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Ulipristal acetate for treatment of 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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24 million European women and 20 million North American women between 35 and 55 years are suffering from uterine fibroids; they account for 40% of all women in this age group. Uterine fibroids or leiomyomas are characterised by extremely heavy uterine bleeding, anaemia, pain and infertility. Many women find their quality of life severely compromised; in many cases, this leads to hysterectomy. So far, no effective and well-tolerated drug has been available. The only approved drugs for the treatment of symptomatic uterine fibroids are GnRH agonists with restricted use on account of severe side effects as the resulting low estrogen level causes hot flushes, depression, mood changes, loss of libido, vaginitis and loss of bone mineral density. Since the growth of myomas is progesterone-dependent, 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 (UPA) in the preoperative treatment of uterine fibroids and in the control of a concomitant hypermenorrhea. A dosage of 5 or 10 mg UPA over three months has produced no significant side-effects. A cessation of the hypermenorrhea has been observed after only seven days, a volume reduction of the uterine fibroids by 40% within three months seemed to be visible even six months after stopping the therapy. A preparation containing 5 mg ulipristal acetate is available from spring 2012 under the name **Esmya** *for the preoperative treatment of leiomyomas.*

Uterine leiomyomas are benign, hormone-sensitive tumors arising from smooth muscles and occurring in 20 to 40% of women of reproductive age (1, 2). This means that they are the most common benign uterine tumors in women of reproductive age. The most common concomitant symptoms are menorrhagia and iron deficiency anaemia, which in some cases cannot be treated adequately by iron substitution (3-5). Heavy menstrual bleeding means that the women have to consult their doctors and be absent from work frequently (5). Further symptoms are e.g. abdominal pain, dysmenorrhea, abdominal pressure, pollakiuria, nocturia, obstipation and, depending on the size and location of the fibroids, a negative impact on fertility. Quality of life is greatly compromised (6-9).

Therapy options

Currently, mainly surgical and radiological treatment methods are available; the options for drug-based treatment are limited (s. Tab. 1)(3, 9-13).

Surgical interventions

Many patients require surgical intervention. The procedure to be chosen depends on the patient's age and her wish to preserve her fertility or avoid a hysterectomy (9). Uterine fibroids are the most frequent indication for hysterectomy (1).

Radiological interventions

According to current recommendations, myoma embolisation is a method

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Tab. 1: Different options for the therapy of uterine leiomyomas (according to Miller 2009)[1] (Note: updated version)

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 a subsequent pregnancy
Myolysis/ cryomyolysis	Women with multiple, small myomas who do not wish to preserve their 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 I (ESGE) 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

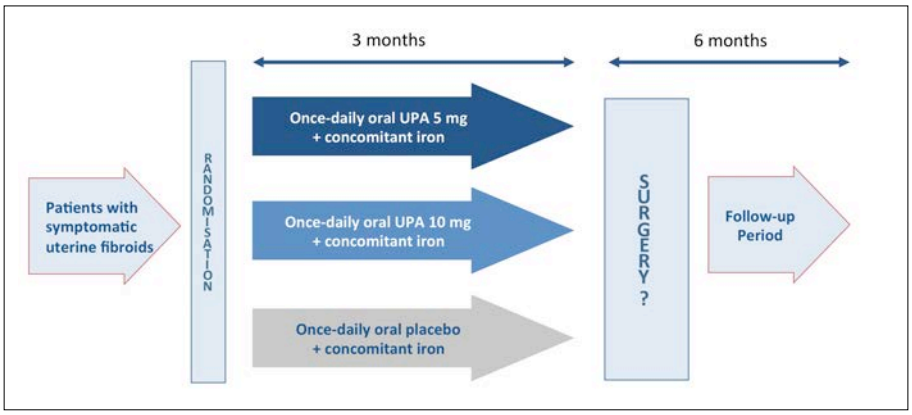
reserved for women who do not wish to preserve their fertility because the fibroid necrosis and infections can result in cavity changes including adhesions which can compromise fertility. Therefore, this method is only suitable for selected patients who do not wish to have any (more) children (14).

Drug therapy

The oral administration of **progestins** for the control of the bleeding and of fibroid growth has not been fully investigated, but small-scale studies have reported breakthrough bleeding (15) and a possible progression of fibroid growth (12, 16-18).

Levonorgestrel releasing intrauterine systems (IUS) lead to bleeding control in some patients, but the respective studies excluded patients with cavity anomalies caused by submucosal fibroids (19). The IUS can be used for fibroids which do not deform the uterine cavity, but it leads to more irregular bleeding, the system expulsion rate is higher than in women without fibroids and the effect on fibroid growth is controversial (20). On the other hand, numerous studies showed that IUS use could help avoid hysterectomies in patients with idiopathic hypermenorrhea (21-24).

Gonadotropin-releasing hormone (GnRH) agonists are the most effective medical therapy (16, 25, 26). In a placebo-controlled study, the GnRH agonist leuprorelin acetate (3.75 mg as a depot) resulted in a cessation of vaginal bleeding in 85% of the patients who were anaemic before the myoma intervention. However, the suppression of estradiol production under the leuprorelin acetate treatment caused hot flushes in 67% of the patients (27). Moreover, the reduction of the uterine and myoma volume was reversed relatively quickly (within 6-12 months)(26, 28-31). In addition, GnRH agonists have only been approved for short-term treatment for drug safety re-



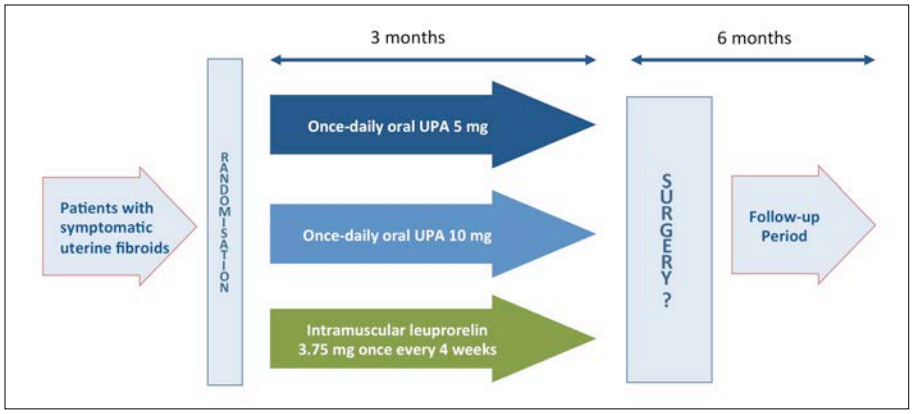


Figure 2: PEARL I study: In this randomised, double-blind, placebo-controlled study, women who initially had excessive bleeding and consecutive anaemia achieved effective control of their bleeding and shrinkage of their myomas by taking oral ulipristal acetate in a dosage of 5 or 10 mg/day. Compared 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: The question was whether daily oral ulipristal acetate (5 or 10 mg) was inferior to a monthly intramuscular injection of leuprorelin 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 **Donnez et al. (2012a)(51)** and **Donnez et al. (2012b)(52)** with kind permission.

asons (loss of bone mineral density). As a result of the preoperative treatment with GnRH agonists the vaginal route of hysterectomy was chosen more frequently instead of the abdominal route and intraoperative blood loss decreased. Compliance with GnRH agonist therapy is compromised by side-effects such as hot flushes and atrophic vaginitis (26). There are promising small studies describing a complementary "add-back" therapy with estrogens/progestins (32), tibolone (33) and raloxifen (34) in order to prevent hot flushes and loss of bone mass density, but this therapy option has not been pursued further. GnRH antagonists (e.g. Cetrorelix) have not been exhaustively tested for this indication either (35).

Selective progesterone receptor modulators (SPRM): The role of progesterone in the proliferation of fibroids has heightened the interest in a modulation of the progesterone signalling pathway. The results of small pilot studies as well as placebo-controlled studies investigating selective progesterone receptor modulators such as asoprisnil, mifepristone, telapristone and ulipristal acetate suggested that these agents could be suitable for myoma therapy (36-39).
SPRMs also have a specific effect on the endometrium, and their antiproliferative effects can lead to reduced bleeding or even amenorrhea (40-43).
In vitro and in vivo, ulipristal acetate (UPA; see Fig. 1) is a potent and selective modulator of progesterone receptor activity (44-46) acting upon the progesterone receptors in the myometrium and the endometrium. It inhibits ovulation without major effects on estradiol formation and has no antiglucocorticoid effect (44, 47).
Small pilot studies and placebo-controlled studies with the selective progesterone receptor modulator mifepristone (48) suggested that these substances could be suitable for therapy of leiomyoma (40, 44, 49).
Investigations on the basis of cultured leiomyoma cells showed antiproliferative, antifibrotic and proapoptotic effects on leiomyoma cells but not on healthy myometrial cells (50).

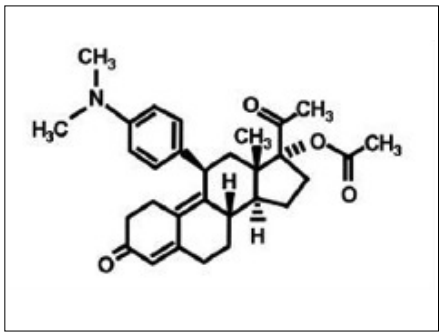


Figure. 1: Structural formula of ulipristal acetate

In small placebo-controlled phase-II-studies (with 18 and 38 patients respectively), UPA taken by women with symptomatic fibroids led to a reduction in uterine and myoma volume (36, 37). Under a three-monthly treatment with 10 or 20 mg UPA daily, the excessive bleeding stopped and the fibroid volume was reduced significantly; the 20 mg dose was not superior to 10 mg.

PEARL I and II studies

This article presents the results of two randomised Phase-III-studies published in the *New England Journal of Medicine* in February 2012 (51, 52), showing the effectiveness of ulipristal acetate in the treatment of uterine fibroids and the rapid control of hypermenorrhea in patients for whom an operation is planned.

Study description

The design of the PEARL I and PEARL II-studies is shown in Figure 2.

Study results

Proof of effectiveness

The **PEARL I study** was intended to show the higher effectiveness of UPA compared to placebo in the treatment of symptomatic uterine fibroids in women with heavy menstrual bleeding leading to anaemia. It was a randomised, double-blind, placebo-controlled,

multi-center study with a total of 242 patients. Over a period of three months, one daily dose of either 5 mg or 10 mg UPA was compared with placebo. All three groups simultaneously received 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 as measured by the percentage of patients with a Pictorial Blood Loss Assessment Chart (PBAC) score below 75 (open-ended score; 0 = no bleeding; ≥ 100 = menorrhagia) (53, 54). At the beginning of the study, the patients had a PBAC score > 100. The total myoma volume was also reduced. This was measured by magnetic resonance imaging (MRI) and then analysed centrally. In more than 90% of the patients treated with ulipristal acetate, the heavy bleeding stopped nearly completely after only 7 days under either 5 or 10 mg UPA. Together with the iron substitution, this led to an improvement of the concomitant anaemia. The pain caused by the fibroids also eased as confirmed by the short form of the McGill pain questionnaire (55). Both the PBAC and the short McGill questionnaire are considered valid instruments of self-assessment.

The **PEARL II study** was intended to show a similar effectivess and superior tolerance profile for ulipristal acetate compared with the GnRH analogue leuprorelin; in this study, heavy menstrual bleeding was defined as a PBAC score of more than 100, but a concomitant anaemia was not a required endpoint. The study was also a randomised, double-blind, controlled, multicenter parallel group study including a total of 307 patients. Over a period of three months, the once-daily administration of either 5 or 10 mg of *Esmya* was compared with three once-monthly injections of 3.75 mg leuprorelin. The study demonstrated that UPA was as effective as leuprorelin in reducing the heavy uterine bleeding defined as in the previous study as a PBAC below 75. Compared with leuprorelin, however, this endpoint was reached faster, as many patients show a "flare effect" in the first month of receiving leuprorelin. Compared with leuprorelin, ulipristal acetate showed an improved safety profile in both treatment groups and led to statistically significantly fewer moderate to severe hot flushes.

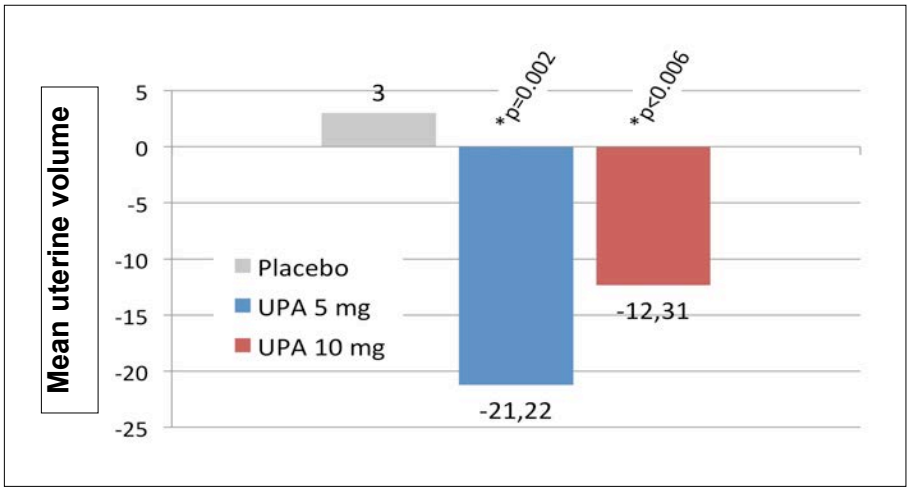


Figure 3: PEARL I study on the use of ulipristal acetate in women with uterine fibroids: Influence of 5 and 10 mg/day UPA vs. placebo on myoma volume if measured centrally by blinded evaluation of MRT findings: Reduction of the myoma volume after 13 weeks of therapy compared to initial volume. (Based on data by **Donnez et al. (2012a)(51)** with kind permission).

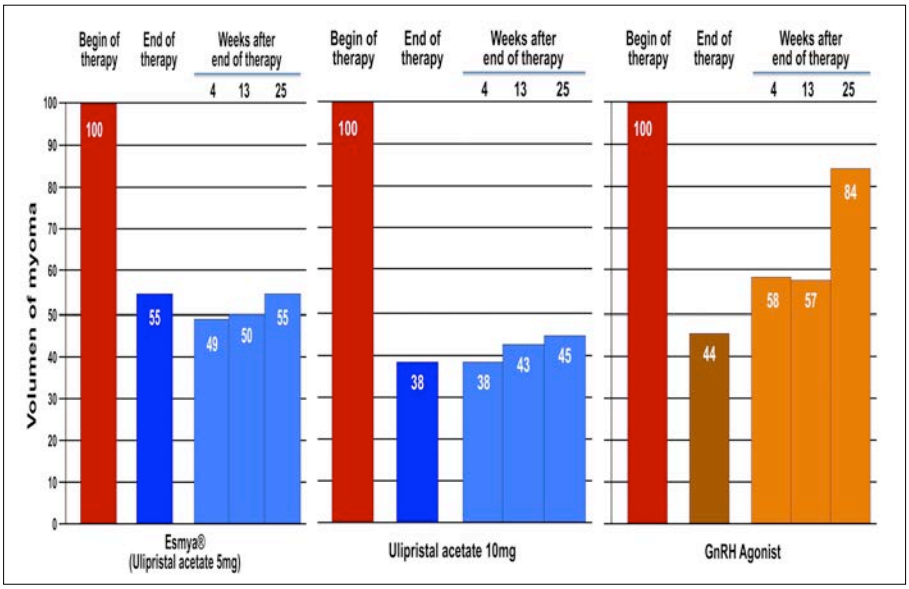


Figure 4: Pearl II study
Mean myoma volume (as percentage of the initial finding, 100% at start of therapy) under treatment with 5 mg and 10 mg UPA/day vs. Lupron over 13 weeks of therapy with 38 weeks of follow-up. After 13 weeks, there was no statistically significant difference between ulipristal acetate and GnRH analogues. (Based on data by **Donnez et al. (2012b)(52)** with kind permission).

Primary endpoints

PEARL I study: Menstrual bleeding was brought under control in 91% of the women receiving 5 mg UPA and 92% of those under 10 mg UPA, compared with only 19% of the women treated with placebo ($p < 0.001$ for the comparison of each UPA group with the placebo group). In each group, the reduction of the **fibroid volume** was statistically and clinically significant compared with the placebo group ($p = 0.002$ (5 mg) and 0.006 (10 mg).

PEARL II study: The percentage of women whose bleeding had decreased by week 13 (PBAC score < 75 in the previous four weeks) was 90% in the 5 mg UPA group, 98% in the 10 mg UPA group and 89% in the leuprorelin acetate group. The difference between 5 mg UPA and leuprorelin acetate was 1.2 percentage points (95% CI: -9.3 to 11.8) and 8.8 percentage points between 10 mg UPA and leuprorelin acetate (95% CI: 0.4 to 18.3). Upon statistical analysis, the data did not show that UPA treatment is inferior to leuprorelin acetate.

Secondary endpoints

PEARL I study: Patients taking 5 or 10 mg UPA saw their bleeding decrease very markedly (mean change in PBAC score), while the score did not change much in the placebo group ($p < 0.001$ for the comparison of each UPA group with the placebo group in weeks 5-8 and 9-12). After four weeks of taking tablets, most patients in the UPA group had developed amenorrhea, but only a few in the placebo group ($p < 0.001$ for the comparison of each UPA group with the placebo group). In approx. 50% of the 5 mg group and 70% of the 10 mg group, the amenorrhea started within the first ten days (s. Fig. 3). Heavy bleeding was controlled within one week (based on the PBAC scores, which stayed below 75); this was the case among more than 75% of the UPA patients but in only 6% of the placebo patients. After 13 weeks, a significantly higher portion of the patients in the UPA groups than in the placebo group had achieved a reduction of the fibroid volume and the uterine volume by at least 25% (s. Fig. 4).

PEARL II study: Bleeding control: In all treatment groups, the median PBAC scores in week 13 were 0.5, and 10 mg of UPA led to a significantly faster control of excessive bleeding than leuprorelin acetate ($p < 0.001$ for both comparisons). Furthermore, 10 mg UPA led to a faster onset of amenorrhea than leuprorelin acetate ($p < 0.001$). In all study groups, similar improvements were achieved in terms of pain, quality of life and hemoglobin levels.

All therapies were associated with a volume reduction of the three biggest fibroids. After 13 weeks, the (median) reduction was 36% in the 5 mg UPA group, 42% in the 10 mg UPA group and 53% in the leuprorelin acetate group. Under treatment with leuprorelin acetate, the reduction of the uterine volume was significantly more pronounced (47%) in the group receiving leuprorelin acetate than in the two UPA groups (20-22%). Compared with treatment with the GnRH analogue leuprorelin, no side-effects occurred under UPA. When patients who had not been hysterectomied or myomectomied after completing the 13 weeks treatment were given a follow-up examination after six months, the fibroids

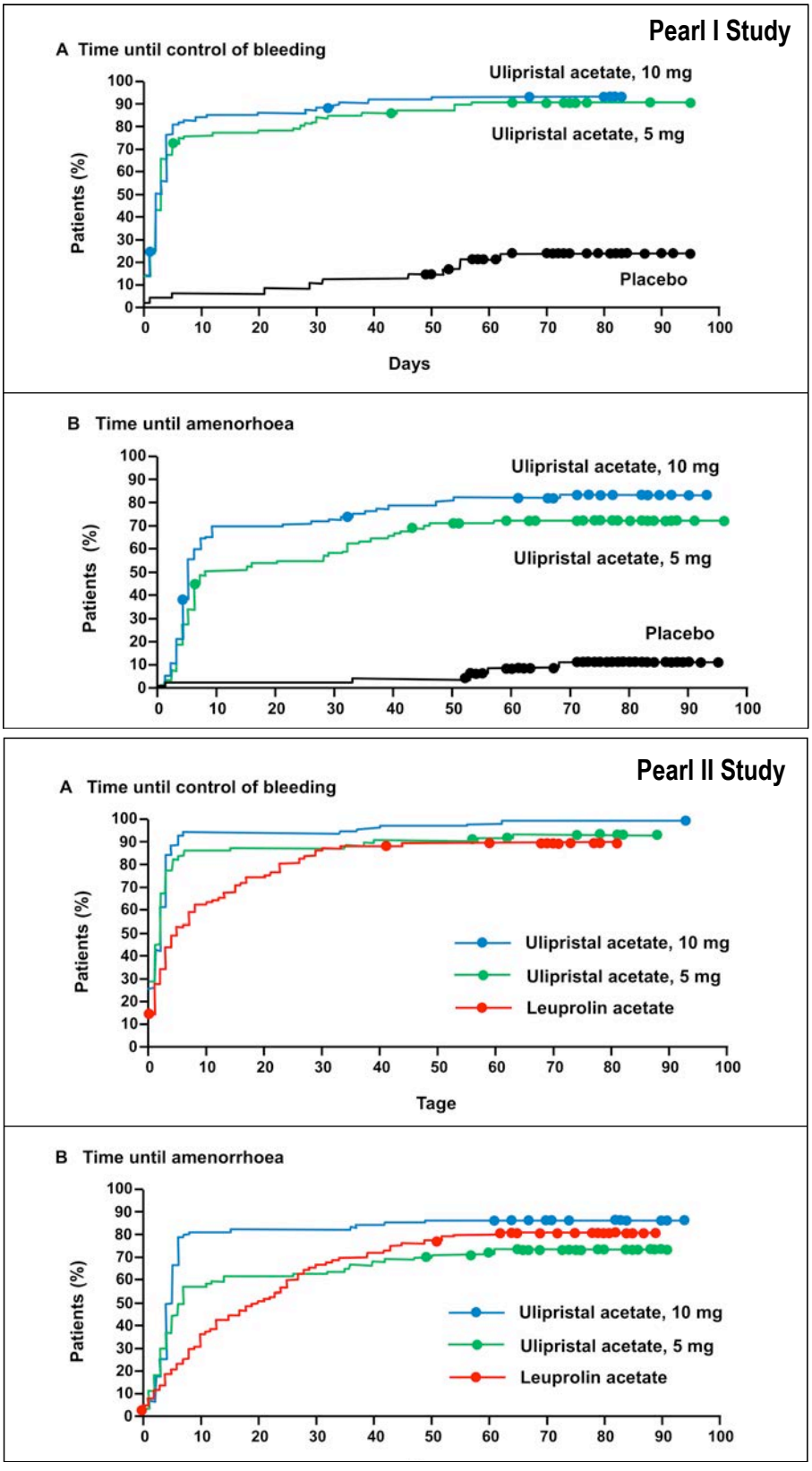


Figure 5: Pearl I (top) and II (bottom) study on the use of ulipristal acetate in women with uterine fibroids and hypermenorrhea leading to anaemia with 5 and 10 mg/day of UPA vs. placebo (Pearl I) or vs. leuprorelin acetate (Pearl II) over a total of 90 days (all patients received iron supplementation).
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 leuprorelin, 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 leuprorelin, the amenorrhea was delayed (Pearl II).
Based on **Donnez et al. (2012a)(51)** and **Donnez et al. (2012b)(52)** with kind permission).

had not started growing again in the UPA groups. By contrast, leuprorelin acetate achieved a 44% reduction of the initial fibroid size immediately after the treatment, but, as expected, the size had returned to 84% of the initial volume six months after discontinuing the therapy. The therapy success achieved in the UPA group was better preserved. Under UPA therapy, the myoma volume was reduced to 55% (5 mg) and 38% (10 mg) of the initial value; after six months, the volume was still reduced to 55% (5 mg) and 45% (10 mg) (s. Fig. 5).

Endometrial changes

In the PEARL I study, mean endometrial thickness did not differ significantly between the groups. It was above 16 mm in a small number of the patients receiving UPA by week 13; in all cases, it returned to normal by week 26 or 38. In week 13, the centrally examined biopsy samples of the endometrium showed no malignant or premalignant lesions or hyperplasia; non-physiological endometrial changes were observed more frequently in the 5 and 10 mg UPA group than in the placebo group (62, 57 and 6% respectively). By week 38 (six months after the end of the treatment phase), these changes were no longer detectable. In the placebo group, there was one case of a complex hyperplasia, which is not unusual in view of the population size and the patient selection (fibroids and hypermenorrhea).

Drug safety data

No significant clinical side-effects were observed in either study (hot flushes 12.7%, reversible endometrial thickening 10-15%, headaches 6.4% and a few cases of breast tenderness). Compared with the GnRH analogue leuprorelin, significantly fewer side-effects occurred under UPA.

Final evaluation

Rapid bleeding control in fibroid-related hypermenorrhea with a preoperative rise in Hb levels and myoma shrinkage are the main advantages of the new treatment option with UPA (5 mg orally, one tablet/day over a maximum of three months). A further advantage is the persistence of the myoma size after the drug-induced shrinkage in case the patient decides against an operation. Based on two large-scale international randomised studies (PEARL I (51) and II (52), *Esmya* (5 mg ulipristal acetate) received European approval in spring 2012 for the preoperative treatment in order to achieve myoma shrinkage and bleeding control. In a recent study published in *The Lancet*, patients with a preoperative anaemia have poorer postoperative results after major non-cardiac operations (56). While GnRH analogues make it more difficult to prepare the layers for a subsequent endoscopic myoma enucleation (57), this does not appear to be the case after UPA treatment (58). Whether UPA will be available in future for the treatment of certain forms of hypermenorrhea alone cannot yet be assessed - a new therapeutic approach along these lines would be desirable.

Conflicts of interest

Hans-Joachim **Ahrendt** does not declare any conflicts of interest.
Christian **Albring** does not declare any conflicts of interest.
Johannes **Bitzer** (Switzerland) does not declare any conflicts of interest.
Philippe **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 Fertility and Sterility, Vol. 96, No. 5, November 2011).
Ulrich **Cirkel** does not declare any conflicts of interests.
Christian **Egarter** (Austria) does not declare any conflicts of interests.
Klaus **König** does not declare any conflicts of interests.
Werner **Harlfinger** does not declare any conflicts of interests.
Alfred **Mueck** does not declare any conflicts of interests.
Thomas **Rabe** has received publication and speaking fees as well as travel expenses from the company PregLem.
Thomas Römer has received travel expenses and fees in connection with a launch symposium in March 2012 in Barcelona and as a participant of an Advisory Board.
Thoralf **Schollmeyer** does not declare any conflicts of interests.
Peter Sinn does not declare any conflicts of interests.
Thomas **Strowitzki** does not declare any conflicts of interests.
Hans-Rudolf **Tinneberg** has received consultancy fees from PregLem as well as conference participation costs and travel or accommodation expenses for a congress from Bayer Health Care, PregLem **and Storz.**
Markus Wallwiener does not declare any conflicts of interests.
Rudy Leon **de Wilde** does not declare any conflicts of interests.

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