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# Effect on surgical decisions: Ulipristal acetate as key player in Belgian phase IV registration trial

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## Abstract

**Objective**: To observe alterations in surgical planning that were due to the use of ulipristal acetate (UPA) 5 mg daily for symptomatic uterine fibroids.

**Methods**: A prospective cohort trial involving women with symptomatic fibroids was undertaken in 23 clinical practice sites within Belgium between October 1, 2014, and March 31, 2016, to compare initial surgical planning to performed surgical procedures following the use of UPA 5 mg daily for 3 months. Secondary outcomes were surgical complications, reduction in fibroids, bleeding control, and adverse effects.

**Results**: Two hundred and twenty-two women were recruited for the trial. The requirement for surgery decreased with the use of UPA, with 54% of women undergoing surgery after treatment. The reduction in surgery performed was lower for women willing to conceive (40%) compared to women who were not (49%). The volume of the fibroids decreased significantly, with the largest measured fibroid decreasing by 50%. Bleeding and pain were significantly decreased with the use of UPA. No major complications were recorded, and no liver function abnormalities were reported during the treatment and in follow-up.

**Conclusion**: By administering UPA, the required rate of surgery was significantly decreased. Also, the resulting reduction in size of the fibroids could have the potential benefit of reducing surgery-related complications, and long-term use may be warranted to avoid surgery completely.

KEYWORDS

Fibroid; Hysterectomy; Myomectomy; Phase 4; Surgery; Ulipristal acetate

## 1 | INTRODUCTION

Uterine leiomyomas (also known as fibroids or myomas) are benign growths occurring in about 20%–40% of women.[1] As fibroids increase in size, they may be associated with more clinical problems such as abdominal discomfort, menorrhagia, or infertility.

Not all fibroids warrant a surgical approach, and surgical treatment of fibroids can be challenging as the more invasive procedures hold a greater risk of complications.[2,3] Hysteroscopic myomectomy is generally safer than a laparoscopic or even laparotomic approach, but is of course limited to fibroids in conjunction with the uterine cavity. A hysterectomy to treat fibroids may hold a smaller surgical risk compared to a myomectomy but is an aggressive way to deal with benign disease and sometimes hard to accept for the patient, even if there is no longer a desire for pregnancy.

The size of the fibroid is directly linked to the risk of complications, therefore treatment of smaller fibroids—at an earlier stage in the disease process—may be warranted.[4] This was demonstrated for all surgical approaches to the treatment of fibroids, so downscaling surgery presents a direct benefit for the safety of the patients. The

surgical risk has, however, shown to be low in larger series.[5,6] On the other hand, repetitive myomectomy may injure the myometrium and could decrease fertility and the functionality of the uterus. Therefore, repetitive myomectomy should be avoided where possible.

One approach to decreasing the operative risk would be to reduce the size of the fibroid. Ulipristal acetate (UPA) (Gedeon Richter PLC, Gyömrői út 19-21, Budapest, Hungary) is a selective progesterone receptor modulator (SPRM) and has been shown to work directly on the fibroid by inducing apoptosis. Trials with UPA have demonstrated a significant reduction in the size of fibroids over a period of 3 months.[7–10] The use of UPA should be balanced against gonadotropin releasing hormone (GnRH), which also reduces the size of the fibroid, but has a less favorable adverse effect profile. The mode of surgery planned before treatment could be altered as a result of the treatment, but this has not been studied before.

The aim of the present study was to investigate if reduction in fibroid size would result in less invasive surgery, and to evaluate the therapeutic value of UPA and efficacy outcomes among patients with symptomatic uterine fibroids, including characterization of severity and burden of illness prior to, and following, use of UPA. The aim was also to describe tolerability outcomes, and a safety profile of UPA in patients with symptomatic uterine fibroids during routine medical care in Belgium.

## 2 | MATERIALS AND METHODS

Belgian women treated with UPA 5 mg daily as preoperative treatment of moderate to severe symptoms of uterine fibroids were recruited to a multicenter prospective non-interventional study between October 1, 2014, and June 30, 2015. Symptoms included heavy menstrual bleeding and abdominal discomfort as these were a prerequisite to obtain reimbursement. Infertility was not regarded as a symptom as no reimbursement existed for this indication.

Twenty-three clinical practice sites within Belgium, chosen to be representative of Belgian clinical practice (academic and non-academic sites), participated in the trial where patients were treated according to good clinical practice. All patients eligible for UPA as described by reimbursement criteria could be included. Surgical planning at the start of treatment and after 3 months of UPA was made by the treating physician in consultation with the patient.

The patient's outcomes were evaluated within the context of normal clinical practice over a 9-month recruitment period (start date upon approval of the protocol by the ethics committee, end date June 30, 2015) and this was followed by a maximum of 9 months follow-up, with the last patient visit being on March 31, 2016.

Data were collected prospectively by the physicians at baseline, at the end of treatment, and after surgery when performed within 6 months after end of treatment, in conjunction with usual care visits. Patients were asked to fill out a patient diary during their treatment, reporting pain using the Visual Analog Scale (VAS), and amount of bleeding, after 1, 2, and 3 months of use (T1, T2, and T3). A Simplified Bleeding Assessment tool was used scoring bleeding as: 1. No bleeding; 2. Spotting; 3. Normal bleeding; and 4. Heavy bleeding. Participating physicians did not perform any medical procedure that was outside of their normal clinical practice. Fibroids were measured using ultrasound at enrollment and after 3 months.

Adverse events, serious and non-serious, were followed up and reported.

Inclusion criteria for the present trial were women who were aged 18 years or over; were pre-menopausal with a diagnosis of moderate or severe symptoms of uterine fibroids and who were initiating preoperative treatment with UPA; had agreed to participate in the study and to disclose any medical events to the treating physician; had provided the required medical data and completed the patient reported outcomes questionnaires about uterine fibroids-associated symptoms (simplified bleeding assessment tool and VAS); and were willing and able to provide written informed consent. Exclusion criteria were participation in other concurrent clinical studies; Compassionate Use Programs; or medical need protocols with UPA 5 mg.

Statistical analyses used were descriptive, reporting number of patients, means with standard deviations, medians, minima and maxima for continuous variables (e.g. age and duration of symptomats), and frequencies and percentages for categorical variables (e.g. disease symptoms, and adverse events). Result were statistically significant with a $P<0.05$. The analyses were conducted based on all enrolled patients. No imputation was performed for any missing data. Analyses were performed using SAS Version 9.2 for Windows software or higher (SAS Institute Inc., SAS Campus Drive, Cary, NC, USA).

The trial was supported by Gedeon Richter as an obligatory requisite to introduce UPA on the Belgian market.

The study protocol and all its amendments were reviewed and approved by the leading ethics committees of KU Leuven. The protocol was approved by the local ethical commission at each site as a prerequisite to start the observation of the first patient.

## 3 | RESULTS

In the present trial, 222 women were recruited from 20 participating sites (Fig. 1).

Demographic data of the participants are shown in Table 1, demonstrating a non-statistically significant difference in the number of fibroids according to race. Indeed, black women had more fibroids (mean 7.1 ± 8.9 fibroids) compared to white (mean 2.2 ± 2.6) and Asian women (mean 6.0 ± 3.9). Pain scores decreased over time as reported by the patients. At baseline we observed a VAS mean score of 42.3 (±28.1) which significantly decreased to a mean of 21.4 (±24.5) after 3 months of treatment ($P<0.05$).

At baseline, 106 out of 186 (57%) women reported mild to heavy bleeding at the day of consultation, which decreased to 18 out of 152 (11.8%) after 3 months of treatment (Friedman test repeated measures: $P<0.001$). The hemoglobin level increased in relation to this decrease in bleeding from a mean of 107 g/L (±26) to 121 (±16) (paired $t$ test: $P<0.001$).

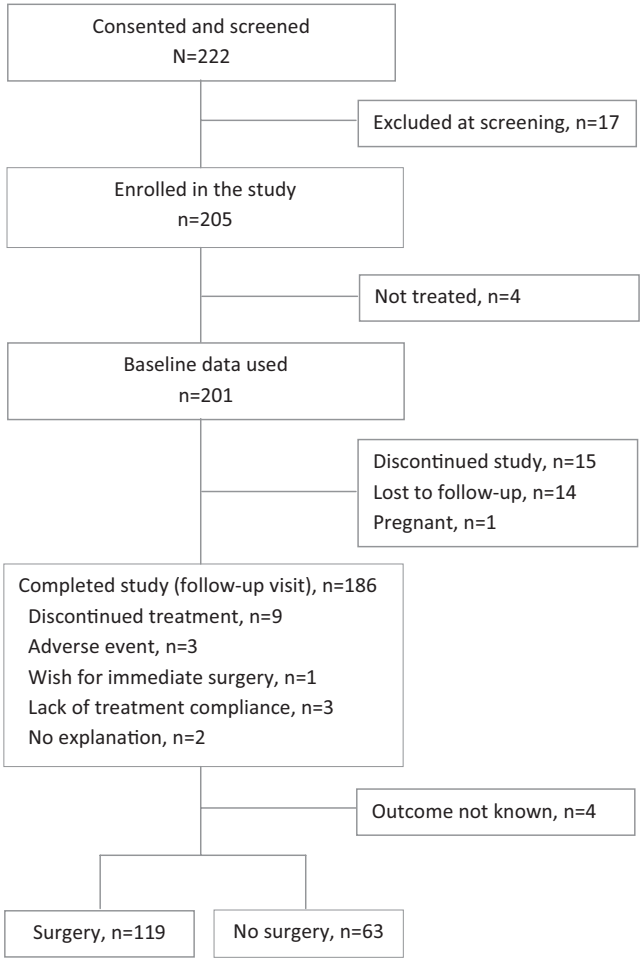


**FIGURE 1** CONSORT flow diagram.

The sum of the volume of the three largest fibroids decreased over the 3-month period from a mean volume of 228.6 $cm^3$ (±737.5 $cm^3$) to 154.4 $cm^3$ (±410.8 $cm^3$) (Wilcoxon signed rank test: $P<0.001$), where the volume of the biggest fibroid decreased by 50% from a mean of 197.6 $cm^3$ ± 675.8 to 133.6 $cm^3$ ± 378.8 ($P<0.001$). Two women discontinued the treatment because of a lack of efficacy.

Of all patients receiving UPA 5 mg, only 54% underwent surgery after the end of treatment (3 months). The number of procedures for all surgical interventions were decreased (Table 2). Fourteen women (7.9%) received a second course of UPA, of whom four underwent surgery thereafter. Most of the planned surgeries at baseline were laparoscopic myomectomy (33%) and hysterectomy (27%). At the end of treatment with UPA, most of the planned surgeries were still hysterectomies (19%) and myomectomies by laparotomy (13%). Six women underwent uterine artery embolization.

Planned surgery was different when stratified by age: in women less than 41 years of age, 47.9% were planned for a laparoscopic myomectomy compared to only 21.2% of women older than 41 years. On the contrary, planned hysterectomy was 12.5% in women less than 41 years and in 42.4% of women older than 41 years. Planned hysterectomy was actually performed in 92.9% of cases. This is in contrast to planned laparoscopic myomectomy which was only performed in 47.5% of cases. Laparoscopic myomectomy was also performed in one patient (8.3%) planned for hysteroscopic myomectomy and in two patients (10.5%) planned for laparotomic myomectomy. Seven patients (17.5%) planned for laparoscopic myomectomy and one patient (3.6%) planned for hysterectomy underwent a hysteroscopic myomectomy after receiving UPA for 3 months.

Most surgical interventions were performed in women who still had a wish for pregnancy (60%) compared to women who no longer wished to conceive (51%). The surgical interventions performed are listed in Table 2. There was no clear downscaling in surgery (i.e. switching from laparotomy to laparoscopy or hysteroscopy), but surgery in total was decreased after the use of UPA 5 mg.

Surgery was performed in 94.4% of cases without major adverse events. Major adverse events were reported in six patients (5.6%), four of whom had bleeding and blood transfusion, one a gas embolism during hysteroscopic resection, and one a conversion due to difficult exposure. No liver function test abnormalities were reported before and during the treatment with UPA. As a result of the effect of UPA 5 mg, surgical intervention was postponed and 8.1% of women received a second course of UPA, which was off-label at the time of the trial.

Women who opted for surgery were younger and also had a lower hemoglobin level than those who did not have surgery; no other factors differed significantly between the two groups (Table 3). The type

**TABLE 1** Demographic data of the women included in the trial.

| Variable | | |
|---|---|---|
| Age, y[a] | Overall (n=201) | 39.8 (41.0) |
| | Caucasian (n=108) | 42.5 (44.0) |
| | Black (n=70) | 36.4 (35.0) |
| | Asian (n=5) | 40.8 (41.0) |
| | Other (n=18) | 36.6 (36.5) |
| Age categories[b] | ≥ 18 and <40 y | 88 (43.8) |
| | ≥ 40 and <45 y | 53 (26.4) |
| | ≥ 45 y | 60 (29.9) |
| Race[b] | Caucasian | 108 (53.7) |
| | Black | 70 (34.8) |
| | Asian | 5 (2.5) |
| | Other | 18 (9.0) |
| Pregnancy wish[b] | <40 y | 66 (65.3) |
| | ≥41 and <51 y | 17 (17.2) |
| | ≥51 y | 0 (0) |
| BMI[a] | Caucasian | 23.4 (23.5) |
| | Black | 24.0 (24.4) |
| | Asian | 20.0 (21.6) |
| | Other | 23.8 (25.7) |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).
[a]Values are given as mean (median) unless indicated otherwise.
[b]Values are given as number (percentage).

**TABLE 2** Planned and performed surgery in women receiving 3 months of ulipristal acetate.

| Planned surgical intervention | Performed surgical intervention[a] | | | | | | No intervention (n) |
|---|---|---|---|---|---|---|---|
| | Hysteroscopic myomectomy | Laparoscopic myomectomy | Laparotomic myomectomy | Hysterectomy | Other | Total | |
| Hysteroscopic myomectomy | 7 (58.3) | 1 (8.3) | 0 (0) | 2 (16.7) | 2 (16.7) | 12 (100.0) | 10 |
| Laparoscopic myomectomy | 7 (17.5) | 19 (47.5) | 8 (20.0) | 4 (10.0) | 2 (5.0) | 40 (100.0) | 26 |
| Laparotomic myomectomy | 0 (0.0) | 2 (10.5) | 17 (89.5) | 0 (0.0) | 0 (0.0) | 19 (100.0) | 11 |
| Hysterectomy | 1 (3.6) | 0 (0.0) | 1 (3.6) | 26 (92.9) | 0 (0.0) | 28 (100.0) | 25 |
| Uterine artery embolization | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 |
| Other | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) | 2 (100.0) | 2 |
| None | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (100.0) | 0 (0.0) | 3 (100.0) | 9 |
| Unknown | 2 (50.0) | 0 (0.0) | 0 (0.0) | 2 (50.0) | 0 (0.0) | 4 (100.0) | 6 |
| Total | 17 (15.7) | 22 (20.4) | 26 (24.1) | 38 (35.2) | 5 (4.6) | 108 (100.0) | 90 |

[a]Values are given as number (percentage) unless indicated otherwise.

of the fibroid was not significantly different in both groups and the bleeding assessment at intake and after 3 months was also comparable. With younger age, women in the group undergoing surgery also had a higher desire for pregnancy (43.5% vs 36.8%).

Treatment discontinuation was observed in nine patients, where an adverse event (n=3) and lack of treatment compliance (n=3) were the main reasons. Other cases included wish for immediate surgery, and two where no explanation was given. Patient satisfaction was high, with 80.3% (n=139 out of 173 respondents) of patients being satisfied or very satisfied. Only one patient was very dissatisfied. Adverse events such as hot flushes (7.5%), depression (5%), and fatigue (5%) were reported in 16 patients (9.2%), corresponding to what was reported in the prospective trials conducted with UPA. Serious adverse events reported during the trial were a uterine fibroid expulsion, two women with heavy uterine bleeding, and one case of neonatal respiratory distress syndrome (exposure to UPA in early pregnancy).

## 4 | DISCUSSION

The present multicenter prospective non-interventional study of Belgian women treated with UPA 5 mg as preoperative treatment of moderate to severe symptoms of uterine fibroids presents real-world data on the use of UPA for management of symptoms related to uterine fibroids during one 3-month course according to the Belgian clinical practice.

The primary objective of the trial was to investigate the effect of UPA on surgical planning: the data show a tendency toward less invasive surgery. Planning a surgical procedure is also linked to the skills of the surgeon and to variables other than the fibroid; we performed this trial in different centers spread over Belgium to attempt to allow for these variables. A great number of women (46%) did not require surgery after 3 months of treatment with UPA, demonstrating a direct benefit on health and economic outcomes.

One of the limitations of the study was that it was not possible to account for the women who did not fulfill the reimbursement criteria and who could also have benefited from treatment with UPA. With fibroids of less than 3 cm in diameter and/or no heavy bleeding, there was no reimbursement and those women were perhaps more likely to undergo surgery.

Another limitation of the study was that no data on the ease of surgery were collected. As this trial was only to demonstrate a direct effect on surgical decision, and as no comparative arm (placebo or GnRH) was included, we did not look at surgical outcome nor at anatomical changes in the uterine fibroid.

Hysterectomy and laparotomic myomectomy were performed, respectively, in 92.9% and 89.5% of initially planned interventions, indicating that downscaling of surgery only occurred in less than 10% of cases. This small effect in downscaling could be explained by the surgeon's preference and skills in performing a myomectomy, and by the remaining symptoms of the patient opting for hysterectomy. Data on the reasons why a certain type of surgery was performed were, however, not collected.

Women who did not undergo surgery after 3 months of UPA because their symptoms had resolved were followed up by their treating physician. No data were collected in the present trial to see if participating women required surgery in the long term. Our results are, however, in accordance with other real-world data, where the

**TABLE 3** Differences between women who underwent surgery and women who did not.[a]

| | Surgery n=115 | No surgery n=95 | *P* value |
|---|---|---|---|
| Age, y | 38.7 (6.9) | 41.2 (7.2) | <0.005 |
| Parity | 1.9 (1.8) | 2.2 (2.2) | NS |
| Number of myomas | 4.4 (7.1) | 3.3 (4.1) | NS |
| Diameter of myoma, cm | 5.8 (2.9) | 5.1 (2.9) | NS |
| Hemoglobin at intake | 10.1 (2.3) | 11.5 (2.4) | <0.01 |
| VAS score at 3 months | 22.1 (24.8) | 20.8 (23.6) | NS |

Abbreviations: NS, not significant; VAS, Visual Analog Scale.
[a]Values are given as mean (standard deviation) unless indicated otherwise.

follow-up lasted 15 months.[11] Therefore, deferring surgery as shown in the present study looking at the short term could potentially avoid surgery in the long term.

Interestingly, 30% of patients were older than 45 years, representing an older population that was excluded from the PEARL clinical trials published previously.[7–10] An evaluation of this particular population is of interest in light of an option to avoid surgery just before menopause.

Decrease in pain scores was as expected, but absence of bleeding at baseline in 35.6% of women was unexpected as this was a prerequisite for reimbursement of UPA. As women filled out the questionnaire during a medical consultation, reported bleeding referred to that moment, although menstruations could be severe. The marked decrease in heavy bleeding over time to 4.6% was in concordance with previous trials.[7–9]

The present study results confirmed the efficacy of UPA in reduction of excessive uterine bleeding, pain and discomfort, and total uterine fibroid volume among patients eligible for surgery. This was demonstrated via the analysis of the primary endpoints, namely the percentage of participants with reduction of excessive uterine bleeding at follow-up visit (increase of 82% in number of patients with no bleeding) and the decrease in total fibroid volume from baseline visit to follow-up visit.

As previously shown in the prospective PEARL trials,[7,8] we also found a decrease in volume of the fibroids, objectively confirming this strong endpoint. We could not find any relation between the volume of the fibroids and surgery planned or performed, as this is also related to the localization of the fibroids and the use and/or skill of the surgical team. As invasiveness of surgery decreased parallel to the volume of the fibroid, we might suspect a direct relationship. Planning surgery before starting treatment with UPA might therefore be difficult and reappraisal of the fibroid is warranted after treatment. As most planned surgery was not downscaled, but rather evaded, it would be difficult to confirm the effect UPA had on the type of surgery performed.

Women undergoing surgery after treatment with UPA were younger and had an increased desire for pregnancy. These women were perhaps less willing to opt for a wait-and-see policy, as this could mean that the fibroids could regrow. The location of the fibroids can also be a hindrance to future pregnancy (i.e. fibroid type 0, 1, 2 which are located complete or partially in the uterine cavity), meaning that surgery is warranted, but this was not studied in the present trial.

As fertility may be influenced by the presence of fibroids it seems logical that most planned interventions were also performed in this group. It was surprising, however, that one fertility patient underwent a hysterectomy.

Safety of UPA was well established before the present study,[1–4] and was confirmed as a result of this trial. Although some serious adverse events were reported, these were within the range of the previous trials with UPA.[7,8] The present trial differed from the PEARL trials in that the percentage of black patients in the present trial was higher.[7,8] As this specific population tends to have more and larger fibroids, the present trial shows that UPA is beneficial for these women. Liver function tests, which were not performed routinely at the time of the present trial, showed no abnormalities. Because not all centers include liver function tests as a routine preoperative check-up, it is not known how many women were tested.

## AUTHOR CONTRIBUTION

JV and MN contributed to the conception and the design of the study, and writing of the manuscript. All authors contributed to the collection, analysis and interpretation of the data and revision of the manuscript.

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## CONFLICTS OF INTEREST

The authors acknowledge to be part of Gedeon Richter local advisory board and receive honorarium for sponsored lectures on UPA. Gedeon Richter had no involvement in drafting or writing the manuscript.

## REFERENCES

1. Wallach EE, Vlahos NF. Uterine myomas: An overview of development, clinical features, and management. *Obstet Gynecol*. 2004;104:393–406.
2. Havryliuk Y, Setton R, Carlow J, Shaktman B. Symptomatic fibroid management: Systematic review of the literature. *JSLS*. 2017;21:e2017.00041.
3. Kundu S, Iwanuk C, Staboulidou I, et al. Morbidity, fertility and pregnancy outcomes after myoma enucleation by laparoscopy versus laparotomy. *Arch Gynecol Obstet*. 2018;297:969–976.
4. Petermans S, Ameye L, Timmerman D, Verguts J. Ultrasonography in the prediction of complications during and after uterine myomectomy. *Gynecol Surg*. 2016;13:507–514.
5. Mallick R, Odejinmi F. Pushing the boundaries of laparoscopic myomectomy: A comparative analysis of peri-operative outcomes in 323 women undergoing laparoscopic myomectomy in a tertiary referral centre. *Gynecol Surg*. 2017;14:22.
6. Bean EM, Cutner A, Holland T, Vashisht A, Jurkovic D, Saridogan E. Laparoscopic myomectomy: A single-center retrospective review of 514 patients. *J Minim Invasive Gynecol*. 2017;24:485–493.
7. Donnez J, Tatarchuk TF, Bouchard P, et al. Ulipristal acetate versus placebo for fibroid treatment before surgery. *N Engl J Med*. 2012a;366:409–420.
8. Donnez J, Tomaszewski J, Vázquez F, et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. *N Engl J Med*. 2012b;366:421–432.
9. Donnez J, Vázquez F, Tomaszewski J, et al. Long-term treatment of uterine fibroids with ulipristal acetate. *Fertil Steril*. 2014b;101:1565–1573.
10. Donnez J, Donnez O, Matule D, et al. Long–term medical management of uterine fibroids with ulipristal acetate. *Fertil Steril*. 2016;105:165–173.
11. Fernandez H, Schmidt T, Powell M, Costa AP, Arriagada P, Thaler C. Real world data of 1473 patients treated with ulipristal acetate for uterine fibroids: Premya study results. *Eur J Obstet Gynecol Reprod Biol*. 2017 Jan;208:91–96.