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Review

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 hypervolemia with or without hyponatremia [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 pretreated 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 myomectomy (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 thickening 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 characteristics 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.

Ethics approval and consent to participate

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Conflict of interest

The authors declare no conflict of interest. ASL is serving as one of the Guest editors of this journal. We declare that ASL had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to MHD.

References

[1] Di Spiezio Sardo A, Bettocchi S, Spinelli M, Guida M, Nappi L, Angioni S, *et al.* Review of new office-based hysteroscopic procedures 2003-2009. Journal of Minimally Invasive Gynecology. 2010; 17: 436–448.

[2] Gizzo S, Saccardi C, Di Gangi S, Bertocco A, Vendemiati L, Righetto L, *et al.* Secondary amenorrhea in severe Asherman's syndrome: Step by step fertility retrieval by Bettocchi's hysteroscope: some considerations. Minimally Invasive Therapy & Allied Technologies. 2014; 23: 115–119.

[3] Alonso Pacheco L, Laganà AS, Garzon S, Pérez Garrido A, Flores Gornés A, Ghezzi F. Hysteroscopic outpatient metroplasty for T-shaped uterus in women with reproductive failure: Results from a large prospective cohort study. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2019; 243: 173–178.

[4] Esteban Manchado B, Lopez-Yarto M, Fernandez-Parra J, Rodriguez-Oliver A, Gonzalez-Paredes A, Laganà AS, *et al.* Office hysteroscopic metroplasty with diode laser for septate uterus: a multicenter cohort study. Minimally Invasive Therapy and Allied Technologies. 2020. (in press)

[5] Garzon S, Laganà AS, Di Spiezio Sardo A, Alonso Pacheco L, Haimovich S, Carugno J, *et al.* Hysteroscopic Metroplasty for T-Shaped Uterus: a Systematic Review and Meta-analysis of Reproductive Outcomes. Obstetrical & Gynecological Survey. 2020; 75: 431–444.

[6] Tanvir T, Garzon S, Alonso Pacheco L, Lopez Yarto M, Rios M, Stamenov G, *et al.* Office hysteroscopic myomectomy without myoma extraction: a multicenter prospective study. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2021; 256: 358–363.

[7] Laganà AS, Garzon S, Alkatout I, Hortu İ, Gitas G, Vitale SG, *et al.* Isthmocele: When Surgery Is Both the Problem and the Solution. Journal of Investigative Surgery. 2020. (in press)

[8] Alonso Pacheco L, Ata B, Bettocchi S, Campo R, Carugno J, Checa MA, *et al.* Septate uterus and reproductive outcomes: let's get serious about this. Human Reproduction. 2020; 35: 2627–2629.

[9] Salazar CA, Isaacson KB. Office Operative Hysteroscopy: an Update. Journal of Minimally Invasive Gynecology. 2018; 25: 199–208.

[10] Laganà AS, Alonso Pacheco L, Tinelli A, Haimovich S, Carugno J, Ghezzi F, *et al.* Management of Asymptomatic Submucous My-

omas in Women of Reproductive Age: a Consensus Statement from the Global Congress on Hysteroscopy Scientific Committee. Journal of Minimally Invasive Gynecology. 2019; 26: 381–383.
[11] Vitale SG, Sapia F, Rapisarda AMC, Valenti G, Santangelo F, Rossetti D, *et al.* Hysteroscopic Morcellation of Submucous Myomas: a Systematic Review. BioMed Research International. 2017; 2017: 6848250.
[12] Bhave Chittawar P, Franik S, Pouwer AW, Farquhar C. Minimally invasive surgical techniques versus open myomectomy for uterine fibroids. The Cochrane Database of Systematic Reviews. 2014; CD004638.
[13] Laganà AS, Ciancimino L, Mancuso A, Chiofalo B, Rizzo P, Triolo O. 3D sonohysterography vs hysteroscopy: a cross-sectional study for the evaluation of endouterine diseases. Archives of Gynecology and Obstetrics. 2014; 290: 1173–1178.
[14] Sudano MC, Vitale SG, Rapisarda AMC, Carastro D, Tropea A, Zizza G. The REP-b (removal of endometrial pathologies-basket) in-office hysteroscopy. Updates in Surgery. 2016; 68: 407–412.
[15] Sleiman Z, Karaman E, Terzic M, Terzic S, Falzone G, Garzon S. Fertility Preservation in Benign Gynecological Diseases: Current Approaches and Future Perspectives. Journal of Reproduction & Infertility. 2019; 20: 201–208.
[16] Vitale SG, Laganà AS, Caruso S, Garzon S, Vecchio GM, La Rosa VL, *et al.* Comparison of three biopsy forceps for hysteroscopic endometrial biopsy in postmenopausal patients (HYGREB-1): A multicenter, single-blind randomized clinical trial. International Journal of Gynecology & Obstetrics. 2021. (in press)
[17] Shveiky D, Rojansky N, Revel A, Benshushan A, Laufer N, Shushan A. Complications of hysteroscopic surgery: "beyond the learning curve". Journal of Minimally Invasive Gynecology. 2007; 14: 218–222.
[18] Giacobbe V, Rossetti D, Vitale SG, Rapisarda AMC, Padula F, Laganà AS, *et al.* Otorrhagia and Nosebleed as first signs of Intravascular Absorption Syndrome During Hysteroscopy: From Bench to Bedside. Kathmandu University Medical Journal. 2016; 14: 87–89.
[19] Deffieux X, Gauthier T, Ménager N, Legendre G, Agostini A, Pierre F. Prevention of the complications related to hysteroscopy: guidelines for clinical practice. Journal De Gynecologie, Obstetrique Et Biologie De La Reproduction. 2013; 42: 1032–1049. (In French)
[20] Haude O, Overdijk LE, Kesteren PJM, Geerts BF, Rademaker BMP. Comparing volumetric and biochemical assessment of intravasation caused by hysteroscopic surgery. Acta Anaesthesiologica Scandinavica. 2020; 64: 232–237.
[21] Frascà C, Tuzzato G, Arena A, Degli Esposti E, Zanello M, Raimondo D, *et al.* The Role of Pelvic Ultrasound in Preoperative Evaluation for Laparoscopic Myomectomy. Journal of Minimally Invasive Gynecology. 2018; 25: 679–683.
[22] Munro MG, Critchley HOD, Broder MS, Fraser IS. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. International Journal of Gynaecology and Obstetrics. 2011; 113: 3–13.
[23] Rai VS, Gillmer MD, Gray W. Is endometrial pre-treatment of value in improving the outcome of transcervical resection of the endometrium? Human Reproduction. 2000; 15: 1989–1992.
[24] Parazzini F, Vercellini P, De Giorgi O, Pesole A, Ricci E, Crosignani PG. Efficacy of preoperative medical treatment in facilitating hysteroscopic endometrial resection, myomectomy and metroplasty: literature review. Human Reproduction. 1998; 13: 2592–2597.
[25] Tan YH, Lethaby A. Pre-operative endometrial thinning agents before endometrial destruction for heavy menstrual bleeding. the Cochrane Database of Systematic Reviews. 2013; CD010241.
[26] Florio P, Filippeschi M, Imperatore A, Mereu L, Franchini M, Calzolari S, *et al.* The practicability and surgeons' subjective experiences with vaginal danazol before an operative hysteroscopy. Steroids. 2012; 77: 528–533.
[27] Cicinelli E, Pinto V, Tinelli R, Saliani N, De Leo V, Cianci A. Rapid endometrial preparation for hysteroscopic surgery with oral desogestrel plus vaginal raloxifene: a prospective, randomized pilot study. Fertility and Sterility. 2007; 88: 698–701.
[28] Triolo O, De Vivo A, Benedetto V, Falcone S, Antico F. Gestrinone versus danazol as preoperative treatment for hysteroscopic surgery: a prospective, randomized evaluation. Fertility and Sterility. 2006; 85: 1027–1031.
[29] Laganà AS, Palmara V, Granese R, Ciancimino L, Chiofalo B, Triolo O. Desogestrel versus danazol as preoperative treatment for hysteroscopic surgery: a prospective, randomized evaluation. Gynecological Endocrinology. 2014; 30: 794–797.
[30] Bifulco G, Di Spiezio Sardo A, De Rosa N, Greco E, Spinelli M, Di Carlo C, *et al.* The use of an oral contraceptive containing estradiol valerate and dienogest before office operative hysteroscopy: a feasibility study. Gynecological Endocrinology. 2012; 28: 949–955.
[31] Laganà AS, Vitale SG, Muscia V, Rossetti P, Buscema M, Triolo O, *et al.* Endometrial preparation with Dienogest before hysteroscopic surgery: a systematic review. Archives of Gynecology and Obstetrics. 2017; 295: 661–667.
[32] Lethaby A, Puscasiu L, Vollenhoven B. Preoperative medical therapy before surgery for uterine fibroids. The Cochrane Database of Systematic Reviews. 2017; 11: CD000547.
[33] Ferrero S, Vellone VG, Barra F, Scala C. Ulipristal Acetate before Hysteroscopic and Laparoscopic Surgery for Uterine Myomas: Help or Hindrance? Gynecologic and Obstetric Investigation. 2019; 84: 313–325.
[34] Somigliana E, Vercellini P, Daguati R, Pasin R, De Giorgi O, Crosignani PG. Fibroids and female reproduction: a critical analysis of the evidence. Human Reproduction Update. 2007; 13: 465–476.
[35] Gutmann JN, Corson SL. GnRH agonist therapy before myomectomy or hysterectomy. Journal of Minimally Invasive Gynecology. 2005; 12: 529–529.
[36] Römer T, Schmidt T, Foth D. Pre- and postoperative hormonal treatment in patients with hysteroscopic surgery. Contributions to Gynecology and Obstetrics. 2000; 20: 1–12.
[37] Sleiman Z, Baba R, Garzon S, Khazaka A. The significant risk factors of intra-operative hemorrhage during laparoscopic myomectomy: a systematic review. Gynecology and Minimally Invasive Therapy. 2020; 9: 6.
[38] Friedman AJ, Lobel SM, Rein MS, Barbieri RL. Efficacy and safety considerations in women with uterine leiomyomas treated with gonadotropin-releasing hormone agonists: the estrogen threshold hypothesis. American Journal of Obstetrics and Gynecology. 1990; 163: 1114–1119.
[39] Mavrelos D, Ben-Nagi J, Davies A, Lee C, Salim R, Jurkovic D. The value of pre-operative treatment with GnRH analogues in women with submucous fibroids: a double-blind, placebo-controlled randomized trial. Human Reproduction. 2010; 25: 2264–2269.
[40] Mencaglia L, Tantini C. GnRH agonist analogs and hysteroscopic resection of myomas. International Journal of Gynaecology and Obstetrics. 1993; 43: 285–288.
[41] Ukybassova T, Terzic M, Dotlic J, Imankulova B, Terzic S, Shauyen F, *et al.* Evaluation of Uterine Artery Embolization on Myoma Shrinkage: Results from a Large Cohort Analysis. Gynecology and Minimally Invasive Therapy. 2019; 8: 165–171.
[42] Kamath MS, Kalampokas EE, Kalampokas TE. Use of GnRH analogues pre-operatively for hysteroscopic resection of submucous fibroids: a systematic review and meta-analysis. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2014; 177: 11–18.
[43] Donnez J, Schrurs B, Gillerot S, Sandow J, Clerckx F. Treatment of uterine fibroids with implants of gonadotropin-releasing hormone agonist: assessment by hysterography. Fertility and Sterility. 1989; 51: 947–950.
[44] Perino A, Chianchiano N, Petronio M, Cittadini E. Role of leuprolide acetate depot in hysteroscopic surgery: a controlled study. Fertility and Sterility. 1993; 59: 507–510.
[45] Campo S, Campo V, Gambadauro P. Short-term and long-term results of resectoscopic myomectomy with and without pretreat-

ment with GnRH analogs in premenopausal women. Acta Obstetricia Et Gynecologica Scandinavica. 2005; 84: 756–760.
[46] Muzii L, Boni T, Bellati F, Marana R, Ruggiero A, Zullo MA, *et al.* GnRH analogue treatment before hysteroscopic resection of submucous myomas: a prospective, randomized, multicenter study. Fertility and Sterility. 2010; 94: 1496–1499.
[47] Favilli A, Mazzon I, Grasso M, Horvath S, Bini V, Di Renzo GC, *et al.* Intraoperative Effect of Preoperative Gonadotropin-Releasing Hormone Analogue Administration in Women Undergoing Cold Loop Hysteroscopic Myomectomy: a Randomized Controlled Trial. Journal of Minimally Invasive Gynecology. 2018; 25: 706–714.
[48] Farquhar C, Brown PM, Furness S. Cost effectiveness of preoperative gonadotrophin releasing analogues for women with uterine fibroids undergoing hysterectomy or myomectomy. BJOG: an International Journal of Obstetrics and Gynaecology. 2002; 109: 1273–1280.
[49] Luisi S, Razzi S, Lazzeri L, Bocchi C, Severi FM, Petraglia F. Efficacy of vaginal danazol treatment in women with menorrhagia during fertile age. Fertility and Sterility. 2009; 92: 1351–1354.
[50] Garry R, Khair A, Mooney P, Stuart M. A comparison of goserelin and danazol as endometrial thinning agents prior to endometrial laser ablation. British Journal of Obstetrics and Gynaecology. 1996; 103: 339–344.
[51] Irvine GA, Campbell-Brown MB, Lumsden MA, Heikkilä A, Walker JJ, Cameron IT. Randomised comparative trial of the levonorgestrel intrauterine system and norethisterone for treatment of idiopathic menorrhagia. British Journal of Obstetrics and Gynaecology. 1998; 105: 592–598.
[52] Bulletti C, Flamigni C, Polli V, Giacomucci E, Albonetti A, Negrini V, *et al.* The efficacy of drugs in the management of endometriosis. The Journal of the American Association of Gynecologic Laparoscopists. 1997; 3: 495–501.
[53] Cobellis L, Razzi S, Fava A, Severi FM, Igarashi M, Petraglia F. A danazol-loaded intrauterine device decreases dysmenorrhea, pelvic pain, and dyspareunia associated with endometriosis. Fertility and Sterility. 2004; 82: 239–240.
[54] Razzi S, Luisi S, Calonaci F, Altomare A, Bocchi C, Petraglia F. Efficacy of vaginal danazol treatment in women with recurrent deeply infiltrating endometriosis. Fertility and Sterility. 2007; 88: 789–794.
[55] Igarashi M, Iizuka M, Abe Y, Ibuki Y. Novel vaginal danazol ring therapy for pelvic endometriosis, in particular deeply infiltrating endometriosis. Human Reproduction. 1998; 13: 1952–1956.
[56] Petraglia F, Luisi S. Local drug release systems in endometriosis. Gynecological Endocrinology. 2007; 23: 662–664.
[57] Mizutani T, Nishiyama S, Amakawa I, Watanabe A, Nakamuro K, Terada N. Danazol concentrations in ovary, uterus, and serum and their effect on the hypothalamic-pituitary-ovarian axis during vaginal administration of a danazol suppository. Fertility and Sterility. 1995; 63: 1184–1189.
[58] Haimovich S, Mancebo G, Alameda F, Agramunt S, Hernández JL, Carreras R. Endometrial preparation with desogestrel before Essure hysteroscopic sterilization: preliminary study. Journal of Minimally Invasive Gynecology. 2013; 20: 591–594.
[59] Florio P, Imperatore A, Litta P, Franchini M, Calzolari S, Angioni S, *et al.* The use of nomegestrol acetate in rapid preparation of endometrium before operative hysteroscopy in pre-menopausal women. Steroids. 2010; 75: 912–917.
[60] Laganà AS, Giacobbe V, Triolo O, Granese R, Ban Frangež H, Vrtačnik-Bokal E, *et al.* Dienogest as preoperative treatment of submucous myomas for hysteroscopic surgery: a prospective, randomized study. Gynecological Endocrinology. 2016; 32: 408–411.
[61] Zanello M, Borghese G, Manzara F, Esposti ED, Moro E, Raimondo D, *et al.* Hormonal Replacement Therapy in Menopausal Women with History of Endometriosis: A Review of Literature. Medicina. 2019; 55: 477.
[62] Mabrouk M, Paradisi R, Arena A, Del Forno S, Matteucci C, Zannoni L, *et al.* Short-term histopathological effects of dienogest therapy on ovarian endometriomas: in vivo, nonrandomized, controlled trial. Gynecological Endocrinology. 2018; 34: 399–403.
[63] Shin D, Lee S, Lim KS, Park JS, Shin S, Jang I, *et al.* Pharmacokinetic study of single and multiple oral administrations of 2 mg dienogest in healthy Korean women. Contraception. 2013; 87: 750–755.
[64] Laganà AS, Garzon S, Götte M, Viganò P, Franchi M, Ghezzi F, *et al.* The Pathogenesis of Endometriosis: Molecular and Cell Biology Insights. International Journal of Molecular Sciences. 2019; 20: 5615.
[65] Raffaelli R, Garzon S, Baggio S, Genna M, Pomini P, Laganà AS, *et al.* Mesenteric vascular and nerve sparing surgery in laparoscopic segmental intestinal resection for deep infiltrating endometriosis. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2018; 231: 214–219.
[66] Riemma G, Laganà AS, Schiattarella A, Garzon S, Cobellis L, Autiero R, *et al.* Ion Channels in The Pathogenesis of Endometriosis: A Cutting-Edge Point of View. International Journal of Molecular Sciences. 2020; 21: 1114.
[67] Baggio S, Pomini P, Zecchin A, Garzon S, Bonin C, Santi L, *et al.* Delivery and pregnancy outcome in women with bowel resection for deep endometriosis: a retrospective cohort study. Gynecological Surgery. 2015; 12: 279–285.
[68] Barra F, Laganà AS, Scala C, Garzon S, Ghezzi F, Ferrero S. Pretreatment with dienogest in women with endometriosis undergoing IVF after a previous failed cycle. Reproductive BioMedicine Online. 2020; 41: 859–868.
[69] Kodama M, Onoue M, Otsuka H, Yada-Hashimoto N, Saeki N, Kodama T, *et al.* Efficacy of Dienogest in Thinning the Endometrium before Hysteroscopic Surgery. Journal of Minimally Invasive Gynecology. 2013; 20: 790–795.
[70] Cicinelli E, Pinto V, Quattromini P, Fucci MR, Lepera A, Mitola PC, *et al.* Endometrial preparation with estradiol plus dienogest (Qlaira) for office hysteroscopic polypectomy: randomized pilot study. Journal of Minimally Invasive Gynecology. 2012; 19: 356–359.
[71] Tsuchiya T, Katagiri Y, Maemura T, Hayata E, Fukuda Y, Kitamura M, *et al.* Preoperative dienogest to improve the surgical field of view in resectoscopic surgery. Gynecology and Minimally Invasive Therapy. 2016; 5: 16–19.
[72] Strowitzki T, Faustmann T, Gerlinger C, Schumacher U, Ahlers C, Seitz C. Safety and tolerability of dienogest in endometriosis: pooled analysis from the European clinical study program. International Journal of Women's Health. 2015; 7: 393–401.
[73] Sugimoto K, Nagata C, Hayashi H, Yanagida S, Okamoto A. Use of dienogest over 53 weeks for the treatment of endometriosis. Journal of Obstetrics and Gynaecology Research. 2015; 41: 1921–1926.
[74] Andres MDP, Lopes LA, Baracat EC, Podgaec S. Dienogest in the treatment of endometriosis: systematic review. Archives of Gynecology and Obstetrics. 2015; 292: 523–529.
[75] Schindler AE. Dienogest in long-term treatment of endometriosis. International Journal of Women's Health. 2011; 3: 175–184.
[76] Garzon S, Laganà AS, Barra F, Casarin J, Cromi A, Raffaelli R, *et al.* Novel drug delivery methods for improving efficacy of endometriosis treatments. Expert Opinion on Drug Delivery. 2021; 18: 355–367.
[77] Grow DR, Iromloo K. Oral contraceptives maintain a very thin endometrium before operative hysteroscopy. Fertility and Sterility. 2006; 85: 204–207.
[78] Lessey BA, Killam AP, Metzger DA, Haney AF, Greene GL, McCarty KS. Immunohistochemical Analysis of Human Uterine Estrogen and Progesterone Receptors throughout the Menstrual Cycle. The Journal of Clinical Endocrinology & Metabolism. 1988; 67: 334–340.
[79] Bastianelli C, Farris M, Bruni V, Brosens I, Benagiano G. Pharmacodynamics of combined estrogen–progestin oral contraceptives: 4. Effects on uterine and cervical epithelia. Expert Review of Clinical Pharmacology. 2020; 13: 163–182.

[80] Moro E, Esposti ED, Borghese G, Manzara F, Zanello M, Raimondo D, *et al.* The Impact of Hormonal Replacement Treatment in Postmenopausal Women with Uterine Fibroids: A State-of-the-Art Review of the Literature. Medicina. 2019; 55: 549.
[81] Morotti E, Casadio P, Guasina F, Battaglia B, Mattioli M, Battaglia C. Weight gain, body image and sexual function in young patients treated with contraceptive vaginal rin. Gynecological Endocrinology. 2017; 33: 660–664.
[82] Donnez J, Tatarchuk TF, Bouchard P, Puscasiu L, Zakharenko NF, Ivanova T, *et al.* Ulipristal acetate versus placebo for fibroid treatment before surgery. The New England Journal of Medicine. 2012; 366: 409–420.
[83] Donnez J, Tomaszewski J, Vázquez F, Bouchard P, Lemieszczuk B, Baró F, *et al.* Ulipristal acetate versus leuprolide acetate for uterine fibroids. The New England Journal of Medicine. 2012; 366: 421–432.
[84] Donnez J, Vázquez F, Tomaszewski J, Nouri K, Bouchard P, Fauser BCJM, *et al.* Long-term treatment of uterine fibroids with ulipristal acetate ⋆. Fertility and Sterility. 2014; 101: 1565–1518.
[85] Tafi E, Scala C, Leone Roberti Maggiore U, Bizzarri N, Candiani M, Venturini PL, *et al.* Drug safety evaluation of ulipristal acetate in the treatment of uterine fibroids. Expert Opinion on Drug Safety. 2015; 14: 965–977.
[86] Frascà C, Arena A, Degli Esposti E, Raimondo D, Del Forno S, Moro E, *et al.* First Impressions Can Be Deceiving: Surgical Outcomes of Laparoscopic Myomectomy in Patients Pretreated with Ulipristal Acetate. Journal of Minimally Invasive Gynecology. 2020; 27: 633–638.
[87] Bizzarri N, Ghirardi V, Remorgida V, Venturini PL, Ferrero S. Three-month treatment with triptorelin, letrozole and ulipristal acetate before hysteroscopic resection of uterine myomas: prospective comparative pilot study. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2015; 192: 22–26.
[88] Sancho JM, Delgado VSDLC, Valero MJN, Soteras MG, Amate VP, Carrascosa AA. Hysteroscopic myomectomy outcomes after 3-month treatment with either Ulipristal Acetate or GnRH analogues: a retrospective comparative study. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2016; 198: 127–130.
[89] Ferrero S, Racca A, Tafi E, Alessandri F, Venturini PL, Leone Roberti Maggiore U. Ulipristal Acetate before High Complexity Hysteroscopic Myomectomy: a Retrospective Comparative Study. Journal of Minimally Invasive Gynecology. 2016; 23: 390–395.
[90] Murji A, Wais M, Lee S, Pham A, Tai M, Liu G. A Multicenter Study Evaluating the Effect of Ulipristal Acetate during Myomectomy. Journal of Minimally Invasive Gynecology. 2018; 25: 514–521.
[91] Wen L, Tseng J, Wang P. Vaginal expulsion of a submucosal myoma during treatment with long-acting gonadotropin-releasing hormone agonist. Taiwanese Journal of Obstetrics & Gynecology. 2006; 45: 173–175.
[92] Yu KJ, Lai CR, Sheu MH. Spontaneous expulsion of a uterine submucosal leiomyoma after administration of a gonadotropin-releasing hormone agonist. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2001; 96: 223–225.
[93] Kriplani A, Agarwal N, Parul D, Bhatla N, Saxena AK. Prolapsed leiomyoma with severe haemorrhage after GnRH analogue therapy. Journal of Obstetrics and Gynaecology. 2002; 22: 449–451.
[94] Willame A, Marci R, Petignat P, Dubuisson J. Myoma migration: an unexpected 'effect' with Ulipristal acetate treatment. European Review for Medical and Pharmacological Sciences. 2016; 20: 1439–44.
[95] Chantraine F, Poismans G, Nwachuku J, Bestel E, Nisolle M. Expulsion of a uterine myoma in a patient treated with ulipristal acetate. Clinical Case Reports. 2015; 3: 240–242.
[96] Singh SS, Belland L, Leyland N, von Riedemann S, Murji A. The past, present, and future of selective progesterone receptor modulators in the management of uterine fibroids. American Journal of Obstetrics and Gynecology. 2018; 218: 563–572.e1.
[97] Hoss M. IUD benefits …here is one more. Evidence-Based Practice. 2020; 23: 4–4.
[98] Lewis BV. Guidelines for endometrial ablation. British Society of Gynaecological Endoscopy. British Journal of Obstetrics and Gynaecology. 1994; 101: 470–473.