoing IVF when compared to a control group (n = 144) [18]. Both groups had comparable clinical pregnancy rates of 31.6 % and 26.4 % respectively. Maubon et al. (2010) conducted a prospective clinical study of 152 infertile women all had a pelvic MRI prior to IVF and the average and the maximal junctional zone thickness were measured [68]. Implantation outcomes were correlated with junctional zone thickness and with the causes of infertility (endometriosis, tubal infertility, anovulation, male infertility and unexplained infertility). They reported higher implantation failure (95.8 %) when the average JZ was >7 mm, compared to 37.5 % in those with JZ <7 mm. They did not directly correlate the findings with adenomyosis, but the highest pregnancy rate was in the group with endometriosis (59.3 %). The proportion with JZ thickness >7 was comparable in the group with endometriosis (14.8 %), male infertility (8.3 %), anovulation (9 %) or tubal factor infertility (13 %), but was lower compared to those with unexplained infertility (32.1 % p = 0.003). This is at variance with the high incidence of JZ thickening in endometriosis reported by Kissler et al. (2006) [45].

Costello et al. (2011) performed a retrospective review of 37 women with adenomyosis compared to 164 women without adenomyosis who were undergoing IVF/ICSI treatment [21]. Adenomyosis was diagnosed based on the findings on TVU and all participants received long down regulation protocols. There were no differences in live birth rates between the two groups (29.7 % Vs. 26.1 %; p = 0.395; OR 1.45 with 95 % CI 0.61–3.43). But the study was retrospective and small and the accuracy of ultrasound diagnosis of adenomyosis cannot be certain and there was heterogeneity in the indications for IVF/ICSI and in the treatment protocols received. Salim et al. (2012) published a prospective controlled study evaluating 275 consecutive women, commencing IVF/ICST for the first time [92]. The control group included 256 women and the adenomyosis group included 16 women. In this study the authors found that the clinical and ongoing pregnancy rates were lower in women with adenomyosis compared to the control group (22.2 % versus 47.2 % and 11.1 % versus 45.9 %, respectively). They concluded that ultrasound evidence of adenomyosis is found in a significant number of women presenting with infertility and that it has a negative impact on the outcome of IVF.

While there was no uniform agreement on the most appropriate therapeutic methods for managing women with uterine adenomyosis and/or adenomyoma who want to preserve their fertility, multiple modalities to restore fertility have been used including hormonal therapy and conservative surgical therapy via laparoscopy or exploratory laparotomy, uterine artery embolization, and magnetic resonance-guided focused ultrasound. The evidence base for these interventions remains poor. The review by Maheshwari

et al. (2012) concluded that there is little data on the epidemiology of adenomyosis associated with subfertility and that most studies on treatment have been uncontrolled and outcomes are usually reported in the form of case series [64]. The conclusion was that there is currently no evidence to support the need to identify or treat adenomyosis in patients who wish to conceive.

Adenomyosis During Pregnancy

Although pregnancy is not rare after spontaneous or assisted conception, there is little data on the epidemiology of adenomyosis in pregnancy. Sandberg and Cohn (1962) analysed 151 caesarean hysterectomies and found adenomyosis in 17 % of the specimen [95]. Azziz (1986) published a comprehensive report of 72 pregnancies in women with adenomyosis; 14 cases where published before 1930 and therefore probably refer to "adenomyoma", a term that was used to encompass both adenomyosis and endometriosis [6]. However, Azziz states that he excluded cases where the distinction was not made. There were 7 ectopic pregnancies. Obstetrical or surgical complications were described in 29 reports and there were 11 cases of uterine perforation or rupture. Today reported complications are rare and may include rapid growth in pregnancy [44], spontaneous rupture of an unscarred uterus [82] and delayed postpartum haemorrhage [116]. Uterine rupture during pregnancy may also occur after adeno-myomectomy [109].

In a case controlled study involving 104 cases and 208 controls, Juang et al. (2007) evaluated the incidence of adenomyosis in women with spontaneous preterm delivery or preterm rupture of membranes [41]. Adenomyosis was identified by ultrasound and/or MRI in 16 (15.4 %) women who delivered <37 weeks compared to 19 (9.1 %) who delivered at term. Whilst the figures do not reach statistical significance ($p=0.13$, Fisher exact test), the odds ratio after adjusting for age, BMI, smoking and previous preterm delivery is reported as 1.96 (95 % CI: 1.23–4.47). Juang et al. (2007) stated that there was a link between adenomyosis and preterm birth [41]. But their study design does not lend itself to this conclusion. The incidence of adenomyosis in women with preterm labour is a distinct question from the incidence of preterm birth in women with adenomyosis. Fernando et al. (2009) found increased risk of preterm birth in infertility patients with ovarian endometrioma, but did not control the study for the presence of adenomyosis [29]. Recently, Shitano et al. (2013) reported on MRI features during pregnancy in three cases with adenomyosis. Low signal intensity areas with embedded bright few millimetre diameter intramyometrial foci were attributed to decidualization [98]. This raises the question about what advice could be given to pregnant women with adenomyosis? Given that the majority will have uneventful pregnancies and that the impact of the disease on the course of pregnancy is unclear, together with the lack of specific interventions, it may best that available information be given to pregnant women in a way that would avoid raising unnecessary anxiety.

Post-menopausal Adenomyosis

The presence of adenomyosis in post-menopausal women is well documented. Lewinski (1931) reported adenomyosis in 26 cases amongst 49 women >50 and in 3 out of the 5 cases >70 years old undergoing autopsy [57]. In the series reported by Dreyfuss (1940) 13 (8.5 %) out of a total of 152 women with adenomyosis were more than 50 years old [25]. Dreyfuss (1940) stated that "*The adenomyotic structures were of the 'resting' type in women who were not menstruating any more*" [25]. There were 55/119 (46 %) postmenopausal women in the study by Reinhold et al. (1996) and 23 % postmenopausal women in the study by Kepkep et al. (2007) [91]. In a series of 1334 consecutive women undergoing hysterectomy, adenomyosis was diagnosed in 332 (24.9 %) of all cases and in 132 (24.3 %) of the postmenopausal cohort (n=544) [112]. In the California Teachers Study, adenomyosis was linked to the pre- or peri-menopause, and to the use of postmenopausal HRT [103]. Contrary to the case in premenopausal women, being overweight

or obese was not associated with increased risk of adenomyosis in postmenopausal women, but case selection may have influenced the conclusions of this study.

Postmenopausal adenomyosis was, however, an incidental finding in most reported cases. As such it seems to have little, if any, clinical significance. Lister et al. (1988) described a case of post-menopausal adenomyosis who had an apparent thickening of the endometrium mimicking a carcinoma [58]. Davies and Oram (1994) described a case where there was flare-up in symptoms and elevated CA125 in response to post-menopausal Tibolone HRT [22]. Özkan et al. (2012) compared women who underwent hysterectomy for fibroids (n = 98) with those who had adenomyosis (n = 106); overall, 40 % were postmenopausal [87]. Women with adenomyosis were statistically significantly older and of higher parity. In a sizable proportion, adenomyosis was an incidental finding. Tamoxifen has been linked to postmenopausal adenomyosis and to an endometrioma in one case report [54] and to adenomyosis and an adenomyomatous endometrial polyp in another [108]; in a small series (n = 8) with endometrial pathology during tamoxifen therapy; one had adenomyosis [49]. Cohen et al. (1995) reported adenomyosis in 8 (57.1 %) out of 14 women who had a hysterectomy whilst receiving tamoxifen [20]. Seven had small microscopic foci and one case had a large fundal adenomyotic lump. Cohen et al. (1997) reported adenomyosis in 15 (54 %) women with breast cancer receiving tamoxifen compared to only 2 of 11 women not receiving tamoxifen, pointing to an association [19]. A comparative histopathologic evaluation concluded that in tamoxifen-associated cases there was more often a cystic dilatation of glands, fibrosis of the stroma and various epithelial metaplasias, indicating a higher proliferation [72]. Tamoxifen also induces distinct MRI patterns in the postmenopausal uterus on tamoxifen. 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 [3].

Conclusion

What is apparent from this review it that there remains considerable uncertainties about adenomyosis including about its clinical presentations and impact. Research into adenomyosis has been hampered by the many methodological challenges posed by the inability to diagnose the condition through non-invasive means and because much of the research has relied on retrospective reviews with little attempt to correlate clinical presentation with gross or macroscopic features. Except in women treated with HRT – adenomyosis becomes silent in the vast majority of cases past the menopause.

Most of the studies reported on adenomyosis are undermined because of classical pitfalls such as selection bias because of the necessity of considering hysterectomy samples, non-blinding, lack of definition of either the disease itself or of the outcome measures and the problem with confounding association and causation.

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