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Presurgical treatment of uterine myomas with the GnRH-antagonist relugolix in combination therapy: an observational study

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To evaluate if a preoperative medical treatment with the GnRH-antagonist relugolix in combination therapy in a series of patients with abnormal uterine bleeding associated with uterine myomas may correct the anemia before scheduled surgery for myoma-associated AUB. Thirty-one patients scheduled for surgery underwent a pre-operative three-month course with a daily oral tablet of 40 mg relugolix, 1 mg estradiol, and 0.5 mg norethindrone acetate. Hemoglobin levels, uterine volumes, largest myoma diameter, and VAS score for dysmenorrhea, pelvic pressure and bleeding discomfort, and indication to surgery were evaluated at study enrollment and at the end of therapy. Mean hemoglobin levels increased by 25%, from 9.3 ± 1.1 to 11.6 ± 1.7 g/dL after three months ($p < 0.001$). Uterine volume decreased from 380.7 ± 273.4 mL to 281.7 ± 198.7 mL ($p < 0.001$), whereas the diameter of the largest myoma decreased from 6.4 ± 2.8 cm to 5.5 ± 2.2 cm ($p < 0.001$). Four patients (13%), initially planned for a laparotomy procedure, were converted to a minimally-access procedure, whereas in eight patients (26%) surgery was avoided after medical therapy. Dysmenorrhea score improved from 4.7 ± 3.2 to 0.6 ± 1.1 ($p < 0.0001$). Pelvic pressure score decreased from 5.9 ± 2.1 to 3.1 ± 2.3 ($p < 0.0001$), whereas bleeding discomfort decreased from 7.4 ± 3.0 to 0.4 ± 1.6 ($p < 0.0001$). Preoperative GnRH-antagonist therapy may enhance hemoglobin levels, decrease uterine and myoma size, and alleviate symptoms, potentially enabling safe surgical procedures.

Keywords Abnormal uterine bleeding, Uterine myomas, GnRH-antagonist, Medical therapy

Uterine myomas are one of the most common problems in gynecology, and they are frequently associated with abnormal uterine bleeding (AUB)[1]. Episodes of chronic and acute bleeding may cause anemia[2], with the consequent need of either medical or surgical treatment of the condition[1,3]. Among the medical treatment options for the management of symptomatic uterine myomas, the oral GnRH-antagonists elagolix, relugolix and linzagolix have recently gained wide attention, due to the availability of randomized clinical trials (RCTs) demonstrating their efficacy in reducing heavy menstrual bleeding associated with uterine myomas[4–6]. In these RCTs, GnRH-antagonists have been combined with a concomitant hormonal add-back therapy (1 mg estradiol and 0.5 mg norethisterone acetate in daily tablets, i.e., "combination therapy"), to prevent the common side effects due to hypo-estrogenism that occur with both GnRH agonists and antagonists[3–6]. This condition can lead to a range of side effects, including hot flashes, mood swings, bone density loss (which may increase the risk of osteoporosis), and vaginal dryness. These effects are particularly problematic when considering long-term use, as they can negatively impact quality of life and overall health. Due to these significant side effects, long-term use of GnRH agonists or GnRH antagonist alone as a standalone treatment is often not feasible. This is the rationale for "add back" to both treatment regimens. The theoretic advantages of GnRH antagonist versus GnRH agonists are the more rapid onset of the action of the former without the initial flare up effect of the latter, the oral route of administration of the former, and the possibility of adjustable and shorter duration of the former therapy.

In the above-mentioned RCTs, GnRH-antagonist combination therapy has been used as a standalone management, i.e., without a pre-planned surgical procedure, with the aim of reducing myoma-associated

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bleeding and anemia[3–6]. Such therapy, however, may have an important role also in the presurgical management of symptomatic myomas, similarly to what has been demonstrated in the past for GnRH-agonist therapy[7–10]. As demonstrated for GnRH-agonist, the use of GnRH-antagonist combination therapy before a planned surgical procedure for symptomatic uterine myomas may theoretically facilitate subsequent surgery by decreasing the size of the uterus and/or of the myomas, yielding an improved surgical field, or even a shift to a less-invasive surgical approach[7,8]. Also, the effect of medical treatment on associated bleeding may guarantee the patient a faster recovery from postoperative anemia[8]. Considering all the above issues, a preoperative course of medical therapy with GnRH-antagonist may possibly translate in a safer surgical procedure.

Currently, no study has reported on the presurgical treatment with GnRH-antagonist, in combination therapy, in case of symptomatic uterine myomas. In the present study, we report on a series of consecutive patients undergoing GnRH-antagonist combination therapy to correct the anemia before scheduled surgery for myoma-associated AUB.

Materials and methods

From July 1st, 2022, to June 30th, 2023, all consecutive patients referred to the Departments of Obstetrics and Gynecology of Sapienza University of Rome, University of Milan, University of Cagliari, and of Civic Hospital in Palermo, for AUB associated with uterine myomas were evaluated for inclusion in the present study. The Institutional Review Board (IRB) approval was obtained (Reference ObGyn20122022 MED/40ConSpec - Mother, Child and UroGynecological Sciences Department). The study was conducted in accordance with guidelines of the International Council for Harmonisation and the principles of the Declaration of Helsinki. All participants provided written informed consent.

Inclusion criteria were:

- AUB attributable to uterine myomas;
- The presence of uterine myomas of any size and location with indication to surgery according to the attending physician;
- Hemoglobin levels below 10.5 g/dL attributable to AUB;
- Women of reproductive age, between 30 and 50 years old.

Exclusion criteria were:

- Condition requiring emergency surgery of any kind for the myoma-associated bleeding;
- Need for transfusion of hemocomponents during evaluation for study inclusion;
- Hemoglobin levels lower than 7.0 gr/dL;
- All cases of AUB, except Type-L (Leiomyoma) of AUB's PALM-COIEN classification[11];
- Previous surgical treatments for uterine myomas;
- Previous or current medical treatments for uterine myomas, except for iron supplementation or tranexamic acid;
- Known or suspected hematological disorders;
- Known or suspected cancer, including cancers of the genital tract.

Patients screened for study inclusion following the criteria outlined above underwent:

- Detailed menstrual and gynecological history;
- Bimanual vaginal examination;
- Transvaginal sonography with detailed evaluation and description of uterine size, uterine myoma number, location, and largest diameter of the myomas (when more than two myomas were identified, only the single largest myomas was considered as the index myoma for data analysis), and evaluation of the endometrium. For larger size uteri and/or myomas, evaluation with a transabdominal probe was also performed. Both adnexa were also evaluated and described, together with any additional pathology present in the uterus, adnexa, and pelvis. Milder forms of adenomyosis were not considered as exclusion criteria if the main symptoms were attributable to the uterine myomas. Also, concurrent endometriosis was not considered as an exclusion criterion if not requiring specific medical or surgical treatment;
- Complete blood count and coagulation, with hematologist consultation if deemed necessary by the attending physician.

During the first visit, the following clinical and demographic data were collected and stored in specifically-designed forms: age, parity, BMI, type and severity of correlated symptoms (a 0 to 10 point visual analog scale, VAS, was used, with 0 representing no complaint, and 10 the worst possible symptom), alongside with measures of the uterus and myomas as detailed above. Moreover, the type of surgery was decided individually in consideration of the clinical and sonographic data, taking into consideration also patients preference.

Patients were prescribed a daily oral tablet composed of 40 mg of relugolix, 1 mg of estradiol, and 0.5 mg of norethindrone acetate for a planned three-month therapy, with subsequent reevaluation of clinical and sonographic data. Follow-up visits were planned every month after initiation of the combined medical therapy with GnRH-antagonist for three months.

During each monthly visit, the presence and severity of side effects attributable to the medical therapy was also assessed using the Menopause Rating Scale (MRS)[12]. The intensity of any possible side effect was reported on the scale from 0 (no complaints) to 4 (very severe complaints) and the most severe reported item was considered in the evaluation of the results.

A complete blood count, a gynecological visit and a transvaginal ultrasound were also performed. Uterine and fibroid dimensions were estimated using ultrasonography, and volumes were calculated by the prolate ellipsoid formula: length × height × width × 0.523.

At three months, patients were reevaluated to confirm the indication to surgical therapy and to confirm the surgical route assigned at study enrollment, or, on the other hand, to possibly assign the patient to a less-invasive surgical approach. The assignment to 2 minimally-access surgical procedure for patients initially scheduled for a myomectomy or hysterectomy by laparotomy was decided by a senior staff member with experience on both surgical and medical treatment of uterine myomas. The possibility of continuing the GnRH-antagonist combined therapy beyond three months was also considered, taking into account the response to therapy in terms of hemoglobin rise, of differences in uterus and myoma size at sonography, patients were asked about any possible side effects, or any other disadvantage due to the usage of the drug.

The primary outcome for the study was hemoglobin rise after three months of therapy.

The secondary outcomes were the changes in uterine volume and largest myoma diameter, any possible change in the planned surgical management, as well as variations in dysmenorrhea, pelvic pressure, and bleeding discomfort, evaluated on a 0 to 10 VAS scale.

Statistical analyses were performed using the Statistical Package for Social Science (SPSS 23.0, IL, USA). Shapiro–Wilk test was used to verify the normal distribution of the data. Due to the normal distribution, data were described as mean ± SD, median (interquartile range: IQR) or number (%), as appropriate. The 95% confidence interval (95% CI) of proportions was calculated using a binomial distribution model. Intra-patient comparisons of hemoglobin level, uterine volume, larger myoma dimension and changes in pain scores, before and after therapy, were made using the Student's t-test for paired data. P values below 0.05 were considered statistically significant.

Results

A total of 36 patients who met the inclusion criteria were evaluated for enrollment in the current study, which focused on the preoperative use of GnRH-antagonist combined therapy for AUB associated with uterine myomas. Of the enrolled participants, 31 completed the scheduled three-month course, while five did not. Two patients discontinued therapy due to symptoms, primarily headaches defined as "severe" by the patients, possibly attributable to the drug; two patients continued to experience bleeding and underwent surgery before completing the scheduled therapy; one additional patient required emergency surgery after two months of medical treatment due to the expulsion of a submucous myoma that had reduced in size during therapy. No other significant side effect, apart from the two cases of headache, or disadvantages possibly related to the therapy were reported. All patients completing the study were satisfied with the therapy.

The 31 patients who completed the study had a mean age of 42.9 ± 5.3 years and a BMI of 23.8 ± 3.3 kg/m². All patients had at least one fibroid, with the mean largest diameter of 6.4 ± 2.8 cm. The most common symptoms associated to AUB were dysmenorrhea (84%) and pelvic pressure (55%). Thirteen patients (42%) had multiple myomas, with eight having two myomas, and five having three or more myomas. A single myoma was present in 18 patients (58%). The single myoma, or the largest myoma in case of multiple lesions, was submucosal in 7 cases (23%), intramural in 12 cases (39%), subserosal in 2 cases (7%), and submucosal-subserosal in 10 cases (32%). Regarding the primary outcome, mean hemoglobin levels increased significantly from 9.3 ± 1.1 to 11.6 ± 1.7 g/dL after three months ($p < 0.001$), representing a 25% increase (Table 1). In 19 out of 31 women (61.3%), HB levels increased by ≥ 2 g/dl. Secondary outcome evaluation (Table 1) showed a significant decrease in mean uterine volume from 380.7 ± 273.4 mL to 281.7 ± 198.7 mL after three months ($p < 0.001$), corresponding to a 26% decrease, as well as a reduction in the diameter of the largest myoma from 6.4 ± 2.8 cm to 5.5 ± 2.2 cm

	T 0	T3	*p*
Hemoglobin concentration (g/dL)	9.3 ± 1.1	11.6 ± 1.7	< 0.001
Uterine volume (cm^3)	380.7 ± 273.4	281.7 ± 198.7	< 0.001
Largest myoma diameter (cm)	6.4 ± 2.8	5.5 ± 2.2	< 0.001
Dysmenorrhea (VAS 0–10)	4.7 ± 3.2	0.6 ± 1.1	< 0.001
Pelvic Pressure (VAS 0–10)	5.9 ± 2.1	3.1 ± 2.3	< 0.001
Bleeding discomfort (VAS 0–10)	7.4 ± 3	0.4 ± 1.6	< 0.001
Surgery			
No	0 (0%)	8 (26%)	
Yes	31 (100%)	23 (74%)	
Type of surgery			
Hysteroscopic myomectomy	5 (16%)	4 (17%)	
Laparoscopic myomectomy	3 (10%)	1 (4%)	
Laparotomy myomectomy	12 (39%)	7 (30%)	
Laparoscopic hysterectomy	3 (10%)	5 (22%)	
Laparotomy hysterectomy	8 (26%)	6 (26%)	

Table 1. Study outcomes evaluated at enrollment (T0) and after a three-month course of GnRH-antagonist combination therapy (T3). Values are expressed as mean ± SD, or as absolute numbers (%).

($p < 0.001$), corresponding to a 14% decrease. Although the reductions in uterine volume, and particularly in myoma size, may appear not clinically relevant, they allowed some patients to undergo a less invasive surgical procedure: two cases of laparotomy myomectomy were converted to hysteroscopic myomectomy, and two cases of laparotomy hysterectomy were converted to laparoscopic hysterectomy. In a fifth case, a planned laparotomy procedure was rescheduled to a laparoscopic approach; however, the procedure was converted to laparotomy at the time of surgery due to unexpected extensive endometriosis-related adhesions. In eight of the 31 cases (26%), the increase in hemoglobin levels and the reduction in myoma volume and associated symptoms after three months of therapy prompted a shared decision between the surgeon and the patient to withhold the surgical procedure temporarily, to continue the medical therapy for three additional months, and re-evaluate the patient. Follow-up is still ongoing for the eight patients without the need of surgery.

Mean dysmenorrhea VAS score improved significantly from 4.7 ± 3.2 at enrollment to 0.6 ± 1.1 after 3 months of therapy ($p < 0.0001$), indicating a decrease of 87%. Mean pelvic pressure VAS score also showed a significant improvement from 5.9 ± 2.1 at enrollment to 3.1 ± 2.3 after 3 months of therapy ($p < 0.0001$), corresponding to a decrease of 48%. Twenty-five patients out of 31 (81%) reached amenorrhea at the end of the three-month therapy. Bleeding discomfort decreased from 7.4 ± 3.0 at enrollment to 0.4 ± 1.6 after 3 months of therapy ($p < 0.0001$), corresponding to a decrease of 95% (Table 1). Twenty-three patients underwent surgery, in four cases with a less invasive approach than previously scheduled, with no cases of intraoperative complications, or intra- or post-operative blood transfusions. In seven patients undergoing myomectomy by laparotomy, and in one patient undergoing laparoscopic myomectomy, no additional difficulty in the enucleation of the myoma from the normal myometrium was reported by the operating surgeon, contrary to what has been previously reported by some authors for pre-surgical treatment with GnRH-agonists1[13,14].

Discussion

The present study reports on a series of 31 patients submitted to a three-month preoperative course of GnRH-antagonist combination therapy before a planned surgical procedure for AUB associated with uterine myomas. The preoperative course of medical therapy, administered for three months, allowed in most cases a safe surgical procedure, due to significantly higher hemoglobin levels at the time of surgery, and a statistically significant reduction of myoma and uterine size, compared to pre-enrollment values. The mean hemoglobin increase after three months of therapy was 25%, whereas the mean reductions in uterine volume and myoma diameter were 26% and 14% respectively. In some cases, the reduction of the myoma and/or uterus allowed the switch to a less invasive surgical procedure than what had been planned at the time of patient enrollment. In fact, in four cases (13%) it was possible to convert the planned procedure to a less invasive approach. In eight cases (26%), after the scheduled three-month course of medical therapy, a re-evaluation of the indication to surgery was performed, the scheduled surgical procedure was temporarily avoided, and the patients are still under medical therapy and follow-up for possible definitive withdrawal from surgery. In the 23 cases that underwent surgery, there was no need for intra- or post-operative blood transfusions. Recent evidence reported that the overall blood transfusion rate after myomectomy was 10% (hysteroscopy, 6.7%; laparoscopy, 2.7%; open/abdominal procedures, 16.4%)[15]. The addition of a low dose of estrogen and progestin to the GnRH antagonist relugolix, i.e. combination therapy, prevented the occurrence of hypoestrogenism side effects, thus allowing the patients to continue the scheduled medical therapy with no cases of withdrawal directly attributable to hypoestrogenic side effects. Two of 31 patients (6.5%) patients discontinued therapy due to headaches. Therefore, the addition of a low dose of estrogen and progestin to relugolix may be associated with the risk of headache and should be administered with caution.

This report is the first description of the use of GnRH-antagonists, either with or without combination therapy, in a pre-surgical setting. A presurgical medical treatment has previously been described for GnRH-agonists[7–9], but the significant side effects, due to the therapy-related hypoestrogenism, preclude the use of this medical approach in the long term[16]. GnRH-antagonist combination therapy has been described, although not in a presurgical setting, for as long as two years, with a reassuring safety profile[17,18]. Therefore, such therapy may be administered preoperatively for longer periods than what reported here, envisaging a possible avoidance of the planned surgery if the favorable effects observed here in the short term persist also for longer periods. In the present series, at the end of the scheduled three-month course of medical therapy, surgery was avoided in one fourth of the cases, maintaining the patients on a longer course treatment. GnRH-antagonist combination therapy has been proved to be effective for AUB related to the presence of myomas in several RCTs[4–6,16]. The use of this class of drugs before a planned surgery reported here should be confirmed in more methodologically robust studies, such as controlled studies, or RCTs. The present series consists of cases that are challenging in the clinical setting. In fact, all the enrolled patients were admitted in the hospital for clinically relevant AUB, determining a condition of anemia, associated with uterine myomas for which surgery would be indicated. In this scenario, immediate surgery carries intra- and post-operative risks, among which transfusion of blood components is the most frequent[19–21]. A RCT may therefore be difficult to conduct in a scenario of acute AUB, and larger case series besides the present one would be warranted as well, in order to confirm the data reported in the present series. Postponing a surgical procedure while achieving higher preoperative hemoglobin levels, together with reduction of the size of the myomas, appears as a valuable pre-operative strategy, with relevant advantages for both the patient and the treating physician.

An important strength of the present study merits to be underlined. This is the first study to evaluate the use of GnRH antagonists in combination therapy in patients with AUB due to uterine fibroids, who are candidates for surgical intervention. This paper describes the effects of a new and relevant therapy for the treatment of uterine fibromatosis both for preoperative treatment and for a conservative approach. The data on this treatment are very important considering that this new hormonal therapy is novelty in the scenario of medical options for presurgical treatment of uterine myomas and related AUB. These findings are relevant for both the present and

future approaches to this bothersome pathology, which affects women during their reproductive period and perimenopausal transition.

The present study has several notable limitations that impact the robustness and generalizability of its findings. Firstly, the small sample size limits the statistical power of the study, raising concerns about the representativeness of the sample, as a small cohort may not adequately capture the variability present in the broader population.

Secondly, the unblinded and uncontrolled nature of the study introduces potential biases. Without blinding, both the participants and researchers may have preconceived notions or expectations that could influence the outcomes and their interpretation. This lack of blinding can result in subjective bias, potentially skewing the results. Additionally, the absence of a control group further weakens the study design. A control group is essential for comparing the effects of the intervention against a baseline, helping to isolate the specific impact of the treatment. Without it, any observed changes cannot be confidently attributed to the medical therapy alone, as other uncontrolled variables might be influencing the results. Thirdly, adherence to treatment was not objectively assessed with a proper questionnaire. However, reassuring data regarding the adherence to the new GnRH antagonists in combination therapy was already reported in the literature[4].

Lastly, the study did not assess bone mineral density (BMD) at critical time points T0 (baseline) and T3 (post-treatment), which is a significant limitation. BMD measurements are essential for evaluating the effects of treatments, especially those involving hormone regulation, on bone health. Without these assessments, the study cannot accurately track changes in BMD over time, limiting the ability to draw conclusions about the intervention's impact on bone health. However, recent evidence from studies on the long-term use of GnRH agonists provides reassurance regarding their safety and efficacy[17,18]. This emerging research suggests that, despite the oversight in the current study, long-term use of GnRH antagonists may not adversely impact BMD as previously feared. These limitations collectively suggest a need for caution when interpreting the findings of the present study. Future research should aim to address these issues by employing larger, well-controlled, and blinded study designs with comprehensive data collection to ensure more reliable and generalizable results.

In conclusion, a preoperative three-month course of GnRH-antagonist combination therapy may be proposed to patients scheduled for surgery in case of clinically significant AUB associated with uterine myomas, in order to operate in a safe surgical scenario in most cases, or to even avoid surgery in approximately one fourth of the cases.

Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

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Author contributions

L.M., M.V., S.A. and A.M. conceived and planned this study. L.M., M.V., S.A., A.M., R.T. and A.M. contribueted to data collection and material preparation. G.G., C.O., L.S. and I.A. processed the data, performed the analysis, drafted the manuscript and designed the table. All authors reviewed the manuscript and approved the final version for submission.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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