Surgical and medical treatment of adenomyosis

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The treatment of adenomyosis has been limited by the difficulty and delay associated with the diagnosis, often not until after hysterectomy. Magnetic resonance imaging, high resolution vaginal ultrasound and uterine biopsy have improved early detection of adenomyosis. Drug therapy may be effective in controlling symptoms but the frequent coexistence of endometriosis and the lack of controlled studies make their efficacy difficult to quantify. Conservative surgery involving endomyometrial ablation, laparoscopic myometrial electrocoagulation or excision has proven to be effective in >50% of patients, although follow-up has been restricted to 3 years. Hysterectomy will still be necessary in severe cases of adenomyosis. Early diagnosis may improve treatment. Investigations are indicated in women with menstrual pain or menorrhagia not responding to drug therapy.

Key words: adenomyosis/conservative surgery/drug treatment

Introduction

The oral contraceptive pill, anti-prostaglandins, oral or parental progestogens, danazol, dimethro, gonadotrophin hormone releasing hormone (GnRH) analogues, and Chinese herbal remedies have all been used to control menstrual pain and menorrhagia in women with adenomyosis or when drug treatments fail or patients indicate a preference for surgery.

Surgical considerations

Diagnosis

Diagnosis of the extent and localization of the disease is difficult, even with magnetic resonance imaging (MRI), colour Doppler vaginal ultrasound and uterine biopsy techniques (Fedele et al., 1992; McCausland, 1992; Popp et al., 1993; Wood et al., 1993, 1994; Brosens and Barker, 1995; Brosens et al., 1995a; Kang et al., 1996; Reinhold et al., 1996). MRI is the most sensitive test for detection of adenomyosis but it is also the most expensive, limiting access to affluent health care systems (Reinhold et al., 1996). Uncertainty in defining the site and more particularly the extent of adenomyosis make it difficult to determine the feasibility and accuracy of complete excision when conserving the uterus. This is one reason why hysterectomy has remained the most popular operation for adenomyosis.

Extent of removal

One factor which may favour attempts at excision of localized areas of adenomyosis is the possibility of reduction or cure of symptoms even when excision is incomplete. Incomplete electrocoagulation or excision in patients has resulted in symptom relief for 3 years (C.Wood, unpublished data).

Technical difficulty in excision

Laparoscopic surgery may be limited by the need to excise ill-defined, tough adenomyotic tissue and to use robust suturing equipment to obtain wound closure after excising significant areas of myometrium. The easier removal of adenomyosis by laparotomy is a less attractive alternative to laparoscopy, particularly as cure cannot be guaranteed.

Pregnancy after myometrial excision and coagulation

One problem when conserving the uterus is the uncertainty of the extent of myometrium which can be removed and still allow normal pregnancy and birth. Comparison with the
relative safety of pregnancy and birth after myomectomy may be inappropriate. Fibroids grow inside normal myometrium which they displace as in a benign tumour. When the fibroids are removed, a capsule demarcates them from normal myometrium. The cavity is then repaired leaving the uterus similar to what it was prior to growth of the fibroid, except for the presence of a scar. Adenomyosis infiltrates normal myometrium so that excision of the diseased area subtracts myometrial mass from the total uterine volume. Removal of significant amounts of myometrium poses two problems, (i) a reduction in myometrial capacity of the uterus during pregnancy, which may predispose to abortion or premature labour, and (ii) the production of uterine scars, which may contain foci of undetectable adenomyosis and may have reduced tensile strength.

Wound apposition may be more difficult to achieve after excision of adenomyosis as the loss of circumference of the myometrium will increase tension in the stretched myometrium when it is opposed to fill the gap. When one-third of the posterior myometrium was excised in a patient with adenomyosis, a size one vicryl stitch placed in two layers at laparotomy was unable to oppose the patient with adenomyosis, a size one vicryl stitch placed in one-third of the posterior myometrium was excised in a myometrium when it is opposed to fill the gap. When myometrium will increase tension in the stretched excision of adenomyosis as the loss of circumference of the myometrium. The cavity is then repaired leaving the uterus in two ways, by replacing normal myometrium and connective tissue with adenomyotic tissue, which may distort both the spiral arrangement of muscle fibres and the three-dimensional network of collagen, or by adding scar tissue subsequent to excision of the adenomyosis. In a study of spontaneous uterine rupture in pregnancy adenomyosis was found at the site of the uterine rupture in three cases (Wood, 1960). The scar tissue following excision is a separate risk factor. Coagulation of adenomyosis will have a similar effect to excision as myometrial mass is reduced and scar tissue is formed. The scar may be more extensive after coagulation as abnormal tissue is not removed.

The increased expansile properties of uterine myometrium and connective tissue in pregnancy may allow excision of a considerable volume of myometrium without preventing normal uterine expansion in pregnancy. The largest area of myometrium removed in our own experience is one-half of the posterior uterine myometrium. The woman conceived and a normal baby was delivered by elective Caesarean section at 37 weeks of pregnancy. The experience of women with pregnancy in a unicorntate uterus may be relevant. The uterus formed from one Müllerian duct is smaller than normal and although premature labour is more frequent (15%) a normal duration of pregnancy is most common. Myometrial mass may be less important than the myometrial integrity of the myometrium and connective tissue.

Pregnancy following excision or coagulation of adenomyosis poses special problems which have not been resolved. Documentation of the extent of the surgical procedures and pregnancy outcomes is necessary so that women may be better informed of the possible risks.

Early detection may favour conservative surgery?

In subfertile women with menorrhagia and dysmenorrhoea, adenomyosis has been found in 28 of 56 women having MRI and uterine histology (Brosens et al., 1995b). MRI diagnosis was based on the presence of a distorted endomyometrial junction (EMJ) and severe menorrhagia was more common in the women with adenomyosis. Such a high frequency of menorrhagia supports the concept that the disease may be underdiagnosed as it is usually recognized only when myometrial thickening and distortion of the surface contour of the uterus are present at the time of surgery, and by histology after hysterectomy. If the only investigative manifestation of adenomyosis is distortion of the EMJ, the possibility of conservative surgery is limited by the need to perform MRI to make the diagnosis and by limitation on the type of surgery. Endometrial ablation may be effective in reducing menorrhagia but would be limited to women not wishing to conceive (Popp et al., 1993; Wood et al., 1994). If the EMJ was distorted over a small area it may be possible to perform a limited endometrial ablation and thus conserve fertility. A 24 week pregnancy has been reported after planned subfundal endometrial ablation (Wood and Rogers, 1993) and also after endometrial ablation when significant areas of endometrium have been unintentionally left intact. There is uncertainty as to how large an area of endometrium is required to sustain a normal term pregnancy. The variety of clinical situations
where endometrium is partially damaged and subsequent full term pregnancy has been recorded, e.g. endometrial ablation, removal of uterine synechiae, and resection of large submucous myomata, suggests that at least one-third of the endometrium may be removed without compromising normal placentation. The placenta normally occupies <50% of the endometrial surface.

**Specific surgical techniques**

The choice of a suitable surgical procedure depends upon the site and extent of disease, the age of the patient, the desire for future pregnancy, the patient’s desire for certain cure or not, and the surgical skill of the gynaecologist.

**Endomyometrial ablation/resection**

Endomyometrial resection is most suited to patients with disease limited to the EMJ as menstrual symptoms may be reduced and the pathology may be removed. It may also be useful when adenomyosis is present in the outer myometrium as laparoscopic myometrial excision alone may not cure menstrual symptoms, either because excision may be incomplete or the menstrual symptoms are not caused by the outer myometrial adenomyosis. Desire for a future pregnancy contraindicates endomyometrial resection (see above). Adenomyosis has been found incidentally in seven of 29 women on hormone replacement therapy having endometrial ablation for menopausal bleeding (Phillips, 1995).

**Technique**

The technique of endometrial ablation has been well described. If MRI or ultrasound shows the extent and site of endomyometrial distortion the procedure can be modified to include 2–3 mm of myometrium in the affected areas. The whole of the endometrium should be removed as menorrhagia may be due to factors other than the adenomyosis. Deeper myometrial removal or ablation carries the risk of causing increased bleeding as significant arteries are situated ~5 mm deep to the myometrial surface. Histology of the excised myometrial fragments may help to confirm or refute the diagnosis.

When endomyometrial resection has been performed as a single operative procedure, menstrual symptoms have been controlled in 55% of women for at least 2 years (Table I).

**Laparoscopic myometrial electrocoagulation**

Electrocoagulation has the capability of shrinking adenomyosis by causing necrosis. The technique has been applied to localized or extensive disease. The adenomyosis can be detected by MRI, vaginal ultrasound, inspection of the uterus at laparoscopy, myometrial needling, or manual palpation during gasless laparoscopy to detect differences in consistency between normal and abnormal tissue. Electrocoagulation may be less accurate than surgical excision as electrical conduction in the abnormal tissue may be incomplete and this cannot be checked at the time of surgery. It may also reduce the strength of the myometrium by replacing abnormal myometrium with scar tissue. The width of the scar may be more extensive than after surgical excision when close apposition of normal myometrium is achieved.

Extensive myometrial electrocoagulation has been performed in two women aged 42 and 46 years with extensive adenomyosis on the anterior and posterior uterine walls; drug therapy had failed, excision was not feasible, and hysterectomy was not wanted. Two years later both are free of severe menstrual pain and bleeding. Diffuse multifocal electrocoagulation of the myometrium containing adenomyosis may be sufficient to control symptoms. The risk of uterine rupture following extensive electrocoagulation is demonstrated by the following experience. One patient had two laparoscopic procedures involving myometrial electrocoagulation, one of which was also associated with excision of an elevated adenomyotic area. The patient was aware of the risk of uterine rupture, she had not responded to GnRH analogue therapy, was not suitable for extensive myometrial excision and had refused hysterectomy as she wished to attempt conception even if this failed. A subsequent pregnancy resulted in uterine rupture at 12 weeks.

<table>
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<th>Table I. Results of conservative surgery, 1991–1997</th>
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<td>Endomyometrial resection</td>
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*aThree patients had a temperature of >37.5°C for >2 days.*
Electrocoagulation is best suited to women over 40 years of age, who do not wish to conceive, and who wish to avoid more extensive surgery such as excision or hysterectomy. Even following recurrence the procedure may be repeated until the onset of the menopause when symptoms cease.

**Technique**

Uterine manipulation with a Valtchev manipulator improves access to the diseased areas by facilitating antero-posterior and lateral movement of the uterus.

Vasoconstricting agents such as adrenaline and vaso-pressin are not used routinely as excessive bleeding has not been experienced and the blanching of the myometrium after vasoconstriction makes it difficult to determine the devascularizing effect of electro-coagulation or uterine vessel closure.

Closure of the ascending uterine artery may be performed if technically feasible, future pregnancy is not wanted, and the site of the adenomyosis is in the upper uterine body. Bipolar forceps, clips or suture ligation may be used to close the uterine vessels.

Electrocoagulation of the adenomyosis may be carried out with unipolar or bipolar needles, using 50 W coagulation current (Figure 1). Bipolar needles have a theoretical advantage of concentrating current between the two needles, but their effectiveness is diminished by the tendency of the two needles to move close together as they penetrate the myometrium. Additionally, the area of coagulation may spread outwards from each needle, simulating the effect of monopolar electrocoagulation.

The extent of coagulation can be controlled by reducing the current strength and changing the time the needle(s) are held in position. In order to reduce the possibility of severe surface necrosis and carbonization, either of which may encourage future adhesion formation, the insulated part of the needle is buried a few millimetres below the uterine surface before electrocoagulation is commenced. The insulation on the bipolar needle can be extended so that the active part of the electrode is shortened in order to avoid surface coagulation and necrosis. Needle punctures are made at 1–2 cm intervals, depending on the spread of the coagulative effect. The depth of needle puncture may vary, depending on the thickness of the adenomyotic myometrium determined preoperatively by ultrasound or MRI. This varies from 3 to 25 mm. If hysteroscopic endomyometrial ablation has also been carried out, the depth of laparoscopic needle electrocoagulation may be reduced. Lasers have been used to shrink fibroids but their use has not been reported in the laparoscopic treatment of adenomyosis.

Hysteroscopic endomyometrial ablation may be performed in association with myometrial electro-coagulation as menorrhagia and dysmenorrhoea may not be related to the presence of outer myometrial adenomyosis. Distortion of the EMJ is probably one of the causes of the menorrhagia and dysmenorrhoea in adenomyosis.

We have not been able to visualize the depth of laparoscopic myometrial coagulation by hysteroscopic inspection of the uterine cavity during the operation. Bleeding is rare during electrocoagulation and can be controlled by using a vasopressor or myotonic drugs such as adrenaline, oxytoxin or vasopressin, or by bipolar electro-coagulation or suture ligation. Patients are usually in hospital for 8–24 h. No complications have been observed including post-operative infection, bleeding or subsequent adhesion formation.

The result of the surgery may be assessed by symptom relief and MRI or vaginal ultrasound. Loss of features of adenomyosis including reduction of myometrial thickness, reduced vascularity and normal myometrial appearance have all been observed. Symptom relief may occur and persist for several years in the presence of reduced ultrasound evidence of adenomyosis. Sterilization should be offered to all women having myometrial electrocoagulation because of the possible future risk of uterine rupture in pregnancy.

**Myometrial excision**

Adenomyosis may be excised if it does not involve the major portion of the uterus, and its extent can be defined as previously described. The technique is also suitable for adenomyomas where the margins of the pathology are more easily defined. It may be useful in women wishing to become pregnant, providing sufficient myometrium remains to allow uterine expansion and term pregnancy and the scar formed...
after excision is not wide or shallow. MRI or colour Doppler ultrasound after surgery should be used to check both for cure, the width and depth of scar, and the possible association of residual adenomyosis close to the scar, before attempts at conception are advised.

**Technique**

Preoperative GnRH analogues or danazol may reduce uterine vascularity, correct anaemia if the patient has severe menorrhagia, and reduce operative bleeding which facilitates surgery by laparoscopy rather than laparotomy. Vasoconstrictor drugs may also reduce bleeding at the time of surgery.

Prior to myometrial excision, as with electrosurgical coagulation, the uterine blood supply may be reduced by suture or clip ligation or bipolar diathermy of the ascending uterine vessels in women not concerned with fertility. Apart from reducing bleeding during surgery the reduction in blood flow may reduce future growth or development of adenomyosis.

Two associated surgical procedures may be offered: sterilization to prevent conception, and hysteroscopic endomyometrial ablation if menorrhagia is present and fertility is not required.

Laparoscopy, and gasless laparoscopy, with or without mini-laparotomy, facilitate myometrial excision avoiding the need to perform laparotomy. Gasless laparoscopy is done with a Maher abdominal elevator, forming an S-shaped loop; this is effective and cheap (Maher, 1995; Wood and Maher, 1996a). A finger or laparotomy instruments can gain entry to the abdomen through a 2–4 cm incision which may be sufficient to remove and repair areas of myometrium up to 6x8 cm.

A Valtchev uterine manipulator is used to position the adenomyotic areas as close as possible to a laparoscopic or mini-laparotomy incision. Sometimes a myoma screw may stabilize the diseased area and aid excision. A diathermy spoon using 100 W monopolar current, or scalpel, is suitable for excision. The spoon has the advantage of cutting effectively with the sharp end close to the tissue, and of coagulating vessels when the convex curve of the spoon compresses the vessel. When the tissue is very firm the scalpel may be preferable, providing more effective and rapid excision. The scalpel can be used safely through a 2 cm accessory laparoscopy incision or a mini-laparotomy incision. The margin of the adenomyosis may be determined by change in appearance, vascularity or consistency; finger palpation may be an advantage.

A myometrial morcellator may also be used to remove adenomyotic tissue, coring pieces up to 15–20 mm in diameter. The difficulty in defining the margin of adenomyotic tissue makes morcellation less precise than scissor or knife dissection. The morcellator hides the tissue as it is cored out. The risk of trauma to other organs is prevented by the myometrium being drawn outwards or by the instrument not being inserted beyond the surface of the uterus. The morcellator may be hand- or electrically driven. It costs Aus$7000–12 000. Lateral insertion in the abdominal wall is essential for safety. A 10 mm laparoscope gives a better view of the procedure. Laparoscopy or gasless laparoscopy, using a large scalpel blade and/or large heavy scissors to morcellate the fibroid as it is withdrawn from a small 2–4 cm incision in the umbilicus, the suprapubic area or vagina, enables removal of fibroids up to 1000 g (Pelosi and Kadar, 1994; Wood and Maher, 1996b). This technique is cheaper than a morcellator, is just as quick, and may be safer as the surgery is done under vision in the abdominal wound.

Closure of incisions longer than 5–6 cm may require laparotomy instruments as excision of a significant volume of myometrium increases the tension at the myometrial edges which may have to be stretched to close the defect. If the uterine wound is brought into a minilaparotomy incision, the defect can be closed more easily and quickly. Absorbable sutures (No. 1) are used in one or more layers. If there is a large defect a single layer through-and-through suture may best approximate the wound, acting as a tension suture, and because of the increased thickness of the whole myometrium it is less likely to tear as tension is increased to attain closure.

Anti-adhesives such as Interceed® and Goretex® membrane may be used (Diamond et al., 1987; Jansen, 1991; Operative Laparoscopy Study Group, 1991; Bulletti et al., 1996) (Figure 2). The frequency of adhesions after excision of adenomyosis has not been reported. Interceed may be used if perfect haemostasis is obtained. Application of Surgicel® prior to Interceed may improve haemostasis and allow the use of Interceed (Figure 3). If bleeding persists Goretex can be stapled over the wound. This need not be removed unless pregnancy is planned. Uterine enlargement may displace the membrane from the uterus which may attach to other organs. Physiological solutions have been used to reduce adhesive formation but their efficacy in animal trials has been less than Interceed or Goretex (Jansen, 1991).

The use and safety of myometrial excision may be assessed by comparison to the results of laparoscopic myomectomy. Fibroids up to 1000 g have been removed laparoscopically by modifying surgical techniques (Pelosi and Kadar, 1994; Wood and Maher, 1996b). The safety of the laparoscopic technique has been established in 346 patients in four reports, one postoperative haemorrhage
Figure 2. Goretex membrane stapled over two-thirds of the posterior uterine surface to prevent adhesion formation.

Figure 3. Surgicel is placed over an extensive myometrial wound following excision of adenomyosis when there was difficulty obtaining haemostasis. This led to wound closure with good haemostasis. Interceed was then placed over a dry suture line.

Partial or subtotal hysterectomy

Myometrial excision can be extended to remove the major portion of the uterus. Women who do not wish to conceive may still prefer to retain the normal part of the uterus, the reasons being: that only diseased uterine tissue need be removed; that retaining the uterus is emotionally important; and that possible complications of hysterectomy, increased operative morbidity, and an earlier menopause may be avoided. In one woman aged 46 years, with a uterus enlarged to the size of a 20 week pregnancy by adenomyosis, 80% of the uterus was removed in association with partial endometrial ablation, and the women has had painless scanty menses for >5 years.

Laparoscopic partial or subtotal hysterectomy

When adenomyosis is extensive, involving more than one-third of the uterus, and fertility is not required, it may be easier to remove the top half or two-thirds of the uterus leaving any normal myometrium. The residual endometrium can easily be removed if menstruation is not wanted. Subtotal hysterectomy is preferable to partial hysterectomy in extensive adenomyosis as recurrence of adenomyosis is less likely and cure of menorrhagia and dysmenorrhoea more certain. Disadvantages of subtotal compared to total hysterectomy are: a small risk of residual or recurrent adenomyosis in the cervix; difficulty in removal of associated rectovaginal adenomyosis or adenomyoma, particularly if attached to the cervix; and the possibility of cervical abnormalities developing which may require further surgery. The possible advantages of subtotal compared to total hysterectomy include shorter operating time, reduced blood loss, earlier patient discharge from hospital and return to normal activity, reduced risk of bladder and ureteric trauma and reduced risk of adverse effects on sexual and bladder function (Wood and Maher, 1997). Controlled trials comparing total and subtotal hysterectomy are inconclusive, because they have mainly dealt with differences in operative and early postoperative events, are too few in number to determine if bladder and ureteric trauma is different, have not shown significant differences in sexual function, and the surgeons involved have not demonstrated comparable efficacy in the two surgical techniques prior to embarking on the trial. If the surgeon finds laparoscopic total hysterectomy difficult because of inexperience, difficult pathology or technical surgical problems, subtotal hysterectomy is certainly preferable. Further multicentre, carefully controlled studies and follow-up of patients for one year by surgeons equally experienced in both techniques is required.

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**Total hysterectomy**

Hysterectomy is the most common operation for adenomyosis as it nearly always ensures cure, and avoids both difficulty in defining the extent of the disease, a requirement for successful conservative surgery, and technical surgical difficulties, which may be associated with myometrial excision or electrocoagulation. Hysterectomy has the disadvantage of being associated with ureteric, bowel and bladder trauma in 1–2% of patients (Wood and Maher, 1997), and prolonged hospital stay and return to normal activity when compared to conservative surgery (Table I). The failure of conservative surgery may result in delayed hysterectomy in at least 10% of patients (Table I).

**Vaginal or laparoscopic total hysterectomy**

Providing no pelvic endometriosis is present, which can be determined by preoperative or operative laparoscopy, vaginal hysterectomy may be the procedure of choice. Controlled trials have shown it to be equally or more effective than laparoscopic hysterectomy, operating time being shorter and costs perhaps lower (Wood and Maher, 1997). A review of 70 articles concerning various types of hysterectomy shows that bleeding, use of blood transfusion and unexplained fever are significantly more common after vaginal than laparoscopic hysterectomy (Wood and Maher, 1997). Providing a check laparoscopy is performed at the completion of vaginal hysterectomy, and any bleeding detected and corrected, it may still be more cost effective than the laparoscopic procedure (Wood and Maher, 1997). As surgeons vary in their ability to perform vaginal hysterectomy—from 20 to 90% of hysterectomies are performed by this technique—laparoscopic hysterectomy also has an important role in performance of hysterectomy for adenomyosis (Wood and Maher, 1997). It has the advantage of enabling detection and removal of associated endometriosis, which is not possible during vaginal hysterectomy, and to deal more easily with very large uteri >500 g and associated adnexal pathology (Wood and Maher, 1997).

Abdominal hysterectomy is associated with increased costs, longer stay in hospital, 2–4 days, and delayed return to normal activities, when compared to laparoscopic hysterectomy in controlled trials (Wood and Maher, 1997). The incidence of trauma to the bladder, ureter and bowel are not different between abdominal, laparoscopic and vaginal hysterectomy (Wood and Maher, 1997). Laparotomy is required if the surgeon is not skilled in the vaginal or laparoscopic technique, if complications occur which may require laparotomy to repair trauma, or if associated pathology such as large fibroids or severe adhesions are present.

In order to completely remove uterine adenomyosis, surgery may need to be extended into the rectovaginal septum or bladder, when adenomyosis is either associated with, or has extended from, uterine adenomyosis.

**Arterial embolization**

Reduction of uterine blood flow by arterial embolization has been shown to reduce the growth of fibroids, (Ravina et al., 1995) and may be applicable to the treatment of adenomyosis.

**Extrauterine adenomyosis**

This has been reported in the broad ligament, the bladder and rectovaginal septum (Figure 4). The one patient with adenomyosis in the broad ligament was on tamoxifen after treatment for breast carcinoma (Chung et al., 1997). A laparotomy and hysterectomy and bilateral salpingooophorectomy was performed and revealed adenomyosis with cyst formation and a thick capsule.

Lesions in the rectovaginal septum have been confused with endometriosis (Donnez and Nissole, 1995). The response to drug therapy is usually ineffectual or incomplete. Surgical removal can be achieved by laparoscopy or laparovaginal surgery with an abdominal elevator (Maher, 1995; Maher et al., 1995; Wood and Maher, 1996a). A bowel preparation, rectal probe and uterine manipulator assist inspection of the pouch of Douglas. Adhesions obscuring the nodule are cleared. Access to the nodule may be assisted by ureteric dissection, surgical dissection in the pararectal space, and finger or probe display of the vaginal vault. Once the rectovaginal space is defined,
the further dissection of the infiltrating lesion is straightforward. Nodules up to 5 or 6 cm have been excised. Although laser, diathermy or scissors can be used to excise the nodule, thermal ablation alone is inadequate as only the superficial portion of the nodule is dealt with.

If the vagina is likely to be opened, placement of an abdominal elevator will allow continued dissection after vaginal opening. In the absence of an elevator, opening of the vagina can be left to the end of the procedure, the nodule being passed into the vagina for final removal.

Adenomyosis on the anterior uterine wall may extend onto the surface of the bladder. This can be removed with the uterine nodule (Figure 4). A cystoscopy excludes extension of disease into the bladder. A metal catheter in the bladder assists identification of the margin of bladder muscle during dissection. If the nodule is >1–2 cm diameter, placement of a metal catheter in the bladder assists identification of the margin of bladder muscle during dissection. A metal catheter in the bladder assists identification of the margin of bladder muscle during dissection. If the vagina is likely to be opened, placement of an abdominal elevator will allow continued dissection after vaginal opening. In the absence of an elevator, opening of the vagina can be left to the end of the procedure, the nodule being passed into the vagina for final removal.

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Adenomyosis is a common gynaecological condition affecting 5–10% of women of reproductive age. It is characterized by the presence of endometrial tissue within the myometrium, leading to a number of clinical symptoms including menorrhagia, dysmenorrhoea and dyspareunia. The exact cause of adenomyosis is unknown, although it is thought to be related to hormonal factors and genetic susceptibility. Fibroids and adenomyosis

Adenomyosis has been found in 23% of uteri removed because of the presence of fibroids (Vercellini et al., 1995). Because they are both common conditions, they often coexist particularly in larger uteri (Lev Gur, 1996). Because conservative treatment for fibroids is also feasible by electrocoagulation (myolysis), laparoscopic or minilaparotomy excision, and ivalon particle artery embolization (Chung et al., 1997), the treatment is unlikely to be different. It is more difficult to diagnose adenomyosis in the presence of fibroids, so that preoperative counselling of the patient may be incomplete. During surgery a fibroid may be easily enucleated and then an adenomyotic nodule without a clear plane of enucleation encountered. It may be difficult to distinguish adenomyosis from a degenerate fibroid or from a fibroid that has adhered to the capsule following necrosis after GnRH analogue treatment. Nodules without a distinct capsule may be removed with a margin of surrounding myometrium to allow for the possibility of the nodule being adenomyosis.

In one patient with both multiple fibroids and adenomyosis, hemihysterectomy was performed, as the patient wished to retain any normal uterus and to menstruate. The cervix and 2 cm of the lower uterine body were conserved. The patient remains symptom-free after 5 years.

If both conditions are diagnosed preoperatively, the results of conservative surgery are most likely to mimic that of adenomyosis, with a higher failure rate for symptom removal. The patient may favour hysterectomy as a more certain cure.


cure.

Adenomyosis and uterine cancer

Precancerous changes, utilizing monoclonal antibodies against P53, were studied in 56 women with endometrial cancer associated with adenomyosis (Taskin et al., 1996). Ten women without endometrial cancer and adenomyosis were a control group. This showed that the precancerous changes in adenomyosis are most likely due to a carcinogenic field effect in the vicinity of the endometrial cancer rather than direct invasion. This makes it less likely that adenomyosis is precancerous any more than the uterine endometrium. The frequency of adenomyotic endometrial cancer in the presence of adenomyosis and normal uterine endometrium is unknown.

Adenocarcinoma within adenomyosis may have a better prognosis than adeno-carcinoma invading the myometrium (Mittal and Barwick, 1993). There were no deaths in 18 cases of adenomyosis cancer and eight deaths in 43 cases (19%) of adenocarcinoma invading the myometrium. The adenocarcinomas in adenomyosis were characterized by frequent preceding oestrogen use, low histological grades and a good prognosis. It is possible that cessation of oestrogen and treatment with medroxyprogesterone acetate may reverse the histology and avoid hysterectomy and oophorectomy in such patients. Hysterectomy may still be preferable if the oestrogen is making a contribution to the patient’s quality of life or future physical health.

It may be prudent to advise women desiring conservative surgery for adenomyosis to consider hysterectomy if they have an increased risk of uterine cancer, e.g. obesity, diabetes, polycystic ovaries or a family history.

In postmenopausal women treated for breast cancer and on tamoxifen, adenomyosis has been found more frequently, affecting 14 (8%) of 173 women, which is 3–4-fold higher than the expected incidence (Cohen et al., 1995). These women had hysterectomy and oophorectomy for bleeding symptoms. In order to avoid adenomyosis and surgery, low dose progestogens may be worthwhile, providing they do not adversely affect the anticancer effect of tamoxifen.

Adenomyosis following endometrial ablation

Adenomyosis has been reported to follow endometrial ablation by use of resection or the rollerball. In a report of two patients ablation was performed in the apparent absence of uterine pathology. The endometrium was not prepared. Adenomyosis was discovered after hysterectomy performed because of recurrence of menorrhagia and dysmenorrhoea (Yuen, 1995).

It is difficult to prove that endometrial ablation or resection causes adenomyosis, because even myometrial biopsy prior to or at the time of resection may be negative in the presence of adenomyosis.
of adenomyosis. It is possible that disorganization of the endomyometrial interface may occur at the time of surgery, removing normal physiological controls that prevent endometrial penetration of the myometrium. The situation may be analogous to placentation when penetration of myometrium may occur in some circumstances and lead to pathological attachment inside the myometrium.

There is circumstantial evidence in case or anecdotal reports that endometrial ablation/resection may have caused adenomyosis where menorrhagia was present before surgery, where menstrual pain and uterine enlargement followed surgery, and where adenomyosis was subsequently proven by histology. The most common explanation for failure of endometrial ablation/resection focuses on the failure to remove sufficient endometrium at the time of surgery and/or subsequent regrowth of the endometrium. Other failures may result from the late development of adenomyosis, or from adenomyosis present at the time of surgery. Checks for the presence of adenomyosis may not have been performed prior to endometrial ablation/resection, and even if they have, ultrasound, MRI and myometrial biopsy may give false negative results. In 42 women having routine myometrial biopsy at the time of endometrial ablation/resection, seven were shown to have adenomyosis (Wood, 1992).

Despite uncertainty, the possibility of a causal link between endometrial ablation/resection and the subsequent development of adenomyosis remains. Pre-preoperative thinning of the endometrium by GnRH analogues, complete endometrial removal, and postoperative suppression of endometrial growth during healing, may reduce the risk of operative or postoperative endometrial penetration and survival in the myometrium.

**Results of conservative surgery**

The results of conservative surgery in a personal series of women with adenomyosis diagnosed by vaginal ultrasound with vascular assessment, percutaneous uterine biopsy, and histology of excised endomyometrial or myometrial fragments at the time of surgery, are presented in Tables I, II and III. Sixty three per cent of women were symptom-free 2 years later and 12% required hysterectomy during the same time period because of persistence or recurrence of severe symptoms. Each of the techniques had a success rate >50%. Nine of 16 women attempting pregnancy conceived, four of seven after myometrial electrocoagulation and five of nine after myometrial excision. One woman who had two electrocoagulation treatments, including one associated myometrial excision, ruptured her uterus in the twelfth week of pregnancy.

| Table II. Indications for conservative surgery for adenomyosis |
|---------------------------------|-----------------------------|
| Indications for surgery          | n = 54                      |
| Failed medical treatment         | 46                          |
| Oral contraceptive pill          | 30                          |
| Progestogens                     | 8                           |
| Danocrine                        | 3                           |
| GnRH analogue                    | 5                           |
| Patient preference for surgical treatment | 8                           |

GnRH = gonadotrophin releasing hormone.

<table>
<thead>
<tr>
<th>Table III. Clinical features of patients having conservative surgery for adenomyosis (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Parity</td>
</tr>
<tr>
<td>Menorrhagia</td>
</tr>
<tr>
<td>Dysmenorrhoea</td>
</tr>
<tr>
<td>Dyspareunia</td>
</tr>
<tr>
<td>Infertility</td>
</tr>
</tbody>
</table>

Site of adenomyosis determined by biopsy or surgical histology: inner myometrium, 18 patients; outer myometrium, 36 patients. Outer myometrium had normal appearance at laparoscopy and vaginal ultrasound examination with colour Doppler. Adenomyosis also present in inner myometrium in 17 patients.

MRI and uterine biopsy were used to diagnose nodular adenomyosis by Phillips et al. (1996). Preoperative GnRH analogue, endomyometrial resection and bipolar coagulation were used in 14 women. One year after treatment menorrhagia was cured in 12 and dysmenorrhoea in eight. Two proceeded to hysterectomy. The advantage of preoperative use of GnRH analogue was shown by a 50.8% mean reduction of uterine volume after leuprolide acetate treatment for 3 months. A further 14.9% mean reduction occurred after the surgery. The beneficial effect of leuprolide may have continued for at least 3 months after surgery so that a 1 year follow-up assessment may give a favourable view of the efficacy of the surgery. In 10 patients laparoscopic bipolar coagulation alone was performed on adenomyomata, and seven of 10 women had symptom relief after 1 year, one requiring hysterectomy (Phillips et al., 1996). In a 2 year follow-up (Table I) the results were similar following electrocoagulation without the use of a GnRH analogue.

Endomyometrial ablation alone may be successful in curing symptoms of menorrhagia and dysmenorrhoea (Table I; Phillips et al., 1996). Using rollerball ablation and performing a posterior uterine wall biopsy prior to this to determine the depth of penetration shows that those with minimal penetration had a good outcome and those with deep penetration a poor outcome. The authors recommended hysterectomy in the presence of deep penetration as a rollerball procedure would only cause necrosis in the superficial 2–3 mm of the myometrium. An electrical loop
may be used to remove >2–3 mm of myometrium, although the risk of bleeding is increased. Laparoscopic myometrial electrocoagulation may be useful in such circumstances as penetration of coagulation may be achieved over the full depth of the myometrium. One of the difficulties assessing results of endomyometrial ablation is the lack of certainty of diagnosis, even with histology, because of false negatives, and uncertainty of the MRI criteria for diagnosis. The specificity of the diagnosis by MRI has been determined by a junctional zone thickness greater than 5 mm. Thickness >5 mm has been found in 40% of normal subjects having serial MRI measurements which also showed thickening up to 12 mm and focal myometrial bulging which may result from uterine contractions (Kang et al., 1996).

The diagnosis of adenomyosis and the assessment of surgical procedures has been complicated further by the hypothesis that adenomyosis is a dichotomous disease characterized primarily by the disruption of the inner myometrium (junctional zone hypertrophy) and its function, with secondary infiltration of endometrium into the myometrium under certain circumstances (Brosens et al., 1995b). The former may exist without the latter and lead to menorrhagia but not menstrual pain. Proliferation of the inner myometrium may result from endometrial or immune factors and medical treatment may become more appropriate than surgical removal of the endometrium, particularly as it is more common in young women with menorrhagia (Brosens et al., 1995b). Both choice of treatment and surgical results may need to be classified by the results of MRI, although the uncertainty of accuracy in detecting both junctional zone thickness and endomyometrial penetration may reduce the clinical value of such a classification (Kang et al., 1996). In the meantime it may be helpful to evaluate results according to the presence or absence of menstrual pain and the depth of endomyometrial penetration determined by histology. This would allow comparison of conservative surgical procedures between centres, particularly to include those centres that cannot afford routine use of MRI in the diagnosis of adenomyosis.

If junctional zone hypertrophy is present without endometrial penetration of the myometrium, it may deserve a new name, or the definition of adenomyosis could be changed to include a pre-invasive stage to describe the junctional zone hypertrophy, adenomyosis, stage 0.

Medical treatment of adenomyosis

There is a paucity of information on the specific effects of drug therapy on adenomyosis. Drugs used in the treatment of adenomyosis are mostly the same as those used for endometriosis, which is easily diagnosed and studied, whereas often adenomyosis is not diagnosed until after surgery — either endometrial resection for the treatment of menorrhagia, or hysterectomy because of the presence of menorrhagia and dysmenorrhea in the presence of an enlarged uterus.

Arguments in favour of medical therapy are the possible avoidance of surgery and associated complications, such as adhesions, the limited types of conservative surgery available, and the tendency of gynaecologists to offer hysterectomy as the only type of definitive surgery. Disadvantages of medical therapy are the few reports of results of treating women with adenomyosis, the commonly held belief that drug therapy is relatively ineffective in treating adenomyosis, and drug side-effects.

Women who pursue hysterectomy for adenomyosis have nearly all been treated previously with drugs for menorrhagia and/or dysmenorrhea. These drugs include the oral contraceptive pill, in continuous mode to avoid menstruation; progestogens, particularly Provera (medroxyprogesterone acetate), by oral or intramuscular injection; and less often danazol, gestrinone and GnRH analogues. The reason the latter three drugs have been used less is that they are generally prescribed specifically for use in women with endometriosis, whereas adenomyosis is often not recognized in young women with menstrual symptoms. The increased availability of diagnostic methods, MRI, colour Doppler vaginal ultrasound and uterine biopsy are improving the recognition of adenomyosis, so that drugs that are specific for endometriosis may be subject to controlled clinical trial in the treatment of adenomyosis.

It is difficult to predict the efficacy of drugs reducing oestrogen or its effect, as comparison of oestrogen receptor (ER) and progesterone receptor (PR) concentrations in endometriotic and adenomyotic tissue has not been found in a literature search. Nevertheless, studies of receptors in peritoneal, ovarian and rectovaginal endometriosis may have some relevance to adenomyosis (Nissole et al., 1996). Cyclic changes are found in both ER and PR content and the concentration of ER is always lower than in uterine endometrium, whereas PR content is similar to that in uterine endometrium. There is hormonal independence of the endometriotic endometrium as shown by persistence of a high inactive PR content during the late secretory phase. The lower level of ER content may be one factor limiting the effect of drugs which act by lowering or blocking oestrogen effects. Haemorrhagic and vesicular (blister-like) lesions, which contain mostly glandular and stromal components, show evidence of proliferative and secretory change with menstruation, whereas nodules or papules, which contain less glands and stroma, and are blue black, brown or white, show proliferative activity but little or no secretory change.
and less or no menstruation (Schweppe, 1996). Only red and blister lesions, which are better differentiated histologically, respond to drug therapy (Schweppe, 1996) and such lesions may be less frequent in adenomyosis.

The results of drug therapy in endometriosis may be most relevant to women with adenomyosis who have symptoms of menorrhagia and dysmenorrhea. Medical therapy aims to suppress cyclical hormonal changes of ovarian steroid secretion and inhibit pituitary gonadotrophic secretion or at least prevent the mid-cycle surge of oestrogen.

**Oral contraceptives**

Low dose combined oral contraceptives using continuous therapy, with withdrawal bleeds every 4–6 months, may be effective in relieving menorrhagia and dysmenorrhea and in endometriosis produce equivalent results to oral contraceptives with higher dose regimens (Moghissi, 1988).

**Progestogen**

Of all the progestogens, oral medroxyprogesterone acetate (MPA) has been best studied. The therapeutic effects of 30 mg and 50 mg daily are similar; 30 mg daily is associated with the option of increasing the dose according to clinical response and bleeding patterns. The major side-effects of progestogen therapy for endometriosis are breakthrough bleeding, weight gain, fluid retention (Luciano et al., 1988), breast tenderness, and mood changes (Mittal and Barwick, 1993).

**Danazol**

Danazol has been the most commonly used medical treatment for endometriosis. Three double-blind, placebo-controlled, prospective trials have randomly assigned patients to treatment with 100 mg, 200 mg, 400 mg or 600 mg of danazol (Wingfield and Healy, 1993). Recurrence rate was lower in those receiving larger doses (Dmowski et al., 1982). A minimum dosage of 400 mg danazol per day seems optimal. The androgenic effects of danazol produce many undesirable side-effects, some of which may be irreversible, e.g. hirsutism and deepening of the voice (Table IV).

**Gestrinone**

Gestrinone is an androgen, a progestogen, an anti-progestogen, and anti-oestrogen which has been used to treat endometriosis. It has similar efficacy to danazol (Fedele et al., 1989). One advantage of gestrinone is its long half-life when given orally, making twice weekly administration therapeutic for most patients. The standard dose has been 2.5 mg twice weekly. The side-effects of gestrinone are predominantly androgenic. It is less androgenic than danazol and has partly replaced the use of this drug (Fedele et al., 1989) (Table IV).

### Table IV. Side-effects of three antiendometriosis medicines

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>Danazol (n = 103) (%)</th>
<th>Gestrinone (n = 19) (%)</th>
<th>GnRH (goserelin) (n = 204) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flushes</td>
<td>58</td>
<td>0</td>
<td>98</td>
</tr>
<tr>
<td>Acne</td>
<td>54</td>
<td>21</td>
<td>37</td>
</tr>
<tr>
<td>Reduced libido</td>
<td>52</td>
<td>–</td>
<td>66</td>
</tr>
<tr>
<td>Oily hair/skin</td>
<td>48</td>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td>Weight gain</td>
<td>27</td>
<td>42</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>–</td>
<td>5</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Voice changes</td>
<td>3</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>12</td>
<td>16</td>
<td>1</td>
</tr>
</tbody>
</table>

*Data from Shaw (1992).*  
*Data from Fedele et al. (1989).*  
GnRH = gonadotrophin releasing hormone.

**RU486 (mifepristone)**

RU486 is a synthetic steroid with antiprogesterone and antiglucocorticoid activity. It blocks progesterone receptors in endometrial tissue. Long-term low-dose RU486, 50 mg daily, achieves anovulation, reducing painful symptoms and decreasing the extent of endometriosis without an antiglucocorticoid effect. One study was carried out on 14 women over 6 months of treatment (Kettel, 1996). Endometriosis scores decreased by ~50%, decreasing pelvic pain and dysmenorrhea in all patients. There was no change in mean serum cortisol.

**GnRH agonists**

There has been a rapid acceptance of GnRH agonists as treatment for endometriosis. The drugs are inactive orally and so must be administered i.v., s.c. (injections or depots) or via nasal sprays. They have a similar efficacy to danazol (Shaw, 1992). The side-effects of GnRH agonists are consequent to the hypo-oestrogenic state induced and are summarized in Table IV.

**Alleviation of pain**

Based on currently published studies, it would appear that GnRH analogues, danazol, gestrinone and MPA show similar efficacy in terms of laparoscopic resolution of disease following therapy (Fedele et al., 1997). All studies quoted showed at least some remission of symptoms in 70–100% of patients. This compares favourably with placebo arms which
show only 18% remission. These effects are most striking for symptoms of dysmenorrhoea and pelvic pain.

All the current treatment regimens appear to be equally effective in terms of symptom relief (Wingfield and Healy, 1993). Choice of drug will depend more on side-effects and cost profiles. While relief of symptoms is effective during therapy, there is a gradual return of symptoms in some 30–60% of patients by 1 year following therapy.

It is not clear how the information on the effect of drugs on endometriosis applies to the management of adenomyosis. There are two considerations. Some patients with adenomyosis also have endometriosis so the drug effects are relevant to patient management. More important is the possibility that women with endometriosis and dysmenorrhoea or menorrhagia may also have adenomyosis or junctional zone hypertrophy (Brosens et al., 1995b). There has been no adequate explanation of why women with endometriosis outside the uterus have menstrual pain identical in nature to that which normal women have with menstruation, i.e. uterine pain. Hysterectomy performed on women with endometriosis and menstrual symptoms does not often show endometriosis on the surface or growing into the uterus from outside. Sometimes adenomyosis is found after removal of the uterus, and there may be junctional zone hypertrophy (JZH), which has only recently been recognized, and may not have been reported by histology. It seems likely that women with endometriosis and uterine pain or menorrhagia may have JZH, or experience pain from prostaglandins released from myometrial endometriotic tissue. It is probable that the effects of drugs on women with endometriosis having menstrual symptoms at least partly reflect the effects of these drugs on adenomyosis or JZH. Only prospective studies of women with menstrual symptoms, both with and without endometriosis, having MRI and uterine biopsy, can elucidate the effects of drugs on endometriosis, adenomyosis and JZH.

**Drugs and adenomyosis**

**GnRH analogues**

A GnRH analogue, leuprolide acetate, has been used to produce a constant hypo-oestrogenic state in a woman with histologically proven adenomyosis (Nelson and Corson, 1993). Dysmenorrhoea and desire for conception were the two complaints. This produced amenorrhoea, control of pain and uterine shrinkage. Subsequent cyclic use of an oral contraceptive resulted in recurrence of pain and uterine growth. Conception occurred after cessation of the GnRH analogue which was used for 9 months. There have been other single reports of pregnancy following the use of GnRH analogues in women with adenomyosis.

Prolonged use of Zoladex for 12 months in women with fibroids showed persistence of a 7.5% loss of bone mineral density 1 year after completion of treatment; this loss was not prevented by coincidental use of medroxyprogesterone acetate for 9 months (Caird et al., 1997). Danazol has been used in low dosage, 100 mg/day, to prolong the shrinkage of fibroids achieved by 6 months of treatment with GnRH analogues, reducing regrowth by 30% (De Leo et al., 1997). This was thought to be due to its anti-progesterone effect which may or may not be relevant to the use of GnRH analogues in the treatment of adenomyosis.

There is a need for improved diagnosis of adenomyosis so that controlled trials of the effect of the GnRH analogues on infertility in adenomyosis can be performed. Numerous controlled trials of anti-endometriosis drugs in women with endometriosis have shown no beneficial effect on fertility when compared to no treatment (Wingfield and Healy, 1993). Nevertheless, GnRH analogues may be used to control pain and bleeding in the presence of adenomyosis.

**Anti-prostaglandins**

An increased production of prostaglandin PG12 has been shown in the tissue of adenomyosis, which is most increased in women with the most severe dysmenorrhoea (Hoike et al., 1996). Anti-prostaglandins may be useful in the control of menstrual pain in adenomyosis. The author uses rectal indomethacin because of the reduced side-effects and the possibility of higher myometrial tissue concentration of the drug compared to oral administration.

**Anti-oestrogen, ICI 182 780**

Adenomyosis in a pigtailed monkey has been diagnosed by MRI and treated with a pure anti-oestrogen, ICI 182 780 (Waterton et al., 1993). The pure anti-oestrogen has a high affinity for the oestradiol receptors but unlike non-steroidal anti-oestrogens such as tamoxifen, has been shown to be devoid of partial agonist (oestrogenic) activity. The drug resulted in a decrease of 87%, 57% and 45% of the endometrial volume, myometrial volume and lesion width respectively in the 4 weeks after the second injection. Oestradiol concentrations remained high. Subsequently there was further decrease in the myometrial and endometrial volume but increase in width of the lesion. Eighty days after treatment began, post-mortem after euthanasia showed diffuse adenomyosis in the uterus. The need to kill the monkey instead of performing hysterectomy is not clear. A pure anti-oestrogen may offer some advantage.
in the treatment of adenomyosis and trials are planned to assess its usefulness in the human.

**Topical danazol/progestogen therapy**

Adenomyosis has been treated by 200 mg of danazol contained in an intrauterine device (DIUD) (Igarashi et al., 1996). Blood danazol levels are undetectable, ovulation was not inhibited, and side-effects did not occur. The DIUD was effective in nine of 10 cases in reducing uterine size and dysmenorrhoea, and pregnancy occurred in three cases after removal of the DIUD. Another study of the DIUD containing 300 µg of danazol produced similar results over 6–12 months (Tanoaka et al., 1996). Symptoms improved in >70% of patients especially for dysmenorrhoea, the DIUD was shown to be active after 12 months use, mean CA125 concentrations decreased from 295 to 115 U/ml, mean uterine volume decreased from 369 to 264 cm³ and there were no changes in liver function or coagulation tests. Cohen et al. (1996) were unable to duplicate the beneficial effects of a 106 mg danazol IUD (18 patients) when comparing this to goserelin (four patients). The patients all had proven junctional zone hypertrophy on MRI. The lack of effect of the DIUD may be due to the high expulsion rate, or to lower endometrial danazol levels resulting from the lower dose of danazol in the DIUD when compared to the other studies. Using the DIUD in Australian women, three of four expelled the DIUD and a larger IUD would be required to test its efficacy.

The levonorgestrel intrauterine device (LNIUD) has proven to be effective not only as a contraceptive but also in the control of menorrhagia. Its action is to produce an atrophic endometrium. It may be useful in the control of menorrhagia in the presence of adenomyosis, and possibly the reduction of dysmenorrhoea. The anti-oestrogenic effect may reduce the growth of the adenomyotic tissue. A study of 25 women with menorrhagia associated with adenomyosis diagnosed by vaginal ultrasound has shown that 23 had relief of menorrhagia persisting for 1 year after use of the LNIUD (Fedele et al., 1997). Spotting in the first 3 months was the most common side-effect, one patient asking to have the device removed because of this. Six patients reported headaches, three breast tenderness, six greasy hair, seborrhoea or acne, and seven weight gain. Spotting was well tolerated.

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**References**


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