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Ulipristal Acetate for Symptomatic Uterine Fibroids and Myoma-Related Hypermenorrhea Joint Statement by the German Society for Gynecological Endocrinology and Reproductive Medicine (DGGEF) and the German Professional Association of Gynecologists (BVF)

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FÜR KLINIK & PRAXIS

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Ulipristal Acetate for Symptomatic Uterine Fibroids and Myoma-Related Hypermenorrhea

Joint Statement by the German Society for Gynecological Endocrinology and Reproductive Medicine (DGGEF) and the German Professional Association of Gynecologists (BVF)*

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Approximately 24 million European and more than 20 million North American women between the ages of 35 and 55 are suffering from uterine fibroids, i.e. 40% of all women in this age group are affected. The symptoms are excessive uterine bleeding, anaemia, pain and infertility. Many women find their quality of life severely compromised, and this leads to hysterectomy in many cases. So far there has been no effective and well-tolerated drug. The only approved drugs for the treatment of symptomatic uterine fibroids are GnRH agonists, but their use is relatively limited because of severe side effects due to the resulting low levels of estrogen causing hot flushes, depression, mood swings, loss of libido, vaginitis and loss of bone mineral density. As fibroid growth is dependent on progesterone, progesterone receptor modulators have proven effective in pilot studies. Two randomised double-blind studies have shown the effectiveness of the progesterone receptor modulator ulipristal acetate in the preoperative treatment of leiomyomas and the control of concomitant menorrhagia. No significant side effects have occurred under a dosage of 5 and 10 mg UPA over 3 months. A cessation of menorrhagia was observed after only 7 days, and a volume reduction of the uterine fibroids by 40% was achieved within 3 months and seemed to persist even 6 months after discontinuing the drug. A preparation with a dosage of 5 mg ulipristal acetate is available as Esmya® from the spring of 2012 for the preoperative treatment of leiomyomas. **J Reproduktionsmed Endokrinol 2013; 10 (Special Issue 1): 82–101.**

Key words: leiomyomas, uterine fibroids, menorrhagia, treatment options, ulipristal acetate, GnRH analogues, steroid hormones

■ Introduction

Myomas are benign monoclonal pelvic tumors with an estimated cumulative incidence of 70% in women aged 50 and above (including small myomas) [1] and thus constitute the leading indication for hysterectomy in the US [2].

The prevalence in clinical populations ranges from 20–77% [3–5]. It increases with age until the menopause [3]. The estimated lifetime prevalence in the different populations is 25–50% [6]. In a pathological examination after hysterectomy, leiomyomata were found in 77% of the cases [5].

The incidence of women with uterine fibroids in the US is estimated at 35 mil-

lion, but only half of them are diagnosed because they are frequently asymptomatic [7–9]. About a third of the patients with diagnosed leiomyomata decided to have an operation [10] (Fig. 1).

The prevalence of uterine fibroids also depends on ethnicity. The incidence rates for Hispanic or Asian populations in the US is comparable with the incidence among Caucasian women [3]. However, all authors state that the risk among African-American women is twice as high as that in other ethnic groups [5, 11, 12].

These results could be biased by other factors like BMI or diabetes or by the fact that African-American women become clinically symptomatic at an early stage [12]. After adjusting for parity and

BMI, the incidence dropped from 2.9 to 2.1 [1].

African-American women usually become clinically apparent at least 4 years earlier than Caucasian women – the peak is between the ages of 30 and 50 [13, 14] (38/10,000 vs 16/10,000 women). Their symptoms are also more pronounced, which accounts for the subsequent hysterectomy rate [15].

Leiomyoma Localisation

Most uterine fibroids are located in the corpus uteri and only 8% in the cervix. Half of them have an intramural, 35% a subserous, 5% a submucosal and 2% an intraligamentary location [16].

The therapy indications depend mainly on the clinical symptoms and factors

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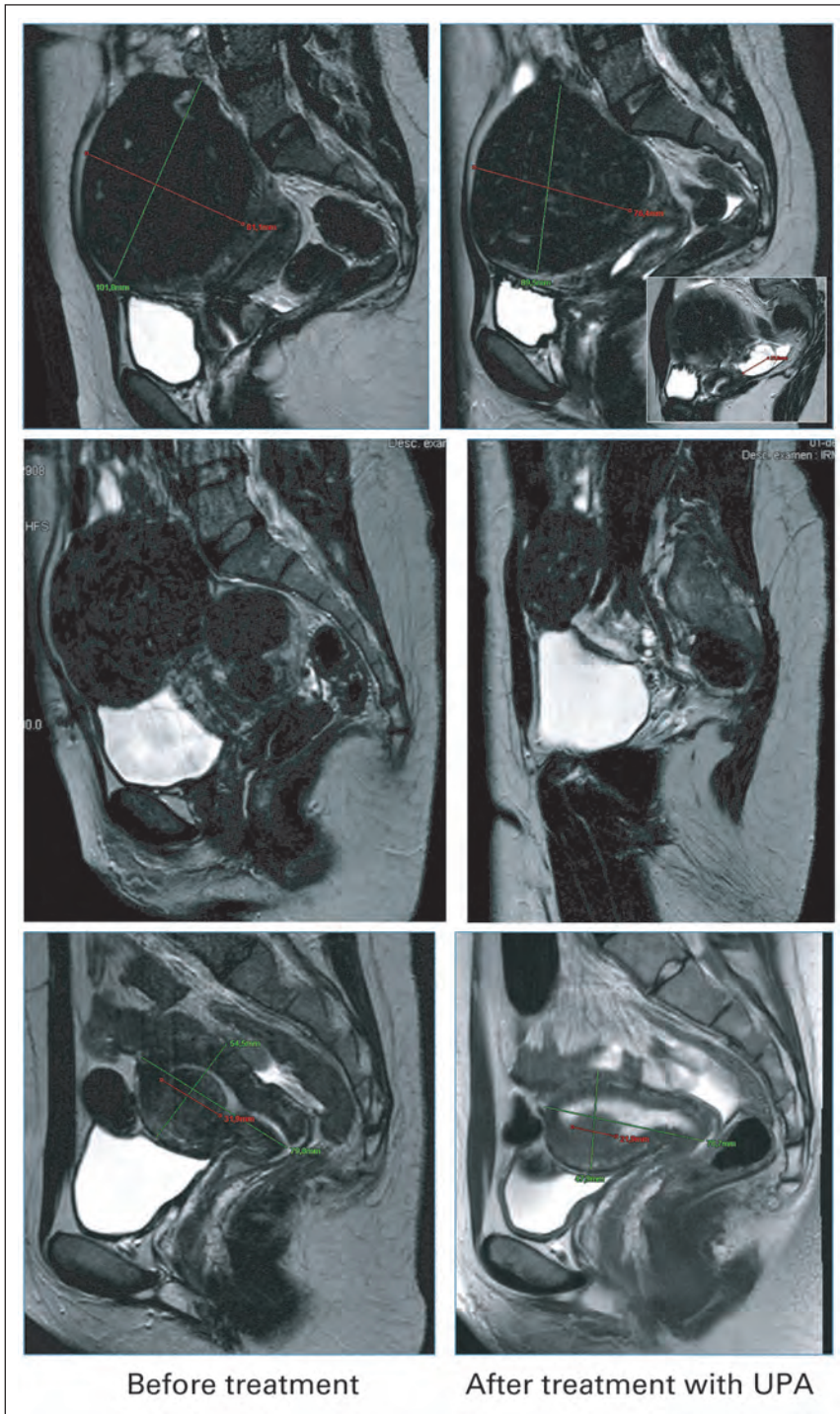


Figure 1. PEARL-I-Study on the use of ulipristal acetate in women with uterine fibroids and hypermenorrhea leading to anaemia. Illustration of three examples of myoma shrinkage under ulipristal acetate based on MRT findings before and after therapy. Courtesy of Jacques Donnez, Brussels. Reprinted with kind permission.

such as size progression, necrosis, infection or torsion. If the patients seek a definitive remedy and want no more children and if the symptoms are severe, hysterectomy is the gold standard, leading to highly satisfied patients [17]. By comparison, myomectomy is associated with longer operating times, higher blood loss and the risk of relapse in 1 out of 5 cases [18].

Histopathology

Uterine fibroids are benign, mesenchymal, smooth-muscle type tumours with a varied fibrous stroma occurring predominantly in the corpus uteri, but also in the uterine ligaments. Generally, they are of monoclonal origin. There are no reliable clinical or image-based criteria for the malignancy of uterine leiomyomata; most leiomyosarcomas of

the corpus uteri are diagnosed accidentally.

Malignancy may be suspected in cases of big and fast-growing fibroids after the menopause or growth increase under GnRH agonist therapy. Nodules which are smaller than 5 cm have a lower risk of malignancy, and no metastasis has been described for a size < 3 cm [19]. Uterine leiomyosarcomas can develop from benign uterine leiomyomas, but they can also develop *de novo* [20]. By contrast with benign uterine leiomyomas, uterine leiomyosarcomas are very rare and only account for around 1% of all malignomas of the corpus uteri [21], the reported incidence is 0.64/100,000 women per year [22]. The average age of patients with leiomyosarcomas is 10 years above that of patients with leiomyomas and is mostly > 40 years. Tumors with some but not all features of a uterine leiomyosarcoma are called STUMP (smooth muscle tumors of unknown malignant potential) [23].

Pathogenesis

A review by Laughlin et al [24] states that metabolism, diet, stress and environmental factors play a role in the genesis of uterine fibroids.

Although the causes of uterine leiomyomas are unclear, it is assumed that their growth is stimulated by estrogens, progesterone and growth factors such as “insulin-like growth factor” and “transforming growth factor- β ” [25–28]. Myomas occur after the menarche [29] and their frequency decreases after the menopause [30, 31]. Based on these findings, the increased hormone levels in pregnancy should promote the growth of leiomyomas. However, the leiomyoma risk is 20–50% lower in parous women compared with nulliparae, and it seems to decline with increasing parity [31–34]. This inverse correlation between parity and the occurrence of leiomyomas is associated with increased coagulation and the resulting transient ischaemia under childbirth [35].

Prevalence studies based on sonographic examination show that the growth of leiomyomas begins at a young age and increases until the menopause in all populations [36, 37].

In a review, Okolo [38] looks at the incidence, etiology and epidemiology of

uterine fibroids and arrives at the following conclusions: The most important regulators for the growth of myomas are ovarian steroids (both estrogens and progestogens), growth factors and angiogenic factors as well as the process of apoptosis. The risk factors are African-American ethnicity, heredity, nulliparity, obesity, PCO syndrome, diabetes and hypertension. There are indications that a family predisposition for leiomyomas is linked to a typical pattern of clinical and molecular characteristics. In this context, a somatic mutation of the MED12 gene is reputed to play a key role [39, 40].

Nothing is known about a link between the genesis of leiomyomas and hormonal contraceptives. However, in a study by the Oxford Family Planning Association [31], a 30% reduction of myomas was shown under the hormonal contraceptives used in the 1980s. Later on, this was confirmed e.g. by a large case control study showing a 50% risk reduction [41], although some studies disagree.

Concomitant Symptoms

Although only 0.5% of the reported cases of uterine fibroids are malignant [42, 43], they are the main cause of hysterectomy in the US [15, 44].

Uterine fibroids are often associated with a loss of energy which can lead to loss of employment and higher individual and social health care costs [45]. Leiomyoma patients typically complain about menorrhagia, anaemia, a feeling of pressure in the small pelvis and/or pain, a feeling of tension in the abdomen, urinary frequency, constipation and (rarely) miscarriage or infertility [14, 46].

Psychological Aspects of Leiomyomas

As many women are shocked when they are suddenly diagnosed with uterine fibroids, they also often worry about the following issues [47]:

1. Risk of malignancy
2. Need for hysterectomy
3. Influence of fibroids on fertility and the course of pregnancy
4. Will the fibroids continue to grow and, if so, how can their growth be stopped?
5. What kind of problems will I face if I do nothing?

Therapy Options for Uterine Leiomyomas

The main therapy options currently available are **surgical** and **radiological** procedures. So far, there have been limited options for effective, long-term **drug** therapy [48–55] (Tab. 1).

Hysterectomy is still the most frequent therapeutic consequence of symptomatic leiomyomas globally. In Germany, 94,066 hysterectomies were performed based on a diagnosis of uterine leiomyomas in 2000. This means hysterectomies with this diagnosis rank 13th on the German league table of operations [56].

In the last decade, the surgical options have expanded, especially for myomas with severe symptoms: laparoscopic operation, supracervical hysterectomy, myomectomy, myoma embolisation etc. But alongside more sophisticated surgical procedures, drug therapies have also developed. The large-scale application of hormonal contraceptives in various dosages, progestogens and administration regimes (21 + 7 days, 24 + 4 days long cycle) means that many women with originally symptomatic uterine fibroids become asymptomatic. GnRH analogues have emerged particularly for infertile patients with submucosal myomas. The possibility of using the progesterone receptor modulator ulipristal acetate, which leads to amenorrhea and shrinking leiomyomas within days, has widened the scope for customised and, crucially, organ-saving treatment. This means that there is now a wide range of therapy options available to each patient depending on the number and size of her fibroids as well as her symptoms, the degree of suffering and her individual wish for adequate treatment, but also depending on whether or not she wishes to retain her uterus and her fertility.

Surgical Options

Many patients require surgical intervention, but the therapy decision should be based on the patient's age and on whether or not she wishes to retain her fertility and avoid hysterectomy [48]. Uterine fibroids are the most frequent cause of hysterectomy [57].

Depending on their location, uterine fibroids can be enucleated by surgical

hysteroscopy, laparoscopy or laparotomy.

Even after a successful primary operation, the patient should be informed about the risk of relapse. Such relapses after myomectomy have been observed in approx. 25% of the cases in a small study (n = 165) [58]. Hirsch [18] also reports a 20% relapse risk.

Myomectomy

In myomectomy, individual myomas are removed while preserving the uterus and the patient's fertility. Depending on the location, they can be removed by laparotomy, mini-laparotomy, laparoscopy, laparoscopically assisted mini-laparotomy, robot-assisted laparoscopy or hysteroscopy [59]. Laparoscopic operations have a lower risk of producing adhesions than open laparotomy [60].

Up to 80% of the patients report an absence of symptoms after myomectomy [61, 62]. However, it should be noted that there are very limited data about the therapeutic long-term success in terms of freedom from symptoms. At the moment, there are no sufficient data about the recurrence of myomas after the therapy, and procedures such as hysterectomy, myomectomy and others cannot be properly compared with each other.

Rein et al. [63] have reviewed the different surgical procedures for the treatment of leiomyomas.

Surgical Hysteroscopy for the Removal of Intracavitary Fibroids

For submucosal myomas, surgical hysteroscopy is the preferred therapy due to optimal access, minimal perioperative morbidity and a short recovery period [64]. Prior administration of GnRH analogues seems to be advantageous, in particular for women who wish to have children or had habitual abortions [65]. The reported complication rate is 1–2% [66]. The main factors which can lead to complications are myoma size above 5 cm, probe length > 12 cm, 3 or more myomas as well as a large intramural portion of the myoma [67].

When enucleating a myoma, a safety margin of > 8 mm should be kept between the serosa and the fibroid capsule

Table 1. Different Options for the Therapy of Uterine Leiomyomas. From [54].

Therapy approach	Suitable patient group	Advantages	Disadvantages	Possible consequences for fertility and subsequent pregnancies
GnRH agonists	Preoperative therapy for young or premenopausal women	Non-surgical	Temporary treatment with renewed myoma growth after cessation; side-effects	None
GnRH agonists + estrogen/progestin ("add back")	Preoperative therapy for young or premenopausal women	Non-surgical	Temporary treatment with renewed myoma growth after cessation	None
GnRH antagonists	Preoperative therapy for young or premenopausal women	Non-surgical	Temporary treatment with renewed myoma growth after cessation	None
Progestin therapy	Women with myomas	Non-surgical	No long-term data; side-effects	No data
Oral hormonal contraceptives	Patients with small myomas and bleeding disorders	Non-surgical; good, also preventive effect for mild to moderate bleeding disorders; contraception	Breakthrough bleeding possible, especially in submucosal myomas; no influence on myoma growth(?)	None
Hysterectomy	Women requiring hysterectomy, about to enter menopause or not wishing to preserve fertility	Final therapy	Loss of fertility; surgical morbidity and/or mortality; high costs	Complete loss of fertility
Myomectomy	Women with visible and/or palpable myomas	Fertility preservation	Myoma recurrence possible; surgical morbidity	Risk of uterine rupture during subsequent pregnancy
Myolysis/cryomyolysis	Women with multiple, small myomas who do not wish to preserve fertility	Uterus retention; outpatient procedure	Risk of adhesions; less effective in large and multiple myomas; under- or overtreatment; subsequent pregnancies not recommended	Reduced fertility due to adhesions, risk of uterine rupture during pregnancy; pathological placental development
UAE (uterine artery embolisation)	Women with symptomatic uterine fibroids irrespective of size and number except isolated, submucosal fibroids type 0 and 1 (ESGE) submuköse Myome Typ 0 and isolated subserous pedunculated fibroids	The whole uterus is treated; no blood loss and no surgical intervention with opening of abdominal cavity	Postinterventional, intense pain therapy; age-dependent risk of premature ovarian insufficiency and transient or permanent amenorrhea; possible post embolisation syndrome; high cost; frequent secondary interventions; radiation exposure similar to 2–3 abdominal CTs; only in the hands of specialised radiologist	Effects on fertility still to be investigated; reduction of ovarian reserve; placentation disorders and increased postpartal bleeding have been described
LUAO (laparoscopic uterine artery occlusion)	Women with small or large subserosal myomas	Effective if practitioner has adequate experience with the method	Requires experience; depends on location of fibroids; fertility unclear; insufficient long-term data	No data
MRgFUS (magnetic resonance imaging-guided focused ultrasound surgery)	Women with small myomas (< 8 cm)	No intraabdominal surgical intervention; no blood loss; patient can resume activity soon	Fertility unclear; relapse rate unclear; high costs; insufficient data; procedure requires specialised radiologist	No sufficient data

[63]. Very extensive coagulation can lead to necrosis, thereby increasing the complication rate of subsequent pregnancies [18].

Patient satisfaction is very high after this surgical procedure (80–100%) [64]. No final conclusion has been drawn about fertility outcome; it seems to depend on many factors [48].

Based on a classification by Wamsteker, submucosal myomas can be hysteroscopically resected if they correspond to grade 0 (no intramural involvement), grade 1 (intramural portion < 50%) and grade 2 (intramural portion > 50%) with a size < 5 cm. As from grade 2 and asize above 5 cm, the intervention should be performed transabdominally [63].

Advantages: Minimally invasive operation, low complication rate, organ retention, fertility preservation, good effects on patients wishing to have children or after habitual abortion.

Disadvantages: Risk of postoperative adhesions in the uterine cavity. Complications through liquid distension, intraoperative bleeding problems possible.

Laparoscopic Enucleation

The laparoscopic enucleation of myomas is a minimally invasive endoscopic operation with a smaller number of peri- and postoperative complications. It is particularly suitable for patients with subserous and intramural myomas. The candidates for this procedure have to be carefully selected: Very extensive transmural myomas or myomas on the back wall of the uterus should rather be treated by laparotomy. With respect to the recurrence of myomas, there is no significant difference between laparoscopic procedures and laparotomies [58].

Intramural myomas located close to the cavity are associated with the highest risk of uterine rupture. However, at 0.002%, it is much lower than after a Caesarean section [65, 66]. In a second-look study, adhesions were found in 36% of the women treated by myomectomy [68].

In large populations, the rate of conversion to abdominal hysterectomy is 1–13.3% and also depends on the surgeon's experience [49, 69, 70].

The fibroid recurrence rate is between 12.7 and 27% for laparoscopic myectomy [58, 59]. It seems to be accepted that childbirth reduces the risk of recurrence after a myomectomy [71].

Advantages: Minimally invasive operation, low complication rate, organ retention, fertility preservation.

Disadvantages: Possibility of perforating the cavity in the case of myomas located in its vicinity. Risk of uterine perforation during pregnancy.

Abdominal Enucleation of Myomas

A laparotomic myomectomy is indicated for multiple fibroids in a location which is difficult to access by laparoscopy, e.g. on the back wall of the uterus, at the cervix or between the ligaments. *“Myomas with a diameter > 10 cm or > 5 myomas > 4–5 cm should primarily be removed by laparotomy”* [63].

Again, pretreatment with GnRH analogues also seems to have a positive influence on the operating conditions as well as on blood loss [64].

Uterine size is also a decisive success factor for the operation. In a retrospective analysis of patients with big uteri (e.g. 16 weeks of gestation), the median operating time was 236 minutes (120–390 minutes) and the average blood loss was 794 ml (50–3000 ml) [72]. It should also be considered that 10–26% of the patients undergoing myomectomy went on to have a hysterectomy at a later stage [73, 74].

Advantages: Depending on the selected operating method: Possibility of removing multiple or very large myomas, removing myomas from the back wall of the uterus, nerve-saving operation in the case of a supracervical hysterectomy.

Disadvantages: Opening of the abdomen, higher likelihood of perioperative complications.

Hysterectomy

In Germany, 125,000 hysterectomies are performed every year to treat a benign disease of the uterus [75]. Between 2004 and 2006, 25,000 of them (20%) were carried out for patients with excessive or too frequent menstruation without any pathological changes of the uterus [76].

In 2000, 94,066 hysterectomies were carried out for a diagnosis of uterine myoma. This means uterine myomas rank 13th on the league table of hospital diagnoses (DRG analysis). In the US, more than 200,000 hysterectomies were carried out annually to treat uterine leiomyomas. This means that myomas were the cause of 60% of all hysterectomies in the US [15, 77].

Alongside abdominal and vaginal hysterectomies, more recent methods such as laparoscopically assisted vaginal hysterectomy (LAVH), laparoscopic supracervical hysterectomy (LASH) and total laparoscopic hysterectomy (TLH) have emerged.

Vaginal hysterectomy is considered the standard method [63].

Laparoscopic hysterectomies are associated with a lower intraoperative blood loss than abdominal hysterectomies [78].

Studies by Gimbel [79] and Jenkins [80] have shown that operating time, blood

loss as well as the peri- and postoperative complication rates are significantly lower if a laparoscopically assisted supracervical hysterectomy (LASH) is performed. The integrity of the pelvic floor is also preserved, the quality of life is much higher and the sexual function is unimpaired [81].

Preoperatively, many women are worried that the hysterectomy and the associated infertility might lead to a loss of femininity and to menopausal symptoms. In a review, Gitlin and Pasnau [82] have shown that depression is no more frequent after hysterectomy than in other life situations.

De Wilde and Hucke [83] stress that it is nearly always possible to carry out a hysterectomy without a laparotomy. For the patients, this leads to a lower operative trauma with only a short postoperative recovery phase.

Advantages: Depending on the operating method chosen, possibility of removing multiple or very large myomas, removal of myomas from the back wall of the uterus, nerve-sparing operation due to supracervical hysterectomy, additional possibility of assessing the surgical site, combination with incontinence and prolapse operations possible.

Disadvantages: Premature onset of the menopause (if the ramus ovaricus of the arteria uterina is ligated) and increased frequency of depressive mood) [84, 85].

Ligation of the Arteria uterina

An alternative to embolising the arteria uterina is to occlude it laparoscopically (LUAO = laparoscopic arteria uterina occlusion). It is a relatively recent surgical procedure requiring advanced laparoscopic skills. Up until now, not many data about its safety and effectiveness are available. In a study including 68 women treated by LUAO, the symptoms improved 3 to 36 months postoperatively in 93% of the patients. After 12 months, the average reduction in uterine volume was 39% and the reduction of the biggest myoma 58% [86]. In another study, 114 women were followed up after LUAO. The median follow-up was 24 months; 7% of the women developed complications, and 9% had a relapse. Two patients needed a hysterectomy/myomectomy because the

myomas necrotised [87]. The limitations of this procedure are the location of the myomas and the associated possible morbidity/mortality due to surgery [87].

Ligating the arteria uterina when performing a laparoscopic myomectomy can also lead to a reduction of the post-operative complaints and of intrauterine blood loss [88]. The advantages of LUAO are that the uterus can be preserved and that it is an outpatient procedure. However, long-term clinical data are necessary to establish whether LUAO is suitable for women wishing to retain their fertility [89].

Doppler-Guided Occlusion of the Arteria uterina

The Doppler-guided occlusion of the arteria uterina is a new option in the treatment of fibroids. Studies on the subject are ongoing in the US, Canada, Mexico and Europe. It is a minimally invasive, outpatient procedure in which the arteria uterina is blocked by a vascular clamp introduced transvaginally. So far, one study has been published, covering 109 healthy premenopausal women [90].

■ Uterus Artery Embolisation (UAE)

In uterus artery embolisation (UAE), polyvinyl alcohol particles are injected into the branches of the uterine artery, which supplies the myoma with blood. As a result, the blood supply to the uterine myoma is reduced.

Many results are available in Europe and the US, where more than 10.000 UAE procedures have been performed to date. Controlled studies have demonstrated a technical success rate of approx. 98%. In more than 90% of the cases, the patients' complaints were successfully reduced [91].

UAE is used to treat symptomatic fibroids [92–94]. The first reports on successful pregnancies after UAE were published shortly after the introduction of the method [95, 96]. However, some case reports described a number of complications; in larger series, premature ovarian insufficiency and an increased risk during placentation occurred age-dependently [94, 97–100].

Indications: According to a consensus paper by Kröncke et al. [101], the indication for a UAE is symptomatic leiomyoma. UAE is also an alternative to the surgical approach for multiple or large myomas and patients with reduced operability or multiple prior operations in the abdomen.

Pregnancy, florid infection, potentially malignant process and the wish to have children are **absolute contraindications**.

The relative contraindications include renal insufficiency, intolerance to contrast media, manifest hyperthyroidism and GnRH analogue treatment in the previous three months (risk of vascular spasms).

The current limitations of the UAE procedure are subserosally pedunculated fibroids and submucosal fibroids type 0 and 1 (ESGE). For the therapy of cervical and parametric myomas, the data situation is still unclear. There is no limitation in terms of the number of fibroids. Good therapy results can even be expected for uteri with diffuse, widespread myomas. From a radiological, technical point of view, there is no upper limit for the treatable fibroid size. Postmenopausal patients should only be treated in exceptional cases.

Advantages: Short, minimally invasive treatment method.

Disadvantages: Risk of radiation exposure [102]. It is also unclear whether the induced necrosis of the myoma leads to further metabolic reactions including immunological reactions and whether a cocarcinogenesis could be triggered. There is a strongly increased risk of infection, and premature menopause is a possible effect. The method is not suitable for women wishing to preserve their fertility. No long-term data are available.

Further information:

Deutsche Röntgengesellschaft: <http://www.myomembolisation.org>

Society of Vascular and Interventional Radiology: <http://www.sirweb.org/patPub/uterine.shtml>

Which Surgical Method is the Best?

The choice of surgical technique depends on location (subserosal, intramural, submucosal), patient age, her wish to preserve her fertility and additional complaints (e.g. bleeding disorders, uterine prolapse). The patient should be informed about the risk of recurrence, which can be up to 20% even after a primarily successful operation [18, 58].

Organ-saving myomectomy is the method of choice if the patient wants to preserve her fertility or if the myomas are submucosal and easily accessible. In these cases, uterine artery embolisation is no option [83].

■ Further Myolytic Methods

Myolysis means the destruction of the muscular tissue. It is generally recommended for smaller myomas but must be excluded for women who want to preserve their fertility. Due to uterine scars and infections after the treatment, it can cause severe pregnancy complications which are dangerous both for the mother and the child.

Further reading:

www.health.ny.gov/community/adults/women/uterine_fibroids/

Laser Myolysis by Laparoscopy

The laser removes the myoma or interrupts the blood supply of the myoma so that it shrinks or possibly dissolves [103, 104].

Laparoscopic or MRT-Guided Cryomyolysis

In cryomyolysis, liquid nitrogen is used to freeze the myoma [105, 106]. The intervention can be carried out under laparoscopic or MRT guidance [107].

Myolysis using Electricity and Myoma Coagulation (by Laparoscopy)

An electrode is introduced into the myoma, causing a strong temperature rise which destroys the myoma and cuts off its blood supply.

Uterine Fibroid Embolisation (UFE)

Alongside UAE (uterine artery embolisation), another option is uterine fi-

broid embolisation, in which the particles are not distributed non-specifically via the uterine artery (via the whole of the uterus and possibly the ovarian arcade, but delivered selectively to the individual fibroid feeders. This leads to greatly reduced side-effects in terms of ovarian damage, fertility and hormone production and causes less damage to the healthy uterine wall. The method should also be considered for women wishing to preserve their fertility if no alternative myoma therapies are available [108].

Magnetic Resonance-Guided Focused Ultrasound Surgery (MRgFUS)

The goal of the focussed ultrasound therapy is to increase the focal temperature inside the uterine myomas non-invasively and without surgical intervention so as to effect their progressive destruction or cause substantial damage to them without injuring neighbouring tissue or skin. The therapy is monitored by MRT (real-time imaging and thermometry). Under MRT control, focussed ultrasound waves are targeted directly at the myoma (web.rad.charite.de/static/pdf/mrgfus-patienteninfo.pdf).

MRgFUS (or FUS) was first used in 2000 for the treatment of symptomatic uterine fibroids and described as an effective method to treat myoma-related symptoms [109–114].

The Hospital for Radiotherapy at the Charité in Berlin and the FUS Center in Dachau have practiced the highly focussed ultrasound therapy of myomas for many years. The procedure has proven effective in alleviating complaints caused by myomas and leads to a reduction in the size of the residual thermoablated tissue.

So far, more than 8,000 patients have been treated with the method. Using the most recent device generation (Insightec Ltd), average ablation rates of more than 85% of the vital fibroid tissue can be achieved (own data, Matzko FUS Center Klinikum Dachau). A good therapy result always depends on the suitability of the patient for the procedure. This is determined by examining the patient's pelvis by MRI. The relevant factors are the position, blood supply and number

of fibroids. The method is particularly suitable for the ablation of intramural and submucosal fibroids without causing scars on the myometrium, which would make the uterus vulnerable to ruptures when it is distended during pregnancy.

Large and vascular myomas as well as adenomyosis can also be treated in this way (<http://www.uterusmyomen.de/?catID=40826&siteLang=8>) [115]. Fertility is not compromised [116]. Cases of pregnancy occurring after the therapy have been reported [116–120].

Advantages: Short, non-surgical, non-invasive outpatient therapy for myomas, adenomyosis and many tumours. After 24 h, the patients can return to their daily routines.

Disadvantages: Very rarely, mild to moderate thermal lesions of the skin surface, and occasionally, thermal damage to the small intestine have occurred which required surgical repair. No adequate data are available about the development of posttherapeutic adhesions. It is also unclear whether the necrosis of the fibroid can lead to further metabolic reactions including immunological reactions and whether cocarcinogenesis can occur. No long-term data are available in this respect.

Note: Experience has already been made in Germany with the successful MRgFUS treatment of nearly 600 fibroid patients. There were few side effects, and 8 pregnancies have been reported [M. Matzko, Radiology Dept., Klinikum Dachau, personal communication 2012].

■ Drug Therapy

Data from fundamental research and clinical studies demonstrate that progesterone and the progesterone receptor (PR) plays a key role in the growth of uterine leiomyomas [121]. Several studies have shown an increased concentration of both progesterone receptor isoforms (PR-A and PR-B) in leiomyoma tissue compared with the adjacent myometrium [122, 123].

Progestogens have an effect either on cell division, apoptosis, uterine blood flow or, indirectly via central hypo-

thalamic-pituitary inhibition, on a decrease in estrogen and progesterone secretion [51]. The estrogen dependency of myoma growth has been shown in studies with GnRH agonists as measured by the shrinkage of the myomas (see GnRH analogues).

Compared with the adjacent myometrium, mitotic activity is reduced in leiomyoma tissue during the luteal phase and after treatment with medroxyprogesterone acetate [124, 125]. Progesterone suppresses apoptosis and stimulates the proliferation of leiomyoma cells in culture, while PR modulators inhibit proliferation and induce apoptosis [126–131].

The oral administration of **progestogens** to control bleeding and myoma growth has not been fully investigated, but smaller studies report a possible progression of the myoma growth caused by progesterone or synthetic progestogens [51, 132–134].

In a study by the Oxford Family Planning Association in the 1980s, oral hormonal contraceptives led to a 30% reduction of myomas [135], a finding later confirmed in a large case-control study showing a risk reduction by 50% [41], although some authors disagree. Whether a higher dosage of the combined oral contraceptives and their composition have played a role in this result is unclear.

Androgens are considered obsolete in myoma treatment (e.g., Danazol leads to bleeding control, anaemia improvement, myoma shrinkage and a reduction in uterus size. However, there are numerous side effects, such as weight gain, dysphoria incl. depression, acne, headache, increased hair growth and deeper voice) (<http://www.mayoclinic.com/health/uterine-fibroids/DS00078>).

Levonorgestrel-releasing intrauterine systems (IUS) led to bleeding control in some of the patients, but the studies excluded patients with uterine cavity abnormalities caused by submucosal myomas [136]. IUS can be used for myomas which do not deform the uterine cavity, but they result in increased bleeding irregularities, the device expulsion rate is higher than in women without uterine fibroids and the effect on myoma growth

Table 2. Progesterone receptor modulators used in the treatment of uterine fibroids. From [Bouchard et al. 2011; by courtesy of the authors and most recent data on ulipristal acetate according to Donnez et al. [143, 144].

Study	Study design	Treatment regimen/dosage	n	Treatment period	Main study results
Ulipristal acetate (UPA)					
Levens et al. 2008 [168]	R, DB, PC			3 cycles or 90–102 days	Change in leiomyoma volume (%) Amenorrhea during cycle 3 (% women)
		Placebo	8		+6 0
		UPA (10 mg daily)	8		–36 87.5
		UPA (20 mg daily)	6		–21 100
UPA was tolerated well.					
Nieman et al. 2011 [169]	R, DB, PC			3 cycles or 90–102 days	Change in leiomyoma volume (%) Amenorrhea during treatment (% women)
		Placebo	12		+7 0
		UPA (10 mg daily)	13		–17 61.5
		UPA (20 mg daily)	13		–24 92
UPA was tolerated well.					
Donnez et al. 2012 [143]	R, DB, PC			12 weeks	Change in leiomyoma volume (%) after 12 weeks Amenorrhea after 12 weeks (% women)
		Placebo	48		+3 6
		UPA (5 mg daily)	95		–21 73
		UPA (10 mg daily)	94		–12 82
UPA was tolerated well.					
Donnez et al. 2012 [144]	R, DB			12 weeks	Volume change of the biggest leiomyoma (%) Amenorrhea after 12 weeks (% women)
		Leuporelin acetate (3.75 mg/month)	93		–36 75
		UPA (5 mg daily)	95		–42 89
		UPA (10 mg daily)	93		–53 80
UPA was tolerated well.					
Asoprisnil					
Chwalisz et al. 2007 [170]	R, DB, PC			12 weeks	Mean change of uterine volume (%) Amenorrhea (% women)
		Placebo	31		+1 0
		Asoprisnil (5 mg daily)	33		–14 16
		Asoprisnil (10 mg daily)	29		–9 36
		Asoprisnil (25 mg daily)	36		–17 70
Asoprisnil was tolerated well.					
Wilkens et al. 2008 [171]	R, DB, PC			12 weeks	Mean volume change of biggest leiomyoma (%) Average number of cycle days in cycle 3
		Placebo	10		+4.9 7.3
		Asoprisnil (10 mg daily)	12		–0.4 1.2
		Asoprisnil (25 mg daily)	11		–25.8 0.2
Asoprisnil was tolerated well.					
Telapristone acetate					
Wiehle et al. 2008 [172]	R, DB, PC			3 months	Change in leiomyoma volume (%)
		Placebo			–10.6
		Telapristone acetate (12.5 mg daily)			–17.9
		Telapristone acetate (25 mg daily)			–40.3
		Telapristone acetate (50 mg daily)			–40.3
		Leuporelin acetate (3.75 mg monthly)			–32.6

Continuation ►

AE: adverse effects; DB: double blind; NS: not statistically significant; OL: open label; PC: placebo-controlled; R: randomised; SB: single-blind

Table 2 (continued). Progesterone receptor modulators used in the treatment of uterine fibroids. From [Bouchard et al. 2011; by courtesy of the authors and most recent data on ulipristal acetate according to Donnez et al. [143, 144].

Study	Study design	Treatment regimen/dosage	n	Treatment period	Main study results
Mifepristone					
Eisinger et al. 2005 [161]	R, OL			1 year	Change of mean uterine volume after 1 year (%)
		Mifepristone (5 mg daily)	18		–52
		Mifepristone (10 mg daily)	10		–53
					1 patient in the 10 mg mifepristone group had a simple endometrial hyperplasia.
Fiscella et al. 2006 [162]	R, PC			26 weeks	Change of mean uterine volume (%)
		Placebo	20		10
		Mifepristone (5 mg daily)	22		–47
Carbonell Esteve et al. 2008 [163]	R			3 months	Change of leiomyoma volume (%)
		Mifepristone (5 mg daily)	50		–57
		Mifepristone (10 mg daily)	49		–45
					1 patient in the 10 mg mifepristone group had a simple hyperplasia.
Bagaria et al. 2009 [164]	R, DB, PC			3 months	Mean change of leiomyoma volume (%)
		Placebo	20		+0.5
		Mifepristone (10 mg daily)	20		–30.2
Eisinger et al. 2009 [165]	OL			6 months	Mean change of uterine volume (%) after 6 months
		Mifepristone (2.5 mg daily)	23		–11
					Cystic, glandular dilation, but no endometrial hyperplasia or atypia.
Engman et al. 2009 [166]	R, PC			3 months	Mean change of leiomyoma volume (%)
		Placebo	16		+6
		Mifepriston (50 mg every other day)	14		–28
					No premalignant changes.
Feng et al. 2010 [167]	Partially, R, PC			6 months	Change of uterine volume (%)
		Placebo	19		+17.7
		Mifepristone (2.5 or 5 mg daily)	43		–17.6

AE: adverse effects; DB: double blind; NS: not statistically significant; OL: open label; PC: placebo-controlled; R: randomised; SB: single-blind

is discussed controversially [137]. On the other hand, numerous studies have shown that the IUS helped avoid hysterectomies in cases of idiopathic hypermenorrhea [138–141].

Agonists of the gonadotropin-releasing hormone (GnRH) belong to the most effective pharmacological therapies [132, 142–144].

Filicori et al. [145] were the first to show that GnRH agonists reduce the size of

leiomyomas in rats. The first clinical study by Maheux et al. [146] showed myoma shrinkage under this therapy in 3 patients. Follow-up studies documented a myoma size reduction under GnRH analogues for at least 3 months [147, 148]. All of this suggests that myoma growth is estrogen-dependent. In a placebo-controlled study, the GnRH agonist leuporelin acetate (3.75 mg as a depot) led to a suppression of the vaginal bleeding in 85% of the patients who were anemic before the myoma treat-

ment. However, under the leuporelin acetate therapy to suppress estradiol formation, hot flushes occurred in 67% of the patients [149].

After discontinuing the GnRH agonists (leuporelin, buserelin), the volume of the uterus/myoma starts increasing again within 3 to 12 months [147, 150–152].

Furthermore, GnRH agonists have only been approved for short-term treatment due to drug safety issues (loss of bone

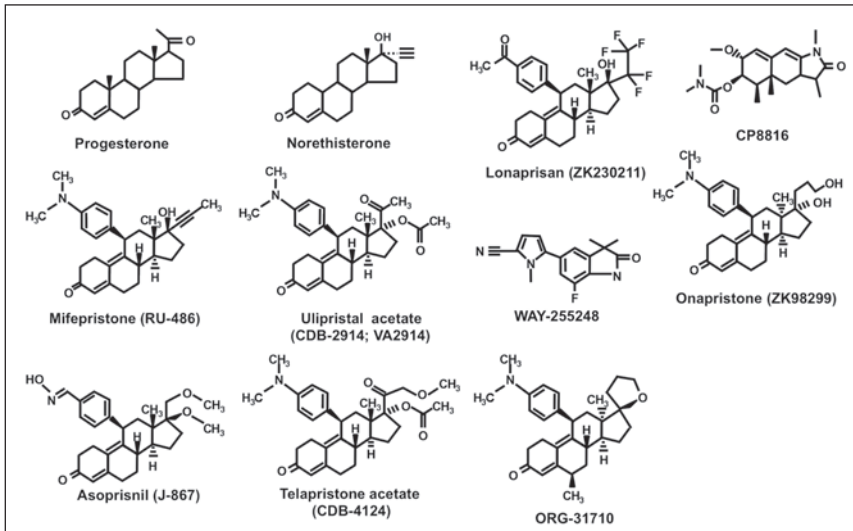


Figure 2. Progesterone receptor modulators – (most important) structural formulas.

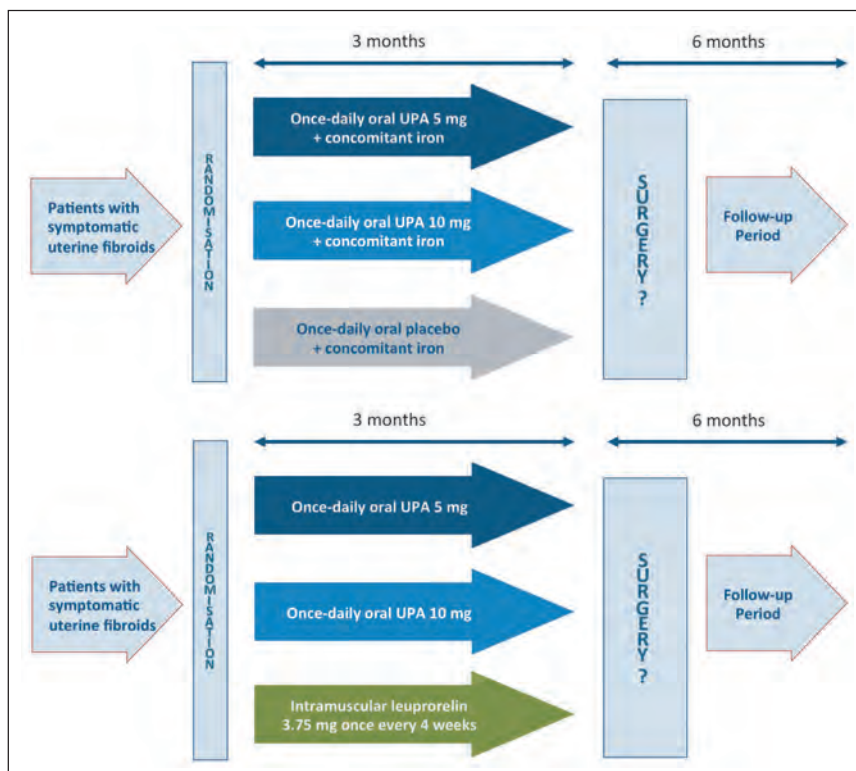


Figure 3. PEARL-I-Study (top): In this randomised, double-blind, placebo-controlled study, women who initially had excessive bleeding and consecutive anaemia achieved effective control of their bleeding and shrinkage of their myomas by taking oral ulipristal acetate in a dosage of 5 or 10 mg/day. Compared with placebo, ulipristal acetate resulted in a clinically relevant rise in hemoglobin and hematocrit levels as well as in a reduction of the myoma-related pain and complaints reported by the patients (the inclusion criteria specified that the patients were due to have a myoma operation, but only a part of the patients had to be operated upon after the treatment). **PEARL-II-Study (bottom):** The question was whether daily oral ulipristal acetate (5 or 10 mg) was inferior to a monthly intramuscular injection of leuporelin acetate (3.75 mg) in terms of controlling the bleeding prior to a planned operation for symptomatic myomas. The side effect profiles of both drugs were compared with each other. Based on data by Donnez et al. [143, 144]. Reprint with kind permission of Preglem SA, Geneva.

mineral density). Preoperative treatment with GnRH agonists resulted in increased use of the vaginal instead of the abdominal route for hysterectomy and the intraoperative blood loss was reduced. The side-effects of the GnRH

agonists such as hot flushes and atrophic vaginitis have a negative impact on compliance [142]. Several small studies describe an “add-back” therapy using estrogens/progestogens together with GnRH analogues for myoma therapy to

avoid hot flushes and bone mass loss [153] (Tibolone: [154]) and Raloxifene: [155]) resulting in a resumption of myoma growth, e.g. under hormone replacement therapy. After an initial volume decrease achieved by the GnRH agonist goserelin, hormone replacement therapy (0.3 mg conjugated equine estrogens and 5 mg medroxy progesterone acetate) as an “add-back” treatment caused the myoma volume to rise again by around 50%. After discontinuing both therapies, the myoma returned to its original volume [152]. GnRH antagonists (e.g. cetrorelix) have also been investigated for this indication [156].

Selective progesterone receptor modulators (SPRMs): The role of progesterone in the proliferation of myomas has led to an increased interest in the modulation of the progesterone signalling pathway. Results of small pilot studies and uncontrolled studies using selective progesterone receptor modulators such as asoprisnil, mifepristone, telapristone and ulipristal acetate suggested that these substances could be candidates for myoma therapy [157–160] (Tab. 2, Fig. 2).

In addition, SPRMs have a specific effect on the endometrium, with the antiproliferative effects leading to a reduction in bleeding volume or even amenorrhea [173–175].

In vitro and in vivo, **ulipristal acetate (UPA)** is a potent and selective modulator of progesterone receptor activity [176–178] with effects on the progesterone receptors in the myometrium and the endometrium. UPA inhibits ovulation without major effects on estradiol formation and without an antiglucocorticoid effect [176, 179].

Mifepristone (no therapeutic option): Small pilot studies and uncontrolled studies with the selective progesterone receptor modulator (SPRM) **mifepristone** [162] provided the first indications that these substances could be suitable for the treatment of uterine fibroids [173, 176].

Tests showed that UPA has antiproliferative, antifibrotic and proapoptotic effects on cultured leiomyoma cells, but not on healthy myometrium cells [180].

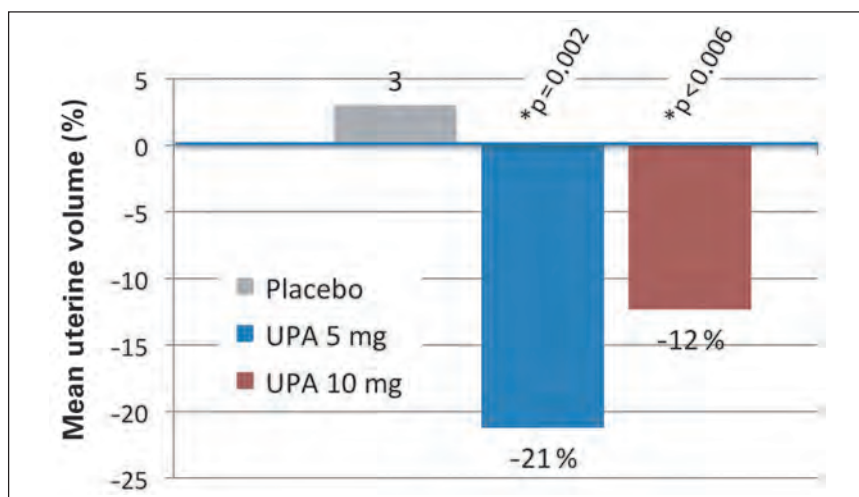


Figure 4. PEARL-I-Study on the use of ulipristal acetate in women with uterine fibroids: Influence of 5 and 10 mg/day UPA vs. placebo on myoma volume if measured centrally by blinded evaluation of MRT findings: Reduction of the myoma volume after 13 weeks of therapy compared to initial volume. Based on data by Donnez et al. [143]. Reprint with kind permission of Preglem SA, Geneva.

In 2 small placebo-controlled phase-II studies (with 18 and 38 patients respectively), UPA administered to women with symptomatic myomas led to a decrease in uterine as well as myoma volume [157, 158]. After 3 months of treatment with UPA in a dosage of 10 or 20 mg/day, there were fewer cases of excessive bleeding, and the myoma volume shrank significantly; the 20 mg dosage was not superior to 10 mg.

PEARL-I and -II-Studies

This article presents the results of 2 randomised Phase III studies published in February 2012 in the *New England Journal of Medicine*, showing the effectiveness of ulipristal acetate in the preoperative treatment of myomas and the rapid control of hypermenorrhea [143, 144].

On the basis of the 2 large international randomised studies **PEARL-I** [143] and **PEARL-II** [144], Esmya® (5 mg ulipristal acetate) received the European approval for the preoperative treatment of moderate to severe myoma symptoms in spring 2012.

Methods

PEARL-I-Study [143] (Fig. 3): In this randomised, double-blind, placebo-controlled study, patients with excessive menstrual bleeding and consecutive anaemia were able to effectively control their excessive bleeding and reduce the size of their myomas by taking oral ulipristal acetate in a dosage of 5mg or 10 mg per day. Compared with placebo,

treatment with ulipristal acetate also led to a clinically relevant rise in hemoglobin and hematocrit levels and to a reduction in the pain and complaints caused by the myomas.

PEARL-II-Study [144]: This randomised, double-blind study involving patients suffering from excessive bleeding was designed to determine how the daily administration oral ulipristal acetate (5 or 10 mg) compared to a monthly intramuscular injection of leuporelin acetate (3.75 mg) in terms of bleeding control prior to a planned operation for symptomatic myomas and in terms of the side effect profiles of both drugs.

Description of the Myoma Studies

Primary and Secondary Endpoints

In each UPA group of PEARL I, the reduction of the **myoma volume** was statistically and clinically significant compared with the placebo group. Bleeding control was another primary endpoint.

PEARL-I-Study: After 13 weeks, a significantly larger share of patients in the two ulipristal acetate groups achieved a reduction of their myoma and uterine volumes by at least 25% than in the placebo group. Compared with placebo, there was no statistical difference in the occurrence of side effects under UPA (Fig. 1, 4).

PEARL-II-Study: All therapies were associated with a **volume reduction of the biggest 3 myomas (secondary end-**

point); the (median) reduction after 13 weeks was by 36% in the 5 mg UPA group, 42% in the 10 mg UPA group and 53% in the leuporelin acetate group. Under leuporelin acetate, the shrinkage of the uterine volume was significantly more pronounced (47%) than in the 2 UPA groups (20–22%). Compared with a treatment with GnRH analogue leuporelin, fewer side-effects occurred under UPA. After a short follow-up period of 6 months, patients not treated by hysterectomy or myomectomy after the 13-week treatment showed no increase in myoma size after discontinuing UPA, while the size did increase after discontinuing leuporelin. In the patient group receiving leuporelin acetate, the myoma volume decreased to 44% of the original size, but 6 months after stopping the therapy, it had returned to 84% of the initial size. Among the UPA patients, therapy success was more sustained. Under UPA therapy, the myoma volume shrank to 55% (5 mg) and 38% (10 mg) of the initial size; after 6 months, it was still at 55% (5 mg) and 45% (10 mg) of the starting volume (Fig. 5). Treatment with leuporelin acetate led to a significantly greater reduction of the uterine volume (47%) than the two UPA dosages (20 to 22%). Compared with the GnRH analogue leuporelin, fewer side effects occurred under UPA

Drug Safety Data

In both studies, no significant clinical side-effects were observed (hot flushes 12.7%, reversible endometrium thickening 10–15%, headache 6.4% and a few cases of breast tenderness) (Fig. 5). Compared with treatment with the GnRH analogue leuporelin, significantly fewer side-effects occurred under UPA. In the PEARL-I-Study there was no statistical difference in the occurrence of side effects in the UPA and placebo groups

Final Evaluation

New minimally invasive therapies are being developed on a regular basis in order to treat myomas in different phases of the patient's life (Tab. 1). The question is which form of treatment is the best for which patient.

Basic issues to be considered before deciding on the therapy:

- bleeding problems, anaemia with low Hb, iron and ferritin levels and resulting fatigue and physical weakness

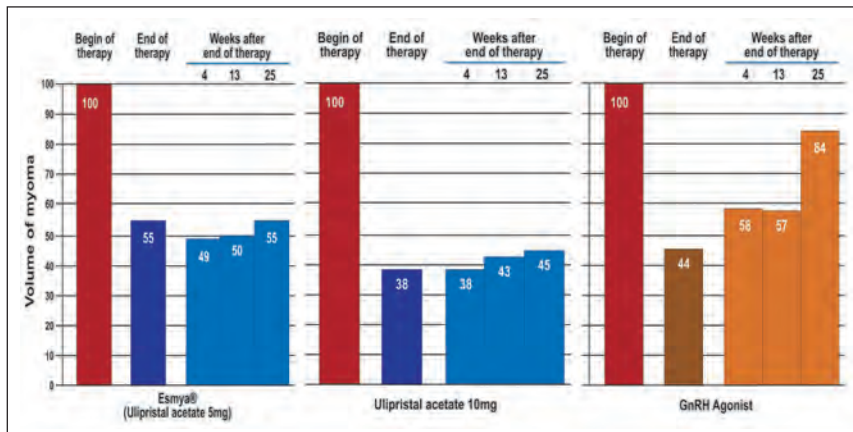


Figure 5. PEARL-II-Study. Mean myoma volume (as percentage of the initial finding, 100% at start of therapy) under treatment with 5 mg and 10 mg UPA/day vs. GnRH over 13 weeks of therapy with 38 weeks of follow-up. After 13 weeks, there was no statistically significant difference between ulipristal acetate and GnRH analogues. Based on data by Donnez et al. [144]. Reprint with kind permission of Preglem SA, Geneva.

- micturition or bowel movement problems,
- pain
- fertility
- patient age and expected time to menopause.

Why should uterine fibroids be treated (see also Tab. 1):

- Not all myomas must be treated

- In the treatment of myomas, their size, size change within a certain period, their number, location (subserosal, intramural, submucosal) as well as the patient's age, a potential wish to preserve her fertility as well as additional complaints (e.g. bleeding disorders, descensus problem) play a role.

- Fast growing leiomyomas must be removed surgically in order to exclude a malignancy.
- The treatment options include pharmaceutical, surgical and radiological interventions.
- Hysterectomy is the only permanent and definitive treatment option.
- Conservative treatment methods should be considered if the patient wishes to preserve her fertility, if she is older and close to her menopause or if the patient is no ideal candidate for an operation.

Rapid bleeding control in cases of myoma-related menorrhagia with a preoperative rise in Hb levels as well as a shrinking myoma are the key advantages of the new treatment option with UPA (5 mg orally, 1 daily tablet over a maximum of 3 months). The fact that this is an advantage was shown in recent study published in *The Lancet* [181], in which the postoperative results after major non-cardiac operations in patients with preoperative anaemia were worse than in those without anaemia. A pharmaceuti-

cal pre-treatment carried out prior to myoma operations of different surgical routes is favorable

1. if the preoperative Hb levels are sufficiently high. A possible pre-existing anaemia has to be corrected
2. if the pharmaceutical pretreatment leads to a reduction in myoma volume
3. if the reduction is not reversible, no operation should be carried out.
4. if the myoma shrinkage does not compromise the layer preparation necessary for endoscopic myomectomy
5. Pretreatment should also not lead to unwanted side-effects which could result in the discontinuation of therapy.

All these requirements are fulfilled by the preoperative use of Esmya®.

While GnRH analogues lead to more difficult layer preparation when preparing endoscopic myomectomy [181], this does not seem to be the case after UPA treatment [Donnez 2012, personal communication]. Whether UPA will be available in future for the sole indication of treating certain forms of hypermenorrhea is still unclear – a new therapeutic approach along these lines would be desirable.

Based on 2 large international studies (PEARL-I [143] and PEARL-II [144]) Esmya® (5 mg ulipristal acetate) received the European approval in 2012 for the treatment of moderate to severe myoma symptoms to achieve myoma reduction and bleeding control.

■ Introduction Therapy Options for Hypermenorrhea

Therapy Options

The current treatment strategies are mainly **surgical** and **radiological** procedures; there are only limited **medicinal** options [48–53].

Surgical Therapy Methods

Removing the Pathological Causes of Hypermenorrhea

If the hypermenorrhea cannot be explained by uterine fibroids, further causes such as cervical or endometrial polyps, inflammation, simple or complex endometrial hyperplasia or endometrial carcinoma must be excluded/treated accordingly.

Endometrial Ablation

Endometrial ablation is another alternative to hysterectomy for patients with menorrhagia or hypermenorrhea [183].

List of Surgical Techniques available for Endometrial Ablation and their Manufacturers

- **Cryoablation** (HerOption®)
- **Thermal balloon ablation** (Gynecare Thermachoice®)
- **Hydrothermal ablation** (HydroThermAblator®)
- **Radio frequency ablation** (NovaSure®)
- **Mikrowave ablation** (Microsulis® Microwave Endometrial Ablation [MEA] System)
- **Manual endometrial ablation techniques:** cf. resectoscopes and laser ablation.

In these procedures, the endometrium and the superficial myometrium are systematically destroyed hysteroscopically by high frequency current applied by a rollerball or resected using an HF loop [184]. The principle of the roller ball method is the thermal destruction of the endometrium by applying heat produced by HF current, leading to the thermal necrosis of the tissue. In the loop electrode method, parts of the endometrium are resected together with the decidua [185].

The effectiveness of endometrial ablation compared with hysterectomy was confirmed in many randomised controlled studies as well as in a meta-analysis [186–188]. The mortality of the procedure is around 0.26/1.000 cases [189].

In a study of patients treated for bleeding disorders, 70% of them did not require hysterectomy after endometrial ablation [190]. In this case, a hysteroscopy should be performed synchronously with a fractioned abrasion. Compared with hysterectomy, the risk of prolapse problems is lower for endometrial ablation (hazard ratio 0.62) [191].

This procedure can be performed if there has been a previous failed therapy with hormones or a hormone coil, if the uterine cavity is normal and the patient does not wish to preserve her fertility. The advantages for the patients are no hospitalisation, short treatment time, high

safety level and low morbidity. The risk is that the therapy may fail due to the carbonisation of the tissue with no in-depth effect. Resection also entails a risk of bleeding from the branches of the uterine artery [192].

Non-hysteroscopic techniques are called “second generation” methods. They are quick and simple and have a similar effectiveness [193, 194]. For bleeding disorders, the ThermoChoice-System™ can be used: A folded balloon is introduced into the uterine cavity. The balloon is then filled with a liquid at a pressure of 160–180 mm Hg and heated to 87 °C by a thermocouple. The result is the thermal destruction of the endometrium and the superficial myometrium [195].

According to one study, many patients subsequently developed amenorrhea or hypomenorrhea [195]. The complications are acceptable and include hematometra, spasmodic pain, fever and cystitis [196].

Advantages: Short, minimally invasive treatment for hypermenorrhea.

Disadvantages: Irreversible endometrial damage resulting in uterine infertility.

Lethaby et al. [197] have investigated the different techniques of endometrial destruction to treat hypermenorrhea in a Cochrane analysis and found that the rates of success and complications are better if the modern non-hysteroscopic techniques are used rather than the conventional hysteroscopic techniques.

See also the **recommendations by the US insurance companies (2012):** <https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Medical%20Policies/Dysfunctional Uterine Bleeding and Uterine Fibroids.pdf>.

Interaction with Blood Coagulation and Fibrinolysis

Certain coagulation disorders can also result in hypermenorrhea. However, for further information, please refer to the corresponding specialised literature.

Antiinflammatory Therapy

Certain infections of the uterus can lead to hypermenorrhea. However, for further information, please refer to the corresponding specialised literature.

Lethaby et al. [198] have investigated the effectiveness of non-steroidal anti-inflammatory drugs for hypermenorrhea. In a limited number of small studies eligible for evaluation, they found no significant difference in effectiveness between nonsteroidal antiinflammatory drugs and other medical therapies such as oral progestogens in the luteal phase, ethamsulate, OCC or a progesterone-releasing intrauterine system (progesta-sert).

Drug Therapy for Bleeding Disorders Caused by Leiomyomas

Progestogen Therapy

The treatment of bleeding disorders with progestogens has been known for a long time. Especially patients with irregular menstruation are treated by the cyclical administration of progestogens (e.g. days 16–25). Patients with a bioptically confirmed endometrial hyperplasia are also treated with high-dose progestogens.

The oral administration of **progestogens** to control bleeding and myoma growth has not been fully investigated, but small studies reported breakthrough bleeding [199] as well as a possible progression of myoma growth [51, 131–133].

See also the Cochrane analysis by Lethaby et al. [200] on the effectiveness of cyclic progestogens for hypermenorrhea in women who did not primarily suffer from uterine fibroids.

Lethaby et al. [200] have investigated the effect of cyclic progestogens on hypermenorrhea in a Cochrane analysis. In this case, myomas were not explicitly mentioned as the cause of the bleeding. It was found that cyclic progestogens from day 15 or 19 to day 26 of the cycle were not superior to other medical therapies such as Danazol (obsolete), tranexamic acid, non-steroidal anti-inflammatory drugs (NSAIDs) or a levonorgestrel-containing intrauterine system (IUS) in the treatment of menorrhagia in women with regular ovulatory cycles. Cyclic progestogens administered over 21 days led to a significant reduction of the menstrual blood loss although the

women considered this treatment less acceptable than an LNG-IUS. Treatment with cyclic progestogens may be suitable for a short-term therapy of menorrhagia.

Oral Hormonal Contraceptives

Oral combined hormonal contraceptives or a progestogen monotherapy can be used to try and treat bleeding disorders in patients with small leiomyomas [201, 202].

Intrauterine Therapy with Progestogens

Insertion of a Levonorgestrel Intrauterine System (Mirena®)

The LNG-IUS is indicated for the therapy of hypermenorrhea and has proven more effective than progestogen or ovulation inhibitors even if they are used in the long cycle [203, 204]. Therapy success in more than 90% of the cases has been confirmed in many studies. LNG-IUS are also more effective than antifibrinolytics and non-steroidal anti-inflammatory drugs [205].

The LNG-IUS is a real alternative to organ-saving surgical procedures. The relevance of the levonorgestrel IUS in the avoidance of hysterectomies for patients with idiopathic hypermenorrhea has been demonstrated in numerous articles: Lahtenmaki et al. [138], Hurskainen et al. [139], Goni et al. [140], Hurskainen et al. [141]. The effect of an LNG-IUS is nearly as good as the results after various methods of endometrial ablation [188, 194]. Therefore, LNG-IUS should always be recommended to the patient as a first line therapy prior to the use of surgical procedures such as endometrial ablation or hysterectomy [194, 206]. Hyper- or dysmenorrhea caused by adenomyosis are also reduced by LNG-IUS due to their strong local progestogenic effect [206]. LNG-IUS are also suitable for the treatment of bleeding disorders in obese women [207]. They have also been successfully employed in patients with hematological diseases and bleeding [208, 209].

Marjoribanks et al. [210] have examined the effectiveness of surgical and medical interventions for hypermenorrhea and found that although surgical interventions, especially hysterectomy, lead to a stronger decrease of menstrual blood loss than medical treatments, the LNG-

IUS is equally effective in terms of improving quality of life.

Ulipristal acetate as an Oral Progesteron-Receptor-Modulator (Esmya®)

On the basis of the 2 large-scale randomised international studies PEARL I [143] and PEARL II [144], Esmya® (5 mg ulipristal acetate) received European approval in 2012 for the treatment of moderate to severe myoma symptoms to achieve myoma reduction and bleeding control.

Study Results

Effectiveness

PEARL I was performed to compare the effectiveness of UPA with placebo in the treatment of symptomatic uterine myomas in women with heavy menstrual bleeding resulting in anaemia. It was a randomised, double-blind, placebo-controlled, multi-centre parallel group study with a total of 242 patients. Over a period of three months, the once-daily administration of either 5 or 10 mg ulipristal acetate was compared with placebo. Each group received simultaneous iron supplementation. The study reached its two effectiveness endpoints with a clear statistical significance. Esmya® was more effective than placebo in reducing excessive uterine bleeding based on the percentage of patients with a Pictorial Blood Loss Assessment Chart (PBAC) score below 75 (open-ended score; 0 = no bleeding; from 100 = menorrhagia [211, 212].

In more than 90% of the patients treated with ulipristal acetate, the heavy bleeding stopped nearly completely after only 7 days of treatment with 5 or 10 mg UPA. The simultaneous iron substitution also led to an improvement in the concomitant anaemia. At the beginning of the study, the patients had a PBAC > 100. At the same time, a reduction of the total myoma volume was achieved. The UPA and placebo groups reported a similar frequency of hot flushes, (less than 1.1% in both groups.

This was measured by magnetic resonance tomography (MRT) and analysed centrally. The pain caused by the myomas was also relieved as measured by the short form of the McGill pain questionnaire [213]. Both the PBAC and the short McGill questionnaire are considered valid self-assessment instruments.

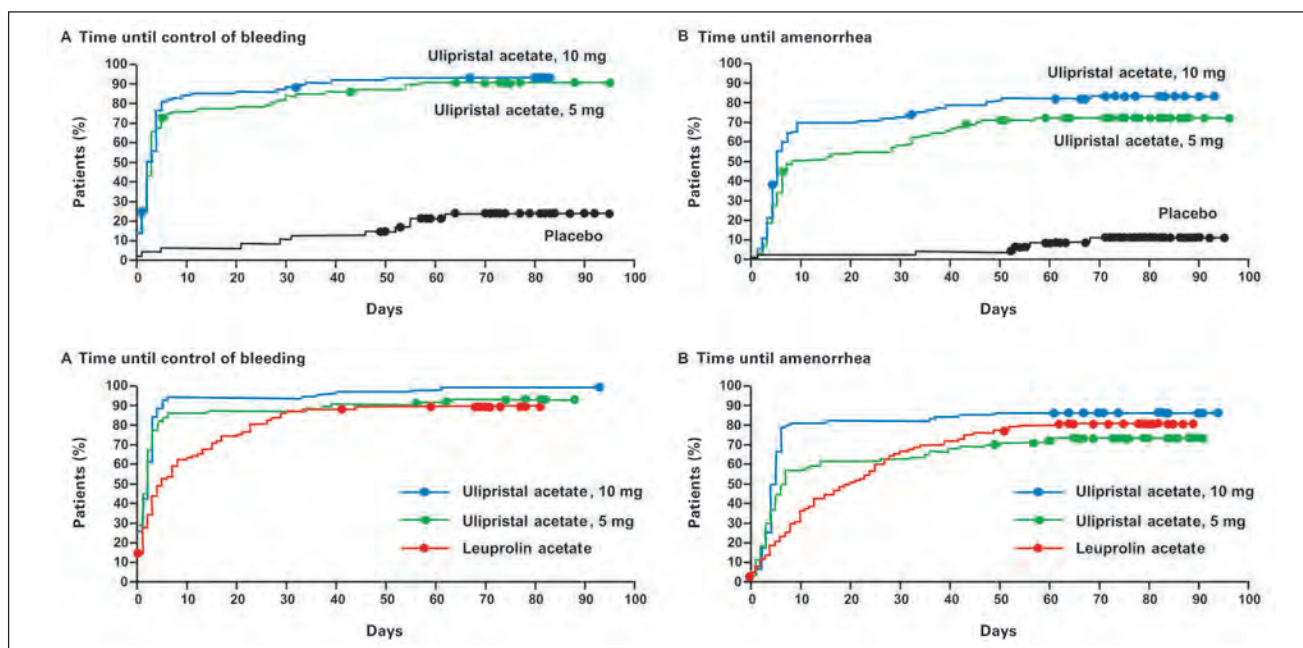


Figure 6. PEARL I (top) and PEARL II (bottom) on the use of ulipristal acetate in women with uterine fibroids and hypermenorrhea leading to anaemia with 5 and 10 mg/day of UPA vs. placebo (PEARL I) or vs leuprolin acetate (PEARL II) over a total of 90 days (all patients received iron supplementation). **A:** Time to bleeding control (PBAC score < 75): Under UPA, excellent bleeding control is achieved. No evidence of bleeding control under placebo (PEARL I); under leuprolin, there was a delayed onset of bleeding control (PEARL II). **B:** Time to amenorrhea (PBAC score < 2): The majority of patients under UPA developed an amenorrhea (PEARL I). Under leuprolin, the amenorrhea was delayed (PEARL II). Based on [143, 144]. Reprinted with permission from Massachusetts Medical Society. © 2012

PEARL II was intended to demonstrate the similar effectiveness and a superior tolerance profile of ulipristal acetate for the treatment of women with heavy menstrual bleeding compared with the GnRH analogue leuporelin; the study also required a PBAC score of more than 100 to reflect heavy menstrual bleeding, but a concomitant anaemia was not required. The study was also a randomised, double-blind, controlled, multi-centre parallel group study including a total of 307 patients. Over a period of three months, once daily dosages of 5 and 10 mg Esmya were compared with a once monthly injection of 3.75 mg leuporelin. The study proved a similar effectiveness as leuporelin in reducing heavy uterine bleeding expressed as the share of patients with a PBAC below 75, as did PEARL I. However, compared with leuporelin, this endpoint was reached faster because a flare-up effect is observed in the first month of treatment among many patients under leuporelin. By comparison, both ulipristal acetate groups reported a better tolerance profile and a statistically significantly reduced number of moderate to severe hot flushes.

Bleeding Disorders

PEARL I: Menstrual bleeding was controlled in 91% of the women receiving 5 mg UPA and 92% of the women

treated with 10 mg UPA compared with only 19% in the placebo group ($p < 0.001$ for the comparison of each UPA group with the placebo group).

PEARL II: The percentage of patients achieving a reduction of the **bleeding** (PBAC score < 75 in the 4 preceding weeks) was 90% in the 5 mg UPA group, 98% in the 10 mg UPA group and 89% in the leuporelin acetate group. The difference between 5 mg UPA and leupro-

relin acetate was 1.2 percentage points (95%-CI: -9.3–11.8) and that between 10 mg UPA and leuporelin acetate 8.8 percentage points (95%-CI: 0.4–18.3). When the data were analysed statistically, no evidence was found suggesting an inferiority of the UPA treatment compared with leuporelin acetate (Fig. 6).

Secondary Endpoints

PEARL I: In the patients receiving 5 or 10 mg UPA, the **bleeding** decreased

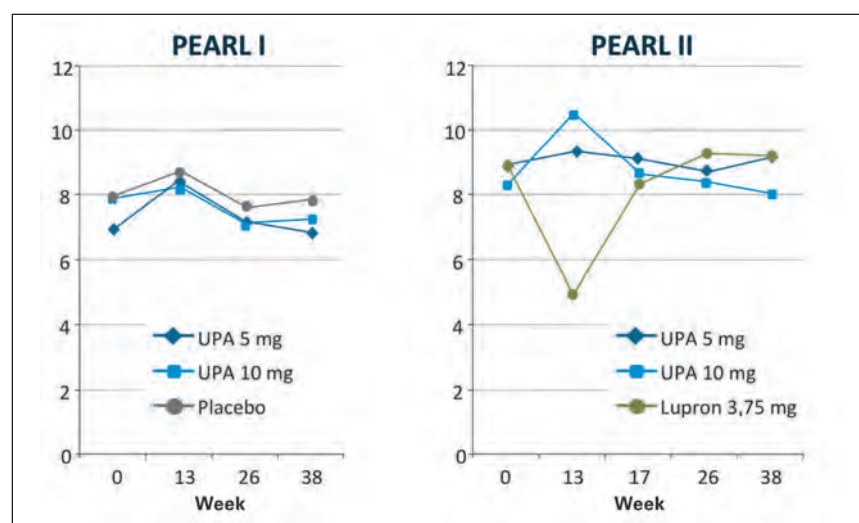


Figure 7. Mean endometrial thickness in the PEARL-I- and -II-Studies: Data at weeks 17, 26 and 38 come from women who did not undergo hysterectomy or endometrial ablation. In the PEARL-I-Study, was examined by MRT (blinded) and in PEARL II by ultrasound. Based on [143, 144]. Reprinted with permission from Massachusetts Medical Society. © 2012

markedly (mean change of the PBAC score > 300) while the score did not change much in the patients receiving placebo ($p < 0.001$ for the comparison of each UPA group with the placebo group in weeks 5 to 8 and 9 to 12). After 4 weeks, the majority of the patients in the UPA groups were amenorrheic, but only a small number of patients in the placebo group ($p < 0.001$ for the comparison of each UPA group with the placebo group). For 50% of the patients in the 5 mg UPA group and 70% in the 10 mg group, amenorrhea occurred within the first 10 days (Fig. 3). Heavy bleeding came under control by day 8, i.e. quickly (according to the definition of the subsequent PBAC scores, which were always under 75). This was the case for more than 75% of the UPA patients, but only for 6% of the placebo patients.

PEARL II: The median PBAC scores were 0 by week 13 in all treatment groups. Administering 5 and 10 mg of

UPA resulted in a significantly faster control of excessive bleeding than leuporelin acetate ($p < 0.001$ for both comparisons). In addition, 10 mg of UPA led to a faster onset of amenorrhea than leuporelin acetate ($p < 0.001$). In all study groups, similar improvements were achieved in terms of pain, quality of life and hemoglobin levels.

Endometrial Changes

In PEARL I, the thickness of the endometrium was examined using MRT (blinded), while it was assessed sonographically in PEARL II. The data on endometrial thickness after 17, 26 and 38 weeks presented in Fig. 7 (left) come from women who had not undergone hysterectomy or endometrial ablation. In PEARL I, during a therapy period of 13 weeks, the endometrial thickness increased under both UPA dosages, but it also grew under placebo. In the subsequent therapy-free interval, the thickness decreased to baseline both in the placebo and the verum groups.

In PEARL II, as expected, endometrial thickness declined by around 50% after 13 weeks in the leuporelin group, whereas it increased slightly in the two UPA groups, reflecting the changes in PEARL I. In the therapy-free interval, all three groups returned to baseline levels in the therapy-free interval (Fig. 7 right).

The histopathological examination of the endometrial biopsies showed no malignant change after 13 weeks or in the follow-up period. Referring to PEARL I, the data presented in the table only show one atypical endometrial hyperplasia in the placebo group after 38 weeks (6 months after the end of the treatment).

In PEARL II, there was a simple endometrial hyperplasia in week 13 under 5 mg UPA and in week 38 after treatment with the GnRH agonist (Tab. 3).

Figure 8 and Table 4 show endometrial changes specific for progesterone recep-

Table 3. Endometrial changes in the PEARL-I- and -II-Studies: Histopathological evaluation of the endometrial biopsies. No endometrial hyperplasia or malignant changes after 13 weeks or in the follow-up period except one case of atypical hyperplasia in the placebo group and one case each of a simple hyperplasia in the UPA 5 mg group after 13 weeks and in the GnRH group after 38 weeks. Based on [143, 144]. © T. Rabe.

	PEARL I			PEARL II		
	Placebo	UPA 5 mg	UPA 10 mg	UPA 5 mg	UPA 10 mg	GnRH-Agonist
Screening	n = 48	n = 95	n = 98	n = 97	n = 103	n = 101
Benign	48 (100 %)	87 (98.9 %)	95 (100 %)	88 (98.9 %)	100 (100 %)	91 (100 %)
Hyperplasia	0	1 (1.1%)	0	1 (1 %)	0	0
Malignancy	0	0	0	0	0	0
Week 13	n = 41	n = 83	n = 81	n = 94	n = 98	n = 95
Benign	39 (100 %)	78 (100 %)	78 (100 %)	85 (98.8 %)	95 (100 %)	88 (100 %)
Hyperplasia	0	0	0	1 (1 %)	0	0
Malignancy	0	0	0	0	0	0
Week 38	n = 31	n = 63	n = 63	n = 63	n = 67	n = 64
Benign	29 (96.7 %)	60 (100 %)	61 (100 %)	58 (100 %)	62 (100 %)	59 (98.3 %)
Hyperplasia	1* (2.6 %)	0	0	0	0	1 (1.3 %)
Malignancy	0	0	0	0	0	0

* complex hyperplasia with atypia

Table 4. PRM-associated endometrial changes (PAEC = PRM-associated endometrial changes) in the PEARL-I- and -II-Studies found in the histopathological evaluation of the endometrial biopsies. Based on [143, 144]: Reprint with kind permission of Pregl SA, Geneva.

Patients having PAEC (%)	PEARL I			PEARL II		
	Placebo	UPA 5 mg	UPA 10 mg	UPA 5 mg	UPA 10 mg	GnRH _a
Screening	0 %	6.5 %	1.3 %	2.6 %	3.8 %	2.5 %
Week 13 (end of treatment)	7.9 %	59.8 %	56.4 %	54.5 %	61.3 %	13.9 %
		↓	↓	↓	↓	
Week 38*	2.6 %	7.8 %	5.1 %	6.5 %	6.3 %	6.3 %

tor modulators (PAEC = PRM-associated endometrial changes) as found histopathologically in the women included in the PEARL-I- and -II-studies. These are benign changes concerning the endometrial glands and the endometrial stroma and can be accompanied by non-physiological cyst formation, atrophy or abortive secretory changes of the glands as well as by abnormal endometrial vascularisation. The histological changes are variable and not found in all patients (see Fiscella et al. [214], Clarke and McCluggage [215], Mutter et al. [174], Ioffe et al. [175]). With respect to the prognostic relevance of the so-called PAEC, there are no histological indications that they can become premalignant. Table 4 illustrates the reversibility of PAEC, since the frequency of PAEC was similar to the control groups 6 months after the end of therapy. Because of the lack of longer-term observations, however, the significance of the PAEC cannot be finally assessed yet.

Final Evaluation

Rapid control of bleeding in myoma-related hypermenorrhea with a preoperative rise in Hb levels and a shrinkage of the myoma are the main benefits of a new treatment option using UPA (5 mg orally, 1 tablet per day over a maximum of 3 months). In a study published recently in *The Lancet*, non-cardiac operations have less favourable results if the patients had an anaemia preoperatively [181]. While GnRH analogues make it harder for surgeons to prepare the layers for a subsequent endoscopic myomectomy [182], this does not seem to be the case after UPA treatment [Donnez 2012, personal communication].

Another advantage for patients opting against an operation is the sustained effect in the myoma size, as it appears that the myoma does not begin growing again after the drug treatment is stopped.

On the basis of 2 large-scale international randomised studies (PEARL I [143] and PEARL II [144]), Esmya® (5 mg ulipristal acetate) has received European approval in 2012 for the preoperative treatment of moderate to severe myoma symptoms to achieve myoma reduction and bleeding control.

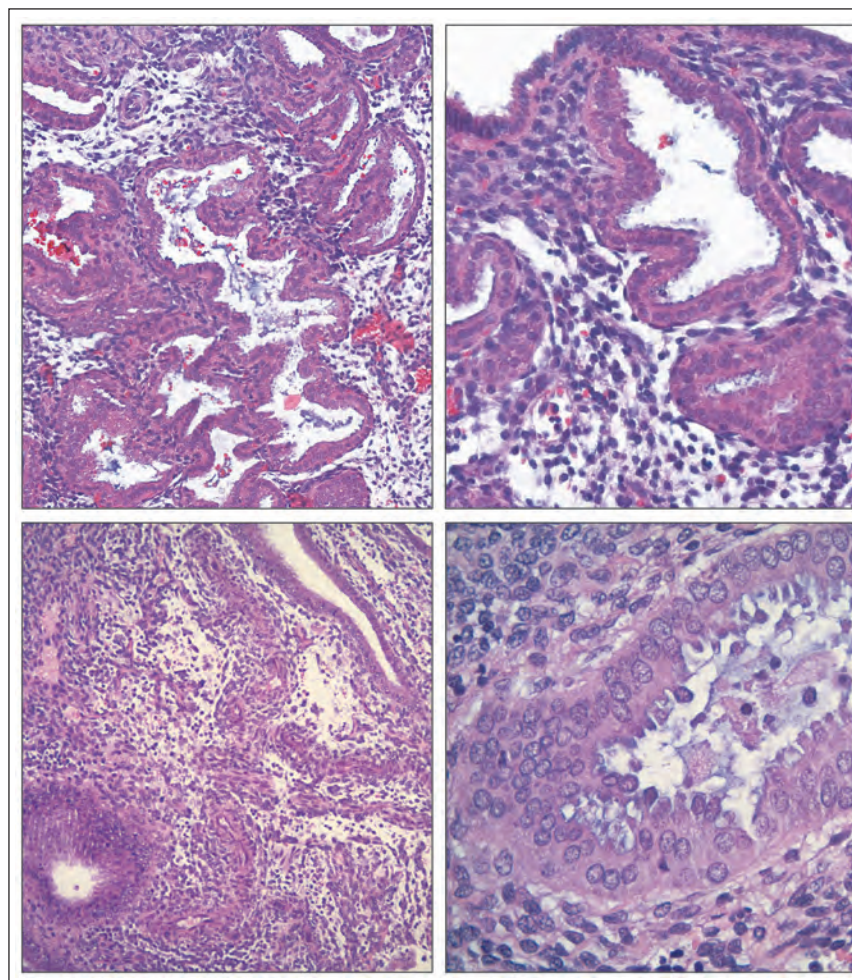


Figure 8. Endometrium before (top) and after (bottom) treatment with ulipristal acetate. **Top:** Normal endometrium in two magnifications (mid-luteal phase). **Bottom:** Left: Endometrium (10×) with thin-walled vessels and largely inactive glands (Case 01_04), right: Endometrium (40×) with abortive secretion and immature stroma (Case01_07). After UPA treatment, you can see the typical changes under the administration of progesterone receptor modulators called PAEC (see text). Courtesy of Peter Sinn, Heidelberg. Reprint with kind permission.

It is not clear yet whether UPA will become available for the sole indication of treating certain forms of hypermenorrhea – a new therapeutic approach along these lines would be desirable.

Conflict of Interest

H-J. Ahrendt is a member of the Advisory Board “UPA und Uterusmyome” and a speaker for the company Preglem. C. Albring does not declare any conflict of interest. J. Bitzer (Switzerland) does not declare any conflict of interest. P. Bouchard has received fees and grants from Ferring, HRA Pharma, Nordic Pharma, Pierre Fabre, Schering Plough, Preglem, Pantarhei Bioscience, Serono, and Wyeth, is a senior consultant at the Population Council (New York), and is a member of the International Committee on Contraceptive Research (quoted from *Fertil Steril* 2011; Vol. 96, No. 5). U. Cirkel

does not declare any conflict of interest. C. Egarter (Austria) does not declare any conflict of interest. K. König does not declare any conflict of interest. W. Harlfinger does not declare any conflict of interest. M. Matzko does not declare any conflict of interest. A. O. Mueck does not declare any conflict of interest. T. Rabe has received author's and speaker's fees as well as travel expenses from Preglem. T. Römer: Consultancy and speaking activity for Preglem. T. Schollmeyer does not declare any conflict of interest. P. Sinn does not declare any conflict of interest. T. Strowitzki does not declare any conflict of interest. H-R. Tinneberg has received consultancy fees from Preglem as well as conference fees, travel and accommodation expenses for a congress by Bayer Health Care, Preglem and Storz. M. Wallwiener does not declare any conflict of interest. R. L. de Wilde does not declare any conflict of interest.

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