

The Use of Ulipristal Acetate (Esmya) Prior to Laparoscopic Myomectomy: Help or Hindrance?

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Abstract

Introduction: The aim of this study was to assess the operative effects, both positive and negative, of pretreatment with ulipristal acetate (UPA) on laparoscopic myomectomy.

Materials and Methods: We conducted a retrospective analysis of prospectively collected data from patients who underwent a laparoscopic myomectomy over a 2-year period.

Results: A total of 62 patients were included, of which 10 received a 3-month preoperative course of UPA, and 52 patients received no pretreatment. There was no statistically significant difference between the two groups (no pretreatment vs. UPA pretreatment) with regard to blood loss (214.4 [\pm 214.96] vs. 160 [\pm 51.64], $P = 0.432$), operating time (111.64 [\pm 41.8] vs. 117.5 [\pm 50.4], $P = 0.694$), and duration of inpatient stay (1.27 [\pm 0.56] vs. 1.11 [\pm 0.33], $P = 0.419$). There were no complications in either group. In 100% of cases with UPA pretreatment, a distortion of the fibroid capsule with a more technically challenging dissection was noted, compared to 0% in the no pretreatment group. This anatomical distortion may result in more cases of incomplete resection and a potentially higher risk of recurrence.

Conclusion: We conclude that UPA confers no operative benefits and should be used with caution in the presurgical treatment of fibroids. The use of UPA may indeed result in a more technically difficult myomectomy with distorted cleavage planes and carry a potential risk of incomplete resection.

Keywords: Esmya, fibroids, laparoscopic myomectomy, ulipristal acetate

INTRODUCTION

Laparoscopic myomectomy remains the gold standard surgical treatment option in the management of uterine fibroids. There is now a wealth of evidence highlighting the benefits of the minimal access approach, including reduced blood loss, less postoperative pain, shorter duration of inpatient stay, and quicker return to normal activities.^[1-3] Even for large and multiple fibroids, a previously considered contraindication, the laparoscopic approach in skilled hands confers significant benefits without an increase in complications.^[4,5] The preoperative treatment of patients with large fibroids can

be beneficial not only to induce amenorrhea and increase preoperative hemoglobin rates but also to potentially reduce fibroid size and thus in theory improves the ease of the operative procedure resulting in a quicker, more bloodless operation.

Historically, gonadotropin-releasing hormone (GnRH) analogs have been used in the presurgical treatment of fibroids; however, since the introduction of ulipristal acetate (UPA) with its better hormonal and side effect profile compared to GnRH analogs, there has been a movement toward using

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UPA before hysteroscopic and laparoscopic myomectomy. UPA is a selective progesterone antagonist and affects uterine fibroids in a number of ways, including inhibiting cell proliferation, inducing apoptosis, inhibiting collagen synthesis, and stimulating extracellular matrix degeneration. Till date, there are very limited data on the effects of the presurgical use of UPA. Some studies have assessed the use of UPA before hysteroscopic resection.^[6-8] However, with regard to laparoscopic myomectomy, there are a paucity of definitive and reproducible data with only two retrospective studies and one prospective observational study identified in the literature.^[9-11] The need for more definitive outcome data is particularly relevant for UPA with the recent concerns around liver damage and the suspension of its use while further analysis and investigations were undertaken.^[12]

Due to this lack of data, the aim of this study was to assess the effects of UPA on laparoscopic myomectomy, particularly with regard to operative outcomes such as blood loss and operating time and to systematically review the wider literature.

MATERIALS AND METHODS

This is a retrospective analysis of prospectively collected data of patients undergoing a laparoscopic myomectomy over a 2-year period (2016–2017). All patients were operated on by a single surgeon at a tertiary referral center in London. The only exclusion criterion was uterine size >28 weeks size limiting access to the pelvis. Patients either underwent surgery directly with no pretreatment or received a 3-month course of UPA. In our practice, the use of UPA was generally limited to patients who were anemic, and all patients, if anemic, were optimized for surgery with oral iron supplementation.

The primary outcome of this study was to assess the effects of UPA on blood loss during laparoscopic myomectomy. Secondary outcomes included assessing the effects of UPA on other operative outcomes such as operating time, duration of inpatient stay, and complications.

All patients were counseled and given patient information leaflets about the use of power morcellation and the risk of leiomyosarcoma in accordance with guidelines from international endoscopic societies.^[13] None of the patients were anemic by the time of surgery.

A standardized technique was used; initial entry was through an intraumbilical incision, or Palmer's point in cases where the uterine size was >14 weeks, with two 5-mm ancillary lateral ports and a suprapubic port. For hemostasis, 800 mcg misoprostol was administered rectally and vasopressin injected intramyometrially. For uterine manipulation, a ClearView™ (Clinical Innovations) uterine manipulator was used to achieve the optimum uterine position. In the majority

of cases, the Thunderbeat™ (Olympus) ultrasonic device was used as the primary energy source, and a 5-mm myoma screw and grasping forceps were used for traction and counter traction. The uterus was closed in two or three layers using the STRATAFIX™ (Ethicon) barbed suture, and an adhesion prevention agent Interceed™ (Gynecare) was applied. Myomas were removed by electromechanical morcellation through the suprapubic port and sent for histology. In-bag morcellation was not used in any of the cases. All histology results were benign.

The data were analyzed using SPSS (IBM Corp, version 22, Armonk, NY, USA). The *t*-test was used for the comparison group analysis, but if the data failed the homogeneity assumption (Levene's test), a Mann–Whitney test was undertaken. Value of *P* = 0.05 was considered statistically significant. Formal ethical approval was not required following discussion with the local research and ethics committee as this was a retrospective evaluation of ongoing surgical practice.

RESULTS

Over the 2-year period, 62 patients underwent a laparoscopic myomectomy, of which 10 had preoperative treatment with UPA. Patient demographics between the two groups were similar and summarized in Table 1. In both groups, the size, number, and weight of fibroids removed were similar [Table 2].

The use of UPA did reduce mean blood loss during laparoscopic myomectomy (214.4 [±214.96] vs. 160 [±51.64], *P* = 0.432); however, this was not statistically significant. There was also no significant difference in duration of surgery (111.64 [±41.8] vs. 117.5 [±50.4], *P* = 0.694) or duration of inpatient stay (1.27 [±0.56] vs. 1.11 [±0.33], *P* = 0.419). There was one conversion to laparotomy in the no pretreatment

Table 1: Patient demographics

	No pretreatment	Preoperative UPA
Age (years)	37.6 (27-50)	38.2 (26-46)
BMI	27.42 (19-41)	26.5 (18-37)
Parity	1 (0-5)	1 (0-4)
Ethnicity (%)		
African/Afro-Caribbean	26 (50)	7 (70)
Asian	11 (21.2)	2 (20)
Caucasian	15 (28.8)	1 (10)
Indication for surgery (%)		
HMB	41 (78.8)	10 (100)
Pain	5 (9.6)	
Pressure	4 (7.7)	
Dyspareunia	1 (1.9)	
Subfertility	1 (1.9)	

Data are presented as median (range) or absolute *n* (%). BMI: Body mass index, UPA: Ulipristal acetate, HMB: Heavy menstrual bleeding

group compared to none in the UPA group. this was due to the size of the fibroid and difficulties with access. There were no major complications in either group. Operative outcomes are summarized in Table 3.

In all cases of pretreatment with UPA, distortion of the cleavage planes was noted by the surgeon [Figures 1 and 2]. This was not reported in any of the cases in the no pretreatment group.

DISCUSSION

Historically GnRH analogs were considered the gold standard presurgical treatment of fibroids, and in a recent Cochrane systematic review, the authors concluded that their use resulted in fibroid shrinkage, corrected anemia, and had the potential to reduce intraoperative blood loss.^[14] However, although the data are limited and based mainly on

surgical experience, many surgeons avoid the preoperative use of GnRH analogs as there are concerns regarding the distortion of the fibroid capsule with a resultant loss of surgical planes making the surgery more difficult and time-consuming with a resultant potential increased risk of recurrence.^[15,16]

Since the introduction of UPA, for the presurgical and medical management of fibroids, there has been a significant shift towards its usage. Many have hailed it as the new wonder drug and hypothesize a monumental shift from standard surgical techniques to more conservative medical approaches. There is no question based on the PEARL studies^[17-19] and more recent VENUS trials^[20,21] that UPA does result in amenorrhea and a reduction in fibroid size and volume; however, there still remains a paucity of data on its long-term efficacy and its surgical benefits, particularly before a laparoscopic myomectomy. There is also an increasing body of “real-world data” that challenges the impressive amenorrhea rates and reduction in fibroid size demonstrated by the PEARL and VENUS trials, particularly in large and multiple fibroids.^[22,23]

Given the effects of UPA on the fibroid capsule, there are increasing concerns regarding distortion and loss of surgical planes leading to technically more challenging cases and higher risks of recurrence similar to the concerns surrounding GnRH analogs.^[10,24] There are also studies that postulate that distortion of the fibroid pseudocapsule and nonintracapsular myomectomy may result in increased risk of recurrence, adhesion formation, and uterine rupture.^[25]

On reviewing the literature, three studies were identified assessing the effect of UPA on laparoscopic myomectomy: two retrospective cohort studies and one prospective observational study, which are summarized in Table 4.

The study by Ferrero *et al.* reported a statistically significant shorter operating time (137.6 ± 26.8 min vs. 159.7 ± 26.8 min; $P < 0.001$) and significantly less postoperative blood transfusions (0/34 vs. 6/43; $P = 0.031$) when patients were pretreated with UPA; however, there was no benefit on

Table 2: Fibroid characteristics

	No pretreatment	Preoperative UPA	P
Largest fibroid removed (cm)	6.9±2.57	8±2.17	0.153
Number fibroids removed	4.3±4.47	4.5±3.17	0.928
Weight of fibroids removed (g)	203±218.71	224.1±141.59	0.772

Data are presented as mean±SD. SD: Standard deviation, UPA: Ulipristal acetate

Table 3: Operative outcomes

	No pretreatment	Preoperative UPA	P
Blood loss (ml)	214.4±214.96	160±51.64	0.432
Duration of surgery (min)	111.64±41.8	117.5±50.4	0.696
Inpatient stay duration (days)	1.27±0.56	1.11±0.33	0.419
Conversion to laparotomy, n (%)	1 (1.9)	0	
Complications (n)	0	0	

Data presented as mea±SD or absolute n (%). SD: Standard deviation, UPA: Ulipristal acetate

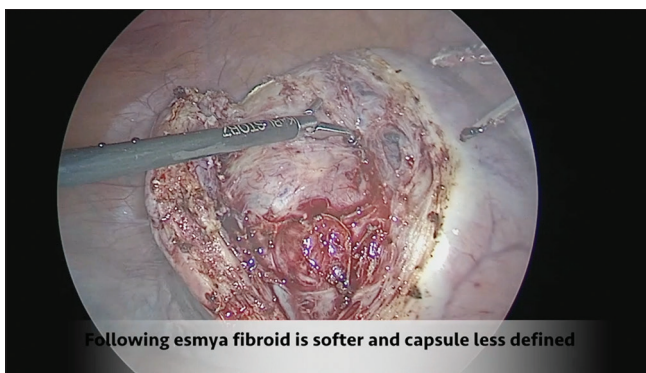


Figure 1: Loss of clearly defined capsule

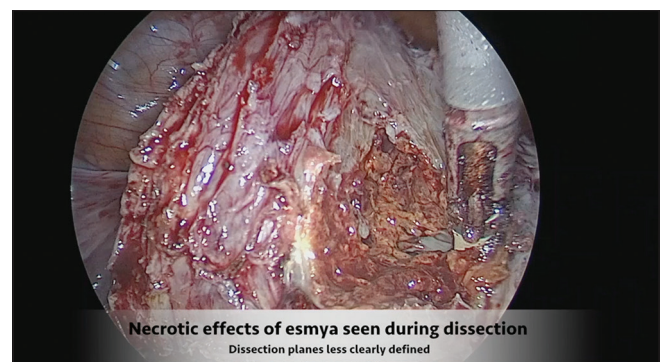


Figure 2: Loss of cleavage planes during dissection

Table 4: Effects of ulipristal acetate on laparoscopic myomectomy

	Procedure number		Largest fibroid removed (cm)			Blood loss (ml)			Operating time (min)		
	UPA	Nil	UPA	Nil	P	UPA	Nil	P	UPA	Nil	P
Ferrero <i>et al.</i> ^[9]	34	43	10.4±1.4	12.1±1.5	<0.001	507.1±214.9	684.2±316.8	0.012	137.6±26.8	159.7±26.8	<0.001
Luketic <i>et al.</i> ^[11]	25	25	7.3±1.7	7.1±2.2	0.72	289±367	316±486	0.82			
Murji <i>et al.</i> ^{[10]*}	46	104	10.4±3.7	10.6±4.3	0.79						

*Laparoscopic and open myomectomies included. Data are presented as mean±SD or absolute *n*. UPA: Ulipristal acetate, SD: Standard deviation

suturing time and no mention of the time taken for and ease of fibroid enucleation.^[9]

The study by Luketic *et al.* compared the surgical experiences of laparoscopic and robotic myomectomies in women pretreated with UPA by assessing surgical videos using a nonvalidated assessment tool containing questions on the depth of the incision in the myometrium and identification of the cleavage planes.^[11] Overall, there was no subjective difference in surgical experience for myomectomies between the two groups; however, the observational nature of this study makes the data very difficult to interpret.

In their study, Murji *et al.* undertook a prospective observational study assessing surgical experience at the time of myomectomy (hysteroscopic/laparoscopic/laparotomic).^[10] Although there was no difference in overall surgical experience for laparoscopic/laparotomic myomectomies between the nontreatment and UPA treatment group, rates of difficult enucleation of the fibroid with distorted surgical planes were lower in the nontreatment group. This finding of distortion of the surgical planes and more difficult enucleation is in keeping with our data. In our experience, in all the cases where UPA was used as pretreatment, we found that due to the very adherent pseudocapsule and fibroid necrosis rather than just traction and counter traction, the energy source had to be used to coagulate and dissect the “microfibers” of the capsule, and once the myoma was free of the capsule traction and counter traction then used to completely enucleate the myoma.

Crucially neither study reported on recurrence rates following laparoscopic myomectomy in women treated with UPA, and no further data could be found in the wider literature, which may be due to the short relatively short time that UPA has been on the market. Furthermore, there are no studies comparing UPA to GnRH analogs. Given this paucity of data, caution must be applied when considering the routine use of UPA before laparoscopic myomectomy until more robust long-term outcome data is available. Such data hopefully will include recurrence risk and long-term complications in relation to uterine rupture, leiomyomatosis, and adhesion formation.

The main limitation of this study is the sample size with 10 patients having UPA pretreatment and a total of 62 laparoscopic myomectomies performed over the 2-year

period and the surgeon was not blinded or the patients randomized. However, given this is a single-surgeon study, the numbers are comparable with the wider literature and remove the bias of surgical technique and experience. Our data will hopefully add to the growing body of “real world data” allowing physicians, surgeons, and patients to make informed choices regarding the use of UPA.

CONCLUSION

UPA does indeed offer a valid conservative medical treatment option for patients with fibroids. On the basis of the current evidence, it does help optimize patients before surgery as exemplified in our study where none of our patients were anemic by the time of surgery and none required blood transfusions. However, without larger studies and more concrete evidence, it should not routinely be used for the pretreatment of fibroids before laparoscopic myomectomy. The present study highlights that UPA does not appear to confer any intraoperative surgical benefits with regard to blood loss, operating time, or duration of inpatient stay. Conversely, it may indeed be an unwanted hindrance resulting in distorted cleavage planes and a more technically challenging procedure thus potentially increasing the risk of incomplete fibroid resection and subsequent recurrence. Without clear operative benefits and further definitive evidence, UPA should be used with caution. Decisions regarding its use should be made on a case-by-case basis, and benefits may indeed outweigh risks in certain situations such as persistent anemia. Future research should focus on randomized comparisons between UPA and GnRH analogs, as well as long-term outcomes such as fertility and recurrence rates, to allow us to fully counsel our patients and allow an informed choice to be made.

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Conflicts of interest

There are no conflicts of interest.

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