European Journal of Obstetrics & Gynecology and Reproductive Biology 252 (2020) 256–264

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Ulipristal acetate versus gonadotropin-releasing hormone agonists prior to laparoscopic myomectomy (MYOMEX trial): Long term results of a double-blind randomized controlled trial

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ARTICLE INFO

Article history:
Received 14 February 2020
Received in revised form 9 June 2020
Accepted 15 June 2020

Keywords:
Fibroid
Myomectomy
Ulipristal acetate
Gonadotropin releasing hormone
Randomized controlled trial
Cost-analysis

ABSTRACT

Objective: The aim of this study was to compare the effect of ulipristal acetate (UPA) and gonadotropin-releasing hormone agonists (GnRHa) before laparoscopic myomectomy on long term secondary outcomes of the MYOMEX-trial, regarding quality of life, ultrasound characteristics, hemoglobin levels 6 weeks post-operative, sexual function and menstrual bleeding control. A cost-analysis was also performed. Short-term primary and secondary outcomes are reported elsewhere.

Study design: A double-blind, randomized, controlled, non-inferiority trial in nine hospitals in the Netherlands. Participants were randomized in a 1:1 ratio (block size of four, stratified per hospital) to either UPA or GnRHa pre-treatment. Additional placebo injections containing saline, respectively daily placebo tablets were given to both groups to ensure double-blinding. Surgery was performed within a month after the last tablet. Women were followed up until six months post-surgery.

Results: A total of 55 participants were randomized: 30 to the UPA- and 25 to the GnRHa-group between May 2015 and July 2017. Uterine volume at six weeks post-operative did not differ significantly between both pre-treatment groups with 170.1 cm^3 (106.8–243.5; N = 29) vs. 152.8 cm^3 (92.3–205.6; N = 23) for the UPA- and GnRHa-group respectively (p = 0.423). Hemoglobin levels six weeks post-operatively recovered back to baseline and were not significantly different between groups with 7.7 mmol/L for the UPA- vs. 8.1 mmol/L for the GnRHa-group (p = 0.157; mean difference -0.4 (CI -0.9, 0.2). Menstrual bleeding pattern, quality of life, effects on general and sexual health showed a significant improvement compared to baseline in both groups without any differences between the treatment groups. Symptom severity scores also decreased significantly at 6 week post-operatively compared to baseline, but did not differ between the treatment groups. Fibroid characteristics at baseline (e.g. mean diameter of largest fibroid) appeared not to be a confounding factor. An exploratory cost analysis showed no significant differences in absenteeism costs, total healthcare and societal costs, after adjustment for confounding factors.

Conclusion: Pre-treatment prior to laparoscopic myomectomy with UPA compared to GnRHa has similar effects on bleeding pattern, menopausal symptoms, sexual functioning, symptom severity and quality of

Abbreviations: BIA, budget impact analysis; CMA, cost minimization analysis; FSFI, Female Sexual Functioning Index; FSDS, Female Sexual Distress Scale; EMA, European Medicine Agency; GnRHa, gonadotropin-releasing hormone agonists; GP, General Practitioner; HMB, heavy menstrual bleeding; HRQL, health related quality of life; PBAC, pictorial blood loss assessment chart; RCT, randomized controlled trial; UFS-QoL, Uterine Fibroid and Quality of Life; UPA, ulipristal acetate.

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https://doi.org/10.1016/j.ejogrb.2020.06.035

life from baseline up to six months post-operative. Due to the small sample size, these findings should be interpreted with caution. Also, no firm conclusions on costs could be made.

Introduction

Laparoscopic myomectomy has several advantages over the laparotomic approach. Smaller incisions result in less post-operative pain, shorter hospital stay and faster recovery [1–3]. However, laparoscopic myomectomy can be difficult when fibroids are large and numerous. This may result in extensive intra-operative bleeding and the need for conversion to laparotomy. Medical pre-treatment before surgery might reduce these risks by decreasing fibroid size and vascularization of the fibroid [4,5]. Fernandez et al. quantified the rate, type and costs of interventions for uterine fibroids in three European countries. In Germany, France and the United Kingdom, respectively 1.53, 1.17 and 0.71 per 1000 women required interventions for uterine fibroids, with annual costs ranging from 51 to over 212 million euros in 2005 [6], making uterine fibroids a major economic burden. Only two medicines are currently registered for fibroid pre-treatment: Gonadotropin-releasing hormone agonists (GnRHa) and Ulipristal acetate (UPA), a selective progesterone receptor modulator. Pre-treatment with GnRHa showed improvement of pre- and post-operative hemoglobin levels and reduced uterine and fibroid volumes [7]. UPA showed pro-apoptotive and anti-proliferative effect on fibroids, resulting in fibroid volume reduction without affecting normal myometrial tissue [8,9].

No randomized controlled trials (RCTs) are currently available reporting on peri- and post-operative outcomes of pre-treated fibroids. We therefore performed a non-inferiority, double-blinded RCT comparing medical pre-treatment with UPA or GnRHa before laparoscopic myomectomy. Previously published short-term results focused on pre- and peri-operative outcomes and showed that UPA, in comparison to GnRHa, seemed less effective in decreasing fibroid volume. Also, surgical outcomes showed longer suturing time and a negative impact on surgical ease [10]. We concluded that non-inferiority of UPA in terms of intra-operative blood loss could not be established. This study did not achieve its required sample size, therefore it is not possible to conclude whether these significant differences were caused by chance (type I error in non-inferiority trial) [11]. In the current paper we perform a cost-analysis and we compare the effect of UPA and GnRHa before laparoscopic myomectomy on quality of life, effects on general and sexual health and menstrual bleeding control.

Methods

The details of our study design have been previously described but will be briefly discussed in this paper [10]. The MYOMEX-trial is a double-blind RCT with nine participating hospitals in the Netherlands. Eligible women met the following inclusion criteria: a planned laparoscopic myomectomy for a maximum of two FIGO (PALM-COEIN classification) type 3, 4, 5, 6 or 2–5 uterine fibroids with a diameter from 5 to 12 cm. Women visiting the outpatient clinic of a participating center were informed about the study. After written consent was provided, participating women were randomly allocated in a 1:1 ratio to receive either UPA or GnRHa. Randomization was done by a computer-generated program and stratified by center (with a block size of four). Participants in the UPA group received daily oral UPA 5 mg tablets for 12 consecutive weeks and a one-time placebo injection containing saline. Women in the GnRHa group received a single intramuscular injection with leuprolide acetate (11.25 mg) and daily placebo tablets for 12 consecutive weeks. Study materials and medication packaging were identical for both groups. Preferably, treatment was started in the first week of menstruation. Surgery was performed within a month after the last tablet. Participants and gynecologists were blinded for treatment allocation during the entire study period. Statistics and cost-analysis were performed by an independent statistician and methodologist respectively, both blinded for the allocated study groups.

Transvaginal ultrasounds to measure uterine and fibroid size in three dimensions were performed at baseline, after pre-treatment and six weeks post-operative. Uterine and fibroid volume were calculated using the formula for ellipsoid: $D1 \times D2 \times D3 \times 0.5233$. Hemoglobin levels were measured at baseline, after pre-treatment, within 48 h post-operative and 6 weeks post-operative. Surgery was performed within a month after the last tablet. Participants and gynecologists were blinded for treatment allocation during the entire study period.

Outcomes

Previously published short-term primary and secondary outcomes reported on intra-operative blood loss, ultrasound measurements and hemoglobin levels 1 day post-surgery [10].

Secondary outcomes

Patient questionnaires

Women received digital online secured questionnaires at baseline, after pre-treatment, six weeks and six months post-operative on general health, sexual functioning, menopausal symptoms and quality of life.

Uterine bleeding was assessed using the pictorial blood loss assessment chart (PBAC) for the month previous to starting medication, during the whole study period and up to three months post-operative. Women were asked to complete the PBAC daily in a specially designed secured app or on paper. According to this scale, the number of tampons or pads used and their subsequent saturation results in a monthly score ranging from 0 (amenorrhea) to over 500. Higher numbers indicate more bleeding [12]. In the Netherlands, the cut-off point for heavy menstrual bleeding (HMB) is 150.

The Female Sexual Functioning Index (FSFI) describes sexual functioning in six domains (i.e. desire, arousal, lubrication, orgasm, satisfaction and pain). Each individual domain has a score range from 0 to 5 or 1 to 5. Each domain score is multiplied by a specific domain factor, resulting in a score ranging from 2.0 to 36.0 (36.0 being the optimal score) [13]. The Female Sexual Distress Scale (FSDS) contains 12 questions on sexual distress. Each question results in a score from 0 to 4 (0=never; 4=always). The individual scores are added up and result in a total score from 0 to 48 (0 being the optimal score) [14].

Menopausal symptoms were assessed using a score developed by Oldenhave et al. [15] yielding three dimensions: vasomotor complaints, atypical symptoms and vaginal dryness. The total score ranges from 0 to 72, where a higher score represents more menopausal symptoms.

The Shaw-questionnaire evaluates six components of health (practical difficulties, social life, psychological health, physical health and wellbeing, work/daily routine, family life/relationships) in women with HMB [16]. Each domain results in a score (the

maximum score for each domain depends on its importance). The sum of these scores forms the total score varying from 0 to 100 (100 indicating optimal score).

The Uterine Fibroid Symptom and Quality of Life (UFS-QoL) questionnaire is especially designed to assess symptom severity and symptom impact on health related quality of life (HRQL) for women with leiomyomata [17]. The questionnaire consists of eight symptom questions and 29 HRQL questions within six subscales (i.e. concern, activities, energy/mood, control, self-conscious, sexual function). Scores on symptom severity range from 0 to 100, where higher scores indicate greater symptom severity. Scores from each of the HRQL subscales also range from 0 to 100, where higher scores are indicative of better HRQL.

The EQ-5D describes health status in terms of five dimensions (i.e. mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension is described using three functional levels (1 = no problems, 2=moderate problems, 3=severe problems). These functional levels are transformed into a score ranging from 0.0 to 1.0 (1.0 being the optimal score) by an algorithm that adjusts for age [18,19].

*Cost*Using the results from the trial, we performed an exploratory cost analysis that focused on the most important cost drivers. Healthcare utilization (hospital admissions, outpatient visits and general practitioner (GP) care), absenteeism days from paid work and costs made by women themselves were measured using retrospective patient questionnaires filled out six months post-operatively. Cost analysis was performed with only complete cases (UPA = 22 women; GnRHa = 18 women), who filled in all the cost-questionnaires. Dutch standard costs were used to value healthcare utilization and absenteeism (Table 1) [20].

Statistical analysis

The MYOMEX-trial was a non-inferiority trial with the following null-hypothesis: UPA is non-inferior to GnRHa in terms of blood loss during surgery with a maximum difference of 150 mL considered acceptable based on previous studies on this subject [21]. The assumed standard deviation was 250 mL for intra-operative blood loss based on a survey in three hospitals in the Netherlands. Based on a two-group *t*-test of equivalence in means, using a one-sided significance level of 2.5 %, and a Type II error of 20 % (80 % power) this yielded a sample size of 90 women (45 in each study arm).

Study outcomes were analyzed using intention-to-treat analysis. To evaluate normality of the data, QQ plots were used. Normally distributed data were summarized as mean and standard deviation and compared with an independent *t*-test. Also mean differences and confidence intervals were calculated. For non-normally distributed data, we presented median and interquartile ranges (IQR). To compare outcomes between the groups, the Mann-Whitney *U*-test was used for non-normally distributed data. To assess differences between and within groups at baseline, 3 months after baseline, 6 weeks post-operative and 6 months post-operative, the paired *t*-test was used for normally distributed variables and the Wilcoxon signed rank test for non-normally distributed data.

Linear regression analysis was performed to correct the analysis for comparison between pre-treatment groups for any potential confounders. A variable was considered a valid confounder when the regression coefficient for groups changed by >10 % when the confounder was added to the model. Of all the baseline characteristics, only mean diameter of the largest fibroid appeared to be a confounder [10].

All analyses were performed using SPSS version 22.0. A two-sided significance level of 5 % was used for all long-term analyses and a *P*-value of 0.05 (2-sided) was considered statistically significant in all analyses presented in this manuscript.

Mean costs were compared between the UPA and GnRHa group using linear regression models with adjustment for fibroid volume at baseline. Bias-corrected and accelerated (BCA) bootstrapping with a 5000 replication factor was used to calculate 95 %-confidence intervals around adjusted cost differences [22]. Analysis was performed with STATA (version 14SE), resulting in a comparison between the UPA and GnRHa group.

Table 1
Standard healthcare costs.

Cost items	Price (€, 2014)	Assumptions
Absenteeism, per hour	31.60	8 working hours per day
Outpatient care, per visit	91	
Hospital admission, per day	476	2 days per admission
GP consultation, per visit	33	1 home visit
GP home visit, per visit	50	

Standard costs used in this cost calculation, based on the Dutch Manual for Costing studies in health care [20].

Results

Participants

Women were enrolled between May 2015 and July 2017. Due to disappointing inclusion rates in most participating centers and expiration of study medication, the intended number of inclusions was not met. Of the original 90 planned only 68 eligible women were recruited of which 55 were randomized: 30 were allocated UPA and 25 Leuprolide acetate (Fig. 1). In retrospect, one woman randomized to UPA did not meet the inclusion criteria (fibroid >12 cm) and was therefore excluded from any analysis. In the UPA-group, two women dropped-out before the end of pre-treatment due to withdrawal of informed consent and persistent symptoms which required hysterectomy [10]. In the GnRHa-group, all women completed pre-treatment. A total of three women did not undergo a laparoscopic myomectomy, because they preferred homeopathic therapy (n = 2) or experienced a significant decrease of fibroid volume, making surgery unnecessary [10]. All women underwent a transvaginal ultrasound at six weeks follow-up and hemoglobin levels were measured. At six weeks follow-up, four women did not complete the questionnaires and at six months follow-up, seven women were lost to follow-up (Fig. 1).

The two treatment groups were similar in demographic characteristics and baseline hemoglobin levels (Table 2). However, treatment groups differed in fibroid characteristics, due to the lack of stratification for fibroid size at baseline. The mean diameter of the largest fibroid was significantly higher in women allocated UPA compared to women allocated GnRHa (8.5 ± 1.9 cm vs. 7.4 ± 1.6 cm; p = 0.035, 95 % CI 0.1–2.0). Other ultrasound characteristics at baseline (i.e. type, uterine volume and total fibroid volume planned for resection) did not show significant differences [10].

Secondary outcomes

Fibroid characteristics and hemoglobin level 6 weeks post-operative

Uterine volume at six weeks post-operative did not differ between both pre-treatment groups with 170.1 cm^3 (106.8–243.5) for the UPA-group vs. 152.8 cm^3 (92.3–205.6) for the GnRHa-group (p = 0.423, Table 3). In two women of the UPA-group and one woman in the GnRHa-group, fibroids were resected incompletely. Hemoglobin levels at six weeks post-operatively recovered back to hemoglobin level at baseline and the hemoglobin level at six weeks

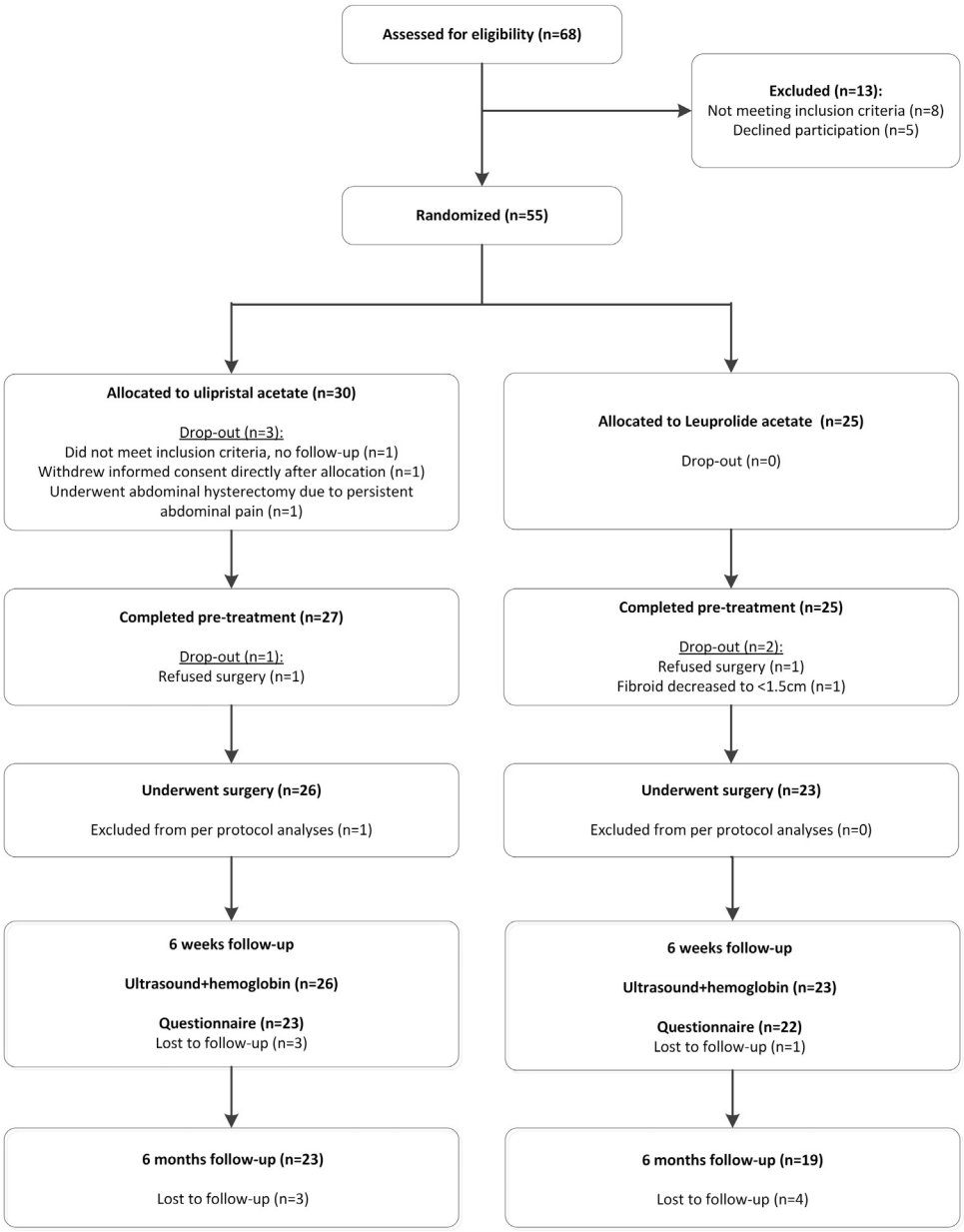

Fig. 1. CONSORT Flow diagram.

post-operatively did not differ significantly between the groups (Table 3). Also, fibroid volume at baseline did not appear to be a confounder for hemoglobin levels.

Patient questionnaires

Both treatment groups showed a significant decrease in PBAC-score (Fig. 2 and Table 4). The change from baseline to three months was not significantly different between the treatment groups (−321 (−515 to −85) vs. −348 (−818 to −112); $P = 0.485$). 62 % In the UPA-group and 52 % in the GnRHa-group had amenorrhea after three months of pre-treatment. Median PBAC-score at three months after surgery was still significantly lower compared to baseline (−178 (−478 to −39) vs. −216 (−630 to −70); p=0.001), but did not differ between both groups ($P = 0.599$).

Regarding the remaining questionnaires completed by the participants (FSFI, FSDS, Shaw, menopause symptoms and UFS-QoL), total scores and change from baseline did not differ between both groups at all measurement moments (Fig. 3 and Table 4). Fibroid characteristics at baseline (e.g. mean diameter of largest fibroid) appeared not to be a confounding factor.

Scores on the Shaw and UFS-QoL HRQL questionnaire in both groups showed a significant increase after three months of pre-treatment and also 6 weeks and 6 months post-operatively which indicates health improvement ($P < 0.001$) (Fig. 3 and Table 4). Regarding the UFS-QoL Symptom Severity score, symptoms were reported as less severe in both groups at all measurements compared to baseline. Women in the UPA-group reported a significant increase in menopausal symptoms at three months and at 6 weeks post-operatively ($P < 0.001$). For the GnRHa-group, this increase was not significantly different. Between and within group analysis did not show significant effects on sexual functioning (FSFI and FSDS; Table 4).

Cost analysis

Medication cost per pre-treatment were comparable for UPA and GnRHa (Table 5). Total healthcare costs, total societal costs and

Table 2
Baseline characteristics of the study population.

	Ulipristal acetate (n = 29)	Leuprolide acetate (n = 25)
Age (years; mean ± SD)	38.4 ± 5.8	41.4 ± 5.6
Body mass index (kg/m^2; median, range)	24.5 (18.8–38.2)	25.9 (18.0–42.5)
Parity (median, range)	0 (0–2)	1 (0–4)
Race (n; %)		
Caucasian	17 (59)	11 (44)
Black	3 (10)	6 (24)
Other	9 (31)	8 (32)
Medical history of abdominal surgery (n, %)	14 (48)	8 (32)
Haemoglobin (mmol/L; mean ± SD)	7.8 ± 1.0	7.7 ± 1.1
Indication for surgery (n)[a]		
Heavy menstrual bleeding	11	13
Abdominal pain	9	8
Subfertility	8	2
Mechanical complaints	15	7
Other	2	1
Type of largest fibroid (n, %)		
Intramural	20 (69)	22 (88)
Subserosal	9 (31)	3 (12)
Mean diameter of largest fibroid at baseline(cm; mean ± SD)	8.5 ± 1.9	7.4 ± 1.6
Total fibroid volume planned for resection (cm^3; median, IQR)	316.3 (184.7–462.6)	246.0 (130.2–344.3)
Uterine volume (cm^3; median, IQR)	530.5 (392.8–774.5)	421.2 (327.5–819.8)

SD = standard deviation; IQR = interquartile range.
[a] Women could have more than one indication for surgery.

Table 3
Changes in characteristics of fibroids and hemoglobin levels at baseline, after 3 months of pre-treatment and 6 weeks post-operative.

	Ulipristal acetate (n = 29)	Leuprolide acetate (n = 25)	Difference (95% CI)	*P*-value
Uterine volume (cm^3; median, IQR)				
Baseline[b]	530.5 (392.8–774.5)	421.2 (327.5–819.8)	–	0.510
After pre-treatment[b]	598.2 (284.6–830.6)	272.1 (180.4–508.8)[a]	–	**0.012**
6 weeks post-operative	170.1 (106.8–243.5)[a]	152.8 (92.3–205.6)[a]	–	0.423
Incomplete resection of fibroids (n/N, %)	2/26 (7.7)	1/23 (4.3)	–	–
Hemoglobin (mmol/L, mean ± SD)				
Baseline[b]	7.8 ± 1.0	7.7 ± 1.1	0.1 (-0.5, 0.7)	0.742
After pre-treatment[b]	8.3 ± 0.8[a]	8.2 ± 0.9[a]	0.1 (-0.4, 0.6)	0.635
Directly post-operative[b]	6.5 ± 1.3[a]	7.3 ± 0.8[a]	**−0.7 (-1.4, -0.1)**	**0.021**
6 weeks post-operative	7.7 ± 1.1	8.1 ± 0.8	−0.4 (-0.9, 0,2)	0.157

SD = standard deviation; IQR = interquartile range; CI = confidence interval. Numbers in **bold** indicate a statistically significant ($P < 0.05$) change from baseline in the within group analysis.
[a] Statistically significant ($P < 0.05$) change compared to baseline in the within group analysis.
[b] These results are already previously published [10].

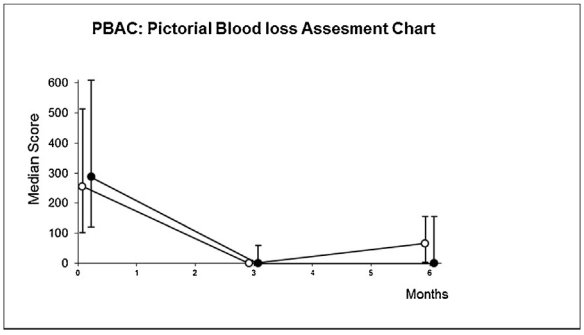

Fig. 2. Results of the Pictorial Blood loss Assessment Chart.
Month 0 resembles baseline. Month 3 is after pre-treatment, but before surgery. Month 6 is 3 months after surgery. Values are displayed as median and interquartile range. Higher numbers indicate more bleeding [12]. In the Netherlands, the cut-off

absenteeism costs were significantly higher in the UPA-group, compared to the GnRHa-group. After adjusting for the confounder 'fibroid size' at baseline, differences were no longer statistically significant. Due to the relatively small study population, one woman in the UPA-group who had a pneumothorax, unlikely to be related to this study, was considered an outlier. This woman had an extra hospital admission, additional patient expenses and a longer absenteeism from work period, resulting in high costs and large standard deviations. After exclusion of this woman, only total societal costs were statistically significantly higher in the UPA-group compared to the GnRHa-group. Again, after adjusting for fibroid size this difference was not significant. Differences in all other cost categories were not statistically significantly different between groups.

Comment

Main findings

In this non-inferiority, double-blind RCT, pre-treatment with either UPA or GnRHa before laparoscopic myomectomy was compared. Short-term results on pre- and peri-operative outcomes were previously described [10]. In this manuscript the post-admission or 'long term results' are presented along with the results on patient questionnaires completed throughout the study period. Fibroid characteristics and hemoglobin levels post-operative did not differ between groups. Hemoglobin levels six weeks post-operative recovered back to baseline level in both groups. Both treatment groups showed a significant decrease in

Table 4
Changes in questionnaire score compared to baseline at 3 months after baseline, 6 weeks post-operative and 6 months post-operative.

	Ulipristal acetate	Leuprolide acetate	P value
	3 months after baseline (before treatment)		
	n = 26	n = 23	
PBAC	**−321 (−515 to −85)**	**−348 (−818 to −112)**	0.485
FSFI	−0.5 (−5.4 to 1.1)	−0.8 (−6.0 to 1.2)	0.868
FSDS	−1.5 (−7.8 to 4.5)	0.0 (−5.0 to 3.5)	0.577
Shaw	**12.4 (1.7–25.8)**	**11.1 (0.0–19.0)**	0.684
Menopause	**5.5 (−2.5 to 8.0)**	3.0 (−8.0 to 12.0)	0.495
UFS-QoL SS	**−9.4 (−34.4 to 5.5)**	**−12.5 (−31.2 to 0.0)**	0.977
UFS-QoL HRQL	**6.5 (−5.0 to 21.6)**	**11.2 (0.0–17.2)**	0.663
	6 weeks post-operative		
	n = 23	n = 22	
PBAC	–	–	–
FSFI	−1.5 (−11.3 to 1.2)	−2.3 (−13.6 to 1.4)	0.699
FSDS	0.0 (−8.8 to 6.0)	0.0 (−7.0–3.3)	0.842
Shaw	**17.4 (5.7–23.0)**	**11.2 (4.6–41.6)**	1.000
Menopause	**3.0 (−2.3 to 12.3)**	1.0 (−9.0 to 11.0)	0.307
UFS-QoL SS	**−18.7 (−46.9 to −6.2)**	**−28.1 (−50.0 to −6.2)**	0.517
UFS-QoL HRQL	**12.9 (−2.6 to 19.0)**	**13.0 (4.3–34.5)**	0.292
	6 months post-operative[a]		
	n = 23	n = 19	
PBAC	**−178 (−478 to −39)**	**−216 (−630 to −70)**	0.599
FSFI	1.4 (−0.8 to 4.5)	−0.8 (-2.3 to 6.3)	0.448
FSDS	−3.0 (−12.3 to 0.5)	−1.0 (−7.0 to 0.0)	0.752
Shaw	**14.3 (5.4–31.0)**	**15.8 (1.0–50.0)**	0.744
Menopause	1.5 (−3.3 to 6.3)	−2.0 (-9.0 to 4.3)	0.130
UFS-QoL SS	**−18.7 (−30.5 to −2.3)**	**−21.8 (−37.5 to 3.2)**	0.374
UFS-QoL HRQL	**23.3 (0.9–35.6)**	**18.1 (7.7–44.8)**	0.744

Values are displayed as median and interquartile range. PBAC: pictorial blood loss assessment chart; FSFI: female sexual functioning index; FSDS: female sexual distress scale; UFS-QoL SS: uterine fibroid and quality of life, symptom severity score; UFS-QoL HRQL: uterine fibroids and quality of life, health related quality of life. Numbers in **bold** indicate a statistically significant ($P < 0.05$) change from baseline in the within group analysis.
[a] PBAC questionnaire was only filled out until 3 months post-operative.

PBAC-score and the level of difference was similar in both groups. At three months after surgery, median PBAC-scores in both groups remained below the level of 150, which is considered the cut-off point for HMB in the Netherlands. Three months after surgery menopausal symptoms increased significantly in the UPA group, although it is questionable if this is directly due to the pre-treatment itself or the direct effect of the course of surgery. Concerning all other questionnaires, the majority showed an improvement in quality of life at 3 months after surgery compared to baseline, with no differences observed between the groups. Myomectomy appears to have a major impact on several quality of life related outcomes, however given the small sample size this would need to be confirmed in larger, randomized trials. Overall, the type of pre-treatment does not appear to have any differentiating effect on QOL.

Total health care costs, absenteeism costs and total societal costs were higher in the UPA-group compared to GnRHa-group. However, these outcomes were not significantly different between groups after adjusting for fibroid size at baseline.

Comparison with previous studies

No previous studies have been published comparing UPA with GnRHa prior to laparoscopic myomectomy only. An extensive comparison on pre- and peri-operative parameters to other available literature was previously published [10]. Our results on bleeding pattern and menopause symptoms are similar to those already published in other literature [7,23–25]. The PEARL-II is the only previous RCT comparing UPA and GnRHa and reported on pain, symptom severity and quality of life [24]. They reported similar improvements in these outcomes in both groups, which were comparable to our results. The study period of the PEARL-II solitary covered the pre-treatment period for three months and no follow-up period was described. In contrast to previous studies, our study has a follow-up period of six months post-operative. However, this follow-up period is too limited to register other long term outcomes like the recurrence of complaints due to growth of new or initial clinically irrelevant fibroids.

A recent cost minimization analysis (CMA) and budget impact analysis (BIA) was performed in the Netherlands in a comparable population to this study. It analyzed the pharmacoeconomic profile of UPA compared to GnRHa for the pre-operative treatment of uterine fibroids. They concluded that UPA has the potential to save healthcare costs in the Netherlands, when implemented gradually as a treatment alternative to GnRHa [26]. Our study did not confirm this: no differences were observed between the groups after adjustment for baseline uterine volume. In addition, we did not include administration cost, which makes the biggest difference in the BIA and CMA from the paper by Zakiyah et al., since women need an additional GP- or hospital visit to have the GnRHa injection administered [26]. Considering recent changes of the European Medicine Agency (EMA) in the policy concerning UPA treatment and additional risk minimization measures, healthcare costs could potentially change due to frequent liver testing, but current exact cost of this remain unknown [27]. The EMA warning came out after all patients in this trial had finished their pretreatment. Therefore no liver function tests have been performed. No patients developed serious liver injury, for this would have become apparent during the follow up. In addition to that, a new case of serious liver injury occurred in February 2020. The EMA has therefore concluded to suspend UPA from the EU-market until more is known about the relation between UPA and possible hepatotoxicity. The EMA report needs to be awaited before new UPA cycles can be prescribed [27,28].

However, our long term results regarding the secondary outcomes, can be explained by myomectomy itself and not primary to pre-treatment with either medication. Future studies on pre-treatment of fibroids prior to surgery should aim for large(r) randomized comparisons of UPA to alternatives such as GnRHa or placebo or GnRHa with placebo with clinically relevant surgical outcomes. It may be considered to extend the follow up period to

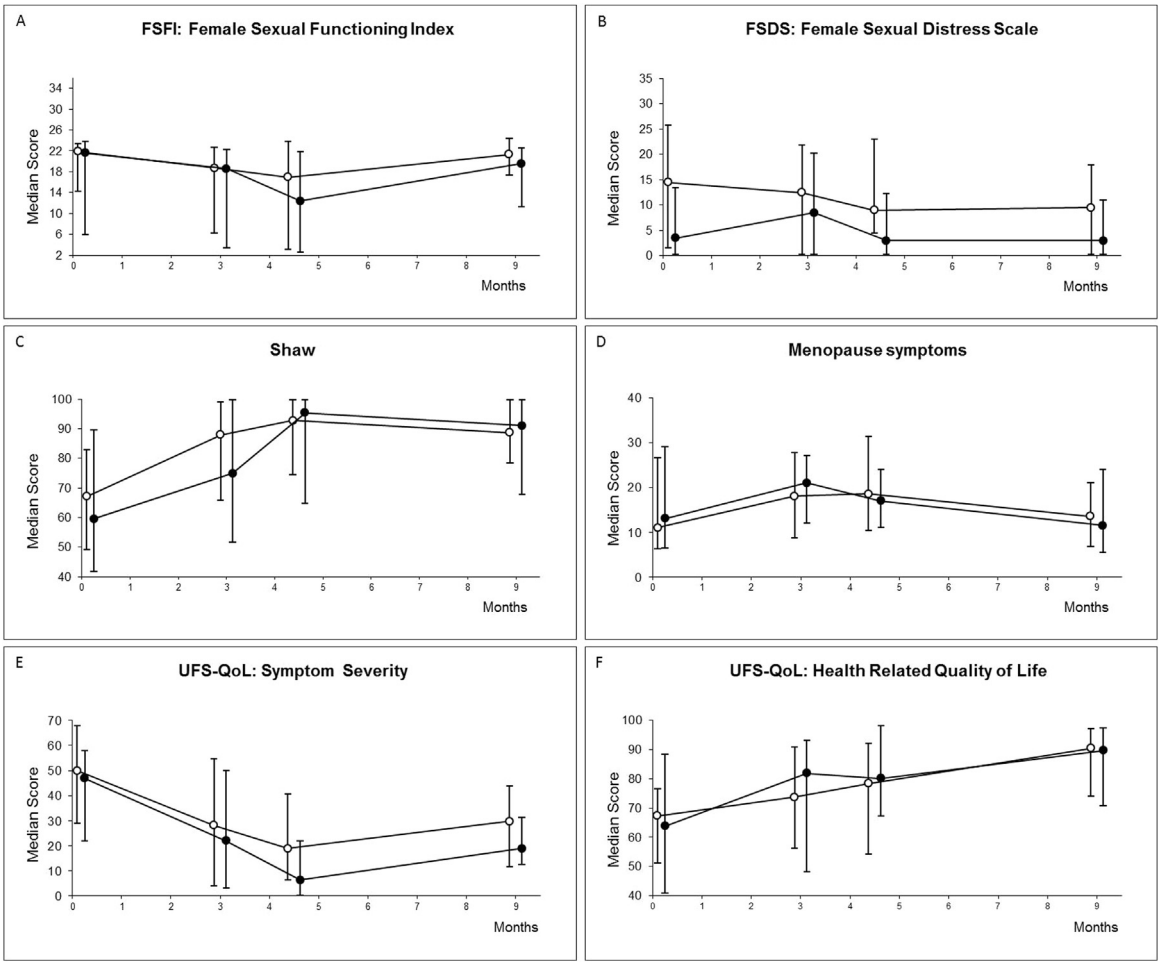

Fig. 3. A–F. Results of FSFI, FSDS, Shaw, Menopause and UFS-QoL questionnaires.
Month 0 resembles baseline. Month 3 is after pre-treatment, but before surgery. Month 4.5 is the 6 week follow-up after surgery. Month 9 is 6 month follow-up after surgery.
FSFI, Shaw, UFS-QoL HRQL: higher scores are better. FSDS, Menopause, UFS-QoL SS: lower scores are better.
Values are displayed as median and interquartile range. ○ = UPA, ● = GnRHa.

Table 5
Mean costs and differences in costs in Euros over 6 months of follow up.

Cost category	UPA (N = 22) Costs (± SD)	GnRHa (N = 18) Costs (± SD)	Difference[a] (95 % CI)	Adjusted difference (95 % CI)[b]
TOTAL HEALTHCARE COSTS	2189 ± 247	1402 ± 120	**492 (74 ; 1171)**	107 (-225 ; 467)
Medication	*423*	*345*	*78*	–
Admission at the time of surgery	*1428 ± 160*	*1216 ± 110*	*212 (-120 ; 619*	–
Outpatient care	*103 ± 28*	*61 ± 18*	*43 (-21 ; 109)*	–
Hospital admissions	*216 ± 107*	*53 ± 53*	*163 (-36 ; 433)*	–
GP care	*18 ± 6*	*22 ± 11*	*4 (-33 ; 15)*	–
Patient expenses	241 ± 227	36 ± 25	205 (-37 ; 1304)	27 (-60 ; 465)
Absenteeism	1759 ± 779	297 ± 158	**1462 (355 ; 3714)**	634 (-226 ; 2372)
TOTAL SOCIETAL COSTS	4189 ± 1179	2030 ± 220	**2159 (544 ; 6001)**	767 (-359 ; 2918)

Numbers in **bold** indicate a statistically significant difference between both treatment groups.
[a] 95 % confidence intervals estimated using bias-corrected and accelerated bootstrapping with 5000 replications [22].
[b] Adjusted difference with 95 % CI, separately analysed with adjustment for diameter of the largest fibroid at baseline. Different subcategories of total healthcare costs were not separately analysed with adjustment for diameter of the largest fibroid at baseline.

track possible recurrence of fibroids. Costs should also be included in these comparisons, using specially developed and officially validated cost-questionnaires.

Strengths and limitations

This is the first double-blind, RCT on peri- and post-operative outcomes comparing UPA and GnRHa, including an investigational cost-analysis. The main strengths and limitations of the overall methodology and design of this study have previously been published [10].

The investigational cost analysis was only a minor part of this trial and as such did not use standardized or officially validated questionnaires for productivity costs or medical costs. In addition, and most importantly, the small sample size limits firm conclusions on costs. Within this population, due to intention-to-treat principle,

a single patient who was hospitalized or had surgical complications which prolonged the hospital stay or absenteeism from work could have influenced the total healthcare and societal costs significantly, and as such the results on a real-world scale should be interpreted with caution.

Conclusions

Pre-treatment prior to laparoscopic myomectomy with UPA compared to GnRHa has similar effects on bleeding pattern, menopausal symptoms, sexual functioning, symptom severity and quality of life from baseline up to six months post-operative. However, due to the small sample size, these findings should be interpreted with caution. Also, since there was no control group (with no pre-treatment), we have not proven that pre-treatment in itself adds to the improvement in HRQL in addition to the surgery itself (myomectomy). The short-term results demonstrate that fibroid volume decreased significantly, which seems to be the most potent predictor of difficulty and length of surgery [10]. Furthermore, the pre-operative condition improves due to a strong decrease in menstrual blood volume. Therefore we believe that pre-treatment for large fibroids (i.e. > 5 cm) can be beneficial, especially stopping the bleeding pre-operative is most important. Both treatments seem to improve this outcome.

Disclosure of interest

JH received several research grants from Samsung, Celenova and ZonMW. WH received a grant from ZonMW. All other authors have no disclosures.

Contribution to authorship

IM, JH and WH made substantial contributions to the design and drafting of this article. IM, MM, JH, JB and WH contributed to the analysis and interpretation of the data. IM, MM, JH, JK, PG, DS, MB, JB and WH critically revised and approved this final version for publication. The funders did approve the study design, but had no role in data collection, data analysis, data interpretation or preparation of the manuscript. The revised and final manuscript has been approved by all co-authors.

Guarantor of the manuscript

W.J.K. Hehenkamp, MD PHD

Details of ethics approval

The study was approved by the National Central Committee on research involving Human Subjects (CCMO – NL49916.029.14) and by the ethics committee of VU Medical Center Amsterdam (Ref. No. 2014/421) and by the boards of all participating hospitals. The trial protocol was registered on ClinicalTrials.gov (NCT02288130).

Funding

This was an investigator initiated trial funded by PregLem S.A. with an amount of EUR 150.000,00

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank the women who participated in the study and all other persons that were involved in the study.

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