The role of hormone therapy before hysteroscopic myomectomy

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Objective: This review analyzes the preoperative treatments used before hysteroscopic myomectomy, trying to identify the main indications for each option. Methods: a comprehensive search of several databases was conducted from inception up to May 2021. The searched databases were MEDLINE, In-Process & Other Non-Indexed Citations, Daily, Ovid EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus. The search strategy included the combinations of the following medical terms: Hysteroscopic myomectomy; Uterine fibroid; Hormonal therapy, preoperative. We selected clinical studies, systematic reviews, and meta-analyses in English to investigate hormone therapy before hysteroscopic myomectomy. We opted for a narrative synthesis of the results, summarizing the evidence provided by the most relevant studies to offer the reader a complete and synthetic overview of the topic. Findings in brief: The hormonal therapies preoperatively used to prepare the endometrium before a hysteroscopic procedure are gonadotropins releasing hormone (GnRH) analog, danazol, progestogen, and combined oral contraceptives. On the one hand, the efficacy of GnRH analogs and danazol administration before hysteroscopic surgery has been demonstrated by several studies, mainly related to the time of surgery and volume of distension medium absorbed. On the other hand, although the evidence is more limited, progestogens and combined hormonal contraceptives have proven a comparable efficacy in achieving adequate endometrial thinning. Conclusions: To date, no definitive data provide strong evidence towards one specific preoperative therapy before myomectomy hysteroscopy. Several variables should be considered using a specific medical therapy (including the different potential effects with a particular drug compared to the others in type 0, 1, or 2 myoma); this element further amplifies the heterogeneity of the available findings in the literature and does not allow to draw a firm conclusion about a best pharmacological management over the others.

Keywords
Hysteroscopy; Hysteroscopic myomectomy; Uterine fibroid; Hormonal therapy; Endometrium

1. Introduction

Hysteroscopic surgery represents the gold standard for the treatment of various intrauterine pathologies, including polyps, congenital malformations, endometrial synechiae, drug-resistant endometrial hyperplasia, and uterine myomas [1–8]. Specifically, hysteroscopic myomectomy is the standard treatment for submucosal uterine myomas [9–12].

The evolution of endoscopic instruments and the introduction of liquid distension media helped to extend hysteroscopic surgery applications. Indeed, progressively smaller hysteroscopes permit less invasive surgeries improving the safety profile and the effectiveness of this procedure [13–16].

Only a limited percentage of cases is complicated, with an estimated incidence of adverse events between 0.95% and 3% [17]; these include hemorrhage (2.4%), uterine perforation (1.5%), cervical laceration (1–11%), and fluid overload. The latter is an excessive absorption or intravasation of the liquid distension medium, leading to hyponatremia with or without hypotension [18, 19]. Duration and type of hysteroscopic surgery, mainly myomectomy, increase the risk of fluid overload [20]. Therefore, interventions that simplify and speed up the procedure are fundamental to increase the success rate and reduce the risk of complications. In addition, a proper preoperative ultrasound evaluation is of paramount importance to correctly evaluate the characteristics and the position of the myomas [21, 22].

Operative hysteroscopy, such as hysteroscopic myomectomy, is facilitated by a thin endometrium. It improves the visualization of the endometrial cavity, enables the identification of intracavitary pathology, and reduces endometrial bleeding, ultimately reducing operating times [23, 24].

The endometrium’s thickness is functionally linked to changes in sex-hormones levels; hence various medical treatments are used preoperatively to modify their circulating concentrations.

The main drug categories used for this purpose are the gonadotropins releasing hormone (GnRH) analogs [25], danazol [26], progestogens [27–29], and combined oral contra-
ceptives [30]. To date, no data allows us to definitively conclude which is the best preoperative treatment option for endometrial preparation before an operative hysteroscopy [31].

In the case of hysteroscopic myomectomy, not only the endometrial thickness but also the characteristics of the myoma(s), i.e., grading, size, and number, might influence the surgical outcome. Indeed, any hormonal treatment capable of reducing the myoma size can further facilitate the surgical procedure, as reported for the GnRH analogs [32] and ulipristal acetate [33].

Consequently, the choice of hormone therapy before hysteroscopic myomectomy must be personalized based on the advantages and disadvantages of every available option and the patient’s characteristics. This review analyzes the preoperative treatments used before hysteroscopic myomectomy, with the attempt to identify the main indications for each option.

2. Materials and methods

For this review, a comprehensive search of several databases was conducted from inception up to May 2021. The searched databases were MEDLINE, In-Process & Other Non-Indexed Citations, Daily, Ovid EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus.

The search strategy included the combinations of the following medical terms: Hysteroscopic myomectomy; Uterine fibroid, Hormonal therapy, preoperative. We selected clinical studies, systematic reviews, and meta-analyses in English investigating hormone therapy before hysteroscopic myomectomy. No additional inclusion or exclusion criteria were used. Titles, abstracts, and the full texts of the potentially eligible studies were retrieved and independently assessed for eligibility by three team members (A.S.L., S.G., S.D.). Disagreement over the studies’ eligibility was solved by a discussion with a fourth author (SU). The reference list of all identified studies was systematically revised to identify other eligible publications. Considering the heterogeneity of the findings, we opted for a narrative synthesis of the results, summarizing the evidence provided by the most relevant studies to offer the reader a complete and synthetic overview of the hormone therapy before hysteroscopic myomectomy. No statistical analysis was performed.

3. Results

3.1 Gonadotropins releasing hormone analogs

GnRH analogs have been widely used before myomectomy to reduce fibroid size, which is estrogen-dependent [34–37]. Continuous administration of GnRH analogs causes a temporary suppression of the hypothalamus-pituitary-ovarian axis leading to a hypoestrogenic state, decreasing the myoma’s volume and vascularization [38]. The size reduction helps expose the intramural part of a submucosal fibroid, thereby increasing the possibility of complete resection with a low recurrence rate [39–41]. Furthermore, the endometrium has been reported to be thinner after GnRH analogs than immediately after the menstrual cycle. These effects have been evidenced to slightly reduce the operating time and the absorption of the intraoperative distension medium, facilitating the procedure [24, 25, 42].

In their prospective study, Donnez et al. [43] documented a reduction in myoma size and absorption of distension media with an increase in the preoperative hemoglobin levels with GnRH analogs before hysteroscopic myomectomy. Perino et al. [44] prospectively assessed the role of endometrial preparation with leuprolide acetate before operative hysteroscopy for endometrial ablation, uterine septum resection, and myomectomy. In the subgroup undergoing hysteroscopic myomectomy, significant reductions in the operative time, intraoperative bleeding, infusion volume, and procedure failure rate were observed in the group treated with the GnRH analog. On the contrary, Campo et al. [45], evaluating short- and long-term surgical outcomes after preoperative GnRH analogs, observed a significantly longer operative time in the GnRH-treated group, possibly resulting from the difficulty encountered in dilating the cervical canal. Although useful in anemic patients, the authors concluded that the preoperative use of the GnRH analog did not improve short and long-term surgical results.

Two mains randomized controlled clinical trials evaluated the use of the GnRH analog before hysteroscopic myomectomy: one of Mavrelos et al. [39], a double-blind, randomized placebo-controlled clinical trial, where the treatment group received the GnRH analog goserelin at 3.6 mg for 12 weeks; and the second of Muzii et al. [46], a randomized controlled multicenter study, with one group pretreated with triptorelin at 3.75 mg for eight weeks before surgery. A meta-analysis of these trials showed no advantage derived from the preoperative administration of GnRH analogs before hysteroscopic myomectomy in terms of complete resection of the myoma [42].

However, operative time was shorter in women receiving GnRH analogs, and consistent with this finding, the volume of distension medium absorbed during the procedure was significantly reduced [42]. On the one hand, in the study by Muzii et al. [46], the surgical difficulty assessed by the surgeon was significantly greater in women who were not pretreated. On the other hand, although the procedure was facilitated, all patients in the GnRH pretreated group experienced hot flashes, mostly mild in severity (80%) [46].

Recently, Favilli et al. [47] performed a well-designed randomized controlled trial, aimed to evaluate the intraoperative effects of gonadotropin-releasing hormone analog pretreatment, compared with no treatment, in patients undergoing cold loop hysteroscopic myomectomy. In this study, the multivariate analysis showed a significant correlation between the multiple-step treatment and the use of GnRH, grading, and size of myomas. In particular, preoperative GnRH analog administration was not found to facilitate the completion of cold loop hysteroscopic myomectomy in a single surgical
procedure in G2 myomas and was correlated with a longer duration of the surgery; in addition, no significant benefits were found for G0 and G1 myomas.

Based on these data, preparation with GnRH before a hysteroscopic myomectomy has several intraoperative benefits with greater satisfaction for the operator. However, it was not associated with a significant difference in the percentage of cases undergoing complete fibroid resection or experiencing full resolution of symptoms.

For these reasons, the available evidence is insufficient to support the routine use of GnRH analogs before a myomectomy [48], especially considering their unfavorable cost-benefit ratio and the induced menopausal symptoms due to estrogen deprivation [34].

### 3.2 Danazol

Danazol is a synthetic steroid related to 17-ethinyltestosterone. It can inhibit the growth of the endometrium due to its intrinsic androgenic properties and its capacity to increase free testosterone and reduce ovarian estrogens [28]. Clinical studies demonstrated comparable efficacy between danazol and GnRH analogs to prepare the endometrium preoperatively [25, 49].

A daily oral dose of 600 mg per day for six weeks can achieve adequate endometrial atrophy with a thickness of around 3 mm, helping the hysteroscopic surgery [50, 51]. This drug can be administered both orally (600 mg) and vaginally (400 mg) with comparable therapeutic efficacy [26, 52–55]. Compared to vaginal administration, the oral route has been associated with a higher incidence of side effects, such as hot flashes, headache, and increased serum concentrations of aspartate and alanine aminotransferase [49, 53–56]. Vaginal drug release allows danazol to reach higher concentrations in the endometrium with a stronger inhibitory effect [27, 55]. A direct comparison of the two routes of administration before an operative hysteroscopy suggests a more pronounced effect of the vaginal route on the endometrial thinning, with shorter operating times and greater surgeon satisfaction [26]. Indeed, the effect on uterus and ovaries of 100 mg/day vaginally active drug is comparable to 400 mg/day oral danazol, with the advantage of lower drug serum concentrations [57]. Consequently, compared to the oral route of administration, vaginal danazol is an optimal choice for endometrial preparation before operative hysteroscopy [28].

### 3.3 Progestogens

Progestogens in monotherapy have always been used for endometrial preparation before hysteroscopic surgery. With limited side effects and costs, various progestogens can achieve adequate endometrial atrophy and correlated endometrial thinning when administered from the first day of menstrual flow [25].

Desogestrel is one of the most studied progestogens for endometrial preparation, causing adequate endometrial atrophy with consequent reduction of operative time, blood loss, and distension medium used [58].

The atrophic effect of desogestrel on the endometrial mucosa, was found superior to danazol [29]. In a randomized clinical trial, desogestrel was administered from the first day of the menstrual cycle for five weeks, at a dose of 75 mg/day vs. 100 mg/day of danazol for the same duration of treatment. The progestogens demonstrated a more atrophic endometrial effect and a marked reduction in bleeding resulting in shorter operative time, lower volume of distension medium infused, and fewer side effects than danazol [29]. Similarly, the administration of nomegestrol acetate has also proved to effectively reduce the thickness of the endometrium by acting on the hypothalamus-pituitary-ovary axis [59].

Dienogest is a progestogen used explicitly in the preoperative treatment for hysteroscopic myomectomy [60], with excellent results in inducing endometrial atrophy with consequent reduction of operating time, infusion volume, and bleeding during the procedure. Dienogest is an orally active progestogen, primarily aimed for the medical treatment of endometriosis [61, 62], combining the advantages of both 19-nortestosterone and progesterone classes of progestogens [63–68]. The positive effects of dienogest have also been documented for polyps, uterine septa, and tubal sterilization [30, 69, 70].

Furthermore, Kodama et al. [69] showed cost advantages and rapid resumption of spontaneous menstruation in the group pre-treated with Dienogest compared to GnRH analogs. For this reason, it could be the preferred choice for couples who want to conceive quickly after the procedure [69]. Duration of treatment varies between 14–28 days, depending on drug dosage [69, 71]. Numerous clinical studies demonstrated the favorable safety profile of Dienogest [72], as it has been associated with few and tolerable side effects, including weight gain, psychiatric disorders (depressed mood, sleep disturbances, nervousness, and loss of libido), headaches, nausea, abdominal pain, acne, alopecia, asthenia, breast engorgement and pain [72–76]. However, it is more expensive and not contraceptive compared to other progestogen-only or COC-based therapy options.

### 3.4 Combined oral contraceptives (COC)

The available evidence on combined oral contraceptives for endometrial preparation before a hysteroscopic myomectomy is limited [30]. However, COCs, initiated in the first follicular phase during the 1st–3rd day of menstrual flow, can achieve and maintain a thin, atrophic endometrium with a thickness between 4 and 1.5 mm on the 18th day of therapy [77]. COCs are associated with an asynchronous maturation of the endometrial epithelium and stroma, a shortening of proliferative and secretory phases, and an epithelial involution during the last days of the cycle. These changes produce great stability of the endometrium that appears thinned and compact. Furthermore, if COCs are used for a longer time, the minimal secretory features of the endometrial glands tend to disappear, resulting in complete atrophy of both glands and stroma [78, 79].
COC improves the visualization of the uterine cavity and intracavitary lesion before an operative hysteroscopy, as it helps the endometrium to appear thin, clear, and uniform [30, 77]. There is no contraindication to COC use before hysteroscopy, as it is considered minor surgery. Nevertheless, several pieces of evidence suggest that Hormonal Replacement Treatment may cause a slight increase of myoma’s size in some postmenopausal women [80]. This element should be taken into account for proper management, also considering the potential general side effects of hormonal contraceptives [81].

In conclusion, this class of drugs can be considered a valid alternative to GnRH analogs and danazol due to their efficacy, the lower cost, the fewer side effects, and the easy availability [77]. In addition, compared to progestins and danazol, these drugs have the advantage of being contraceptives if started from the first day of menstruation.

### 3.5 Ulipristal acetate

Ulipristal acetate (UPA) is a selective progesterone receptor modulator, presenting an antagonist and partial agonist activity. On the one hand, UPA theoretically facilitates hysteroscopic myomectomy as it can decrease the myoma volume and reduce bleeding [82–84]. On the other hand, by modulating the progesterone receptor, UPA can increase the endometrial thickness, interfering with the visualization of the myoma, thus representing a possible disadvantage [85]. In clinical practice, some studies suggested that myomas pre-treated with UPA appeared softer and more difficult to enucleate during laparoscopic myomectomy because of less clear cleavage planes than no pre-treated myomas [86]. In contrast, the same effect does not occur for hysteroscopic myomectomy. Although speculative, this may be due (at least in part) to the different impact of the drug on submucosal myomas, which are treated by hysteroscopy, compared with subserosal and intramural myomas, treated by laparoscopy.

In a prospective non-randomized study, four different groups of patients received for three months respectively 5 mg/day of UPA, triptorelin 3.75 mg intramuscular every 28 days, letrozole 2.5 mg/day, or placebo [87]. All three hormone therapies were associated with a significant reduction of the larger myoma, more remarkable in the UPA group, and complete hysteroscopic myomectomy achieved in all patients. However, only the triptorelin and letrozole groups reported a reduction in operating times, fluid volume infused, and distension medium absorption. Patients treated with UPA had an increase in the endometrial thickness, although not associated with greater operative difficulties. Of note, only seven patients were included in the UPA group; this small sample size does not allow to draw any firm conclusion.

In the retrospective study by Sancho et al. [88], three months of UPA (5 mg/day) were compared with three months of triptorelin 3.75 mg intramuscular every 28 days. No significant difference was reported in terms of surgery duration, distension medium deficiency, or percentage of myoma resected. Nevertheless, the surgeon experienced easier cervical dilation in the UPA prepared group and better visualizing the uterine cavity in the GnRH analog group. In a retrospective study of patients undergoing high complexity hysteroscopic myomectomies (STEPW score 5 or 6 myomas) [89], patients pretreated with 5 mg/day of UPA for three months, compared with no treatment group, reported a more considerable myoma reduction, a higher number of patients with complete resection, a significantly shorter operative time, and greater difficulty related to endometrial thinning in 16% of patients. The volume of distension medium used and the water balance were comparable between the two groups. Finally, in a recent study comparing hysteroscopic myomectomies after no pretreatment, UPA, or other hormonal therapy (GnRH analogs, combined oral contraceptives, and progestogens) [90], no difference was found in the surgical experience and the quality of hysteroscopic visualization; of note, the operators were aware of the pretreatment used.

Reduction in myoma volume represents a possible advantage of UPA therapy and GnRH analog therapy. This effect is associated with a possible change in the position of the myoma within the uterine wall, known as “myoma migration” effect [91–93]. Due to this migration, some submucosal myomas were no longer treatable with a hysteroscopic approach but required laparoscopic myomectomy [94], vaginal myomectomy [94, 95], or no treatment [94].

UPA is generally presented as an alternative GnRH analogs; nevertheless, comparing the two treatments, there was no difference in reducing uterine volume and bleeding but an advantage in fewer side effects [32]. A better safety profile than GnRH analogs has always been considered the most crucial advantage of UPA, with a notable improvement in patients’ quality of life [96]. However, the finding of cases of severe liver damage, which in some of them end up in liver transplantation, led to the implementation of various restrictions aimed at minimizing the risk of these adverse events [33]. Recently the European Medicine Agency has limited the use of UPA to premenopausal women not eligible to surgery or in whom surgery has failed, and FDA has approved the use of UPA only as emergency contraception pill [97]. Therefore, today, UPA cannot be considered a valid option for endometrium preparation before hysteroscopic myomectomy.

### 4. Discussion

The success of hysteroscopic surgery strongly depends on good access and visualization of the whole uterine cavity, decreasing the operating times and complications [28]. For this reason, and to ensure the absence of pregnancy, operative hysteroscopy is usually performed immediately after a menstrual flow, between the fourth and eighth day, when the endometrium appears thin and uniform. However, in patients with irregular menstruation, such as in premenopausal women, it can be challenging to predict the early follicular...
phase and correctly plan the hysteroscopy [77]. Furthermore, even when hysteroscopy is perfectly planned, the endometrium can sometimes be thick, as in obese women or a state of hyperestrogenism [30]. The surgical field is minimal, often reduced by the same intrauterine pathology, and a thick endometrium can hinder identifying the same intrauterine lesion or specific anatomical reference points. For this reason, in certain circumstances, a preoperative hormonal treatment helps obtain the best possible conditions of visibility [98].

Numerous hormonal treatments, such as GnRH analogs, vaginal danazol, progestogens, and combined oral contraceptives, have been designed to achieve optimal intrauterine vision by reducing the endometrial thickness and intraoperative bleeding. In the current scenario, several variables should be considered using a specific medical therapy (including the different potential effects with a particular drug compared to the others in type 0, 1, or 2 myoma); this element further amplifies the heterogeneity of the available findings in the literature and does not allow to draw a firm conclusion about a best pharmacological management over the others. We acknowledge that one limitation of this review is that the search strategy did not include the name of the drug.

5. Conclusions
To date, no definitive data provide strong evidence towards one specific preoperative therapy before myomectomy hysteroscopy [29, 31, 60]. On the one hand, the efficacy of GnRH analogs and danazol administration before hysteroscopic surgery has been demonstrated by several studies, mainly related to the time of surgery and volume of distension medium absorbed [24, 25]. On the other hand, although the evidence is more limited, progestogens and combined hormonal contraceptives have proven a comparable efficacy in achieving adequate endometrial thinning [25]. In addition, important heterogeneity of the findings available in the literature can derive, at least in part, from the difficulty of structuring and organizing multicentric and homogeneous prospective clinical studies due to the inclusion of different types of intrauterine pathologies, different comorbidities, different drugs, dosage, duration of the pharmacological pre-treatment and route of administration.

What most distinguishes these various options are the costs and the side effects associated with them.

In conclusion, the hormonal endometrial preparation before hysteroscopic myomectomy must be carefully evaluated and adapted to the patient, considering the characterististics of the fibroid, side effects, and any contraindications to their use.

Author contributions
All the authors contributed to the intellectual content of the study and approved the final version of the article. ASL and SD—Study Conceptualization. ASL, SD, and MB—Writing the Original Draft. RDP, PP, PCZ and RR—Writing, Review, and Editing. MF and SU—Visualization and Supervision. All authors contributed to the interpretation of results, as well as reviewed and approved the final version.

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