Use of GnRH Analogues in the Reduction of Submucous Fibroid for Surgical Hysteroscopy: A Systematic Review and Meta-Analysis

Uso de análogo de GnRH na redução de mioma submucoso na histeroscopia cirúrgica: Revisão sistemática e meta-análise

Thayane Delazari Corrêa[1] Isabela Maciel Caetano[1] Pedro Henrique Tannure Saraiva[2] Maurício Bechara Noviello[3] Admário Silva Santos Filho[1]

[1] Ginecology Department, Hospital das Clínicas, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil
[2] Ginecology Department, Hospital Metropolitano Odilon Behrens, Belo Horizonte, MG, Brazil
[3] Ginecology Department, Faculdade da Saúde e Ecologia Humana and Faculdade de Ciências Médicas de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

Address for correspondence Isabela Maciel Caetano, Rua Juramento, 1464, Belo Horizonte, MG, 30285-408, Brazil (e-mail: isabelamcaetano@gmail.com).

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Abstract

Objective Gonadotropin-releasing hormone analogues (GnRH-a) have been used preoperatively before hysteroscopic myomectomy to decrease the size and vascularization of the myomas, but evidence to support this practice is weak. Our objective was to analyze the use of GnRH-a in the reduction of submucous fibroid as a facilitator for surgical hysteroscopy from published clinical trials.

Data sources Studies from electronic databases (Pubmed, Scielo, EMBASE, Scopus, PROSPERO), published between 1980 and December 2018. The keywords used were *fibroid*, *GnRH analogue*, *submucous*, *histeroscopy*, *histeroscopic resection* and their correspondents in Portuguese.

Study selection The inclusion criteria were controlled trials that evaluated the GnRH-a treatment before hysteroscopic resection of submucous myomas. Four clinical trials were included in the meta-analysis.

Data collection Two review authors extracted the data without modification of the original data, using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third person.

Data synthesis The present meta-analysis included a total of 213 women and showed no statistically significant differences in the use of GnRH-a compared with the control group for complete resection of submucous myoma (relative risk [RR]: 0.94; 95% confidence interval [CI]: 0.80–1.11); operative time (mean difference [MD]: - 3.81; 95% CI : - 3.81–2.13); fluid absorption (MD: - 65.90; 95%CI: - 9.75–2.13); or complications (RR 0.92; 95%CI: 0.18–4.82).

Keywords

- GnRH analogue
- fibroid
- hysteroscopy
- myoma resection
- submucous fibroid

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Conclusion The present review did not support the routine preoperative use of GnRH-a prior to hysteroscopic myomectomy. However, it is not possible to determine its inferiority when compared with the other methods due to the heterogeneity of existing studies and the small sample size.

Resumo

Objetivo Análogos de hormônio liberador de gonadotrofina (GnRH-a) têm sido usados no pré-operatório de miomectomia histeroscópica para reduzir o tamanho e vascularização dos miomas, mas a evidência que suporta essa prática é fraca. Nosso objetivo foi analisar o uso de GnRH-a na redução do mioma submucoso como um facilitador de histeroscopia cirúrgica em ensaios clínicos publicados.

Fonte de dados Estudos de bases de dados eletrônicas (Pubmed, Scielo, EMBASE, Scopus, PROSPERO), publicados entre 1980 e dezembro de 2018. As palavras-chave usadas foram *fibroid*, *GnRH analogue*, *submucous*, *histeroscopy*, *histeroscopic resection* e seus correspondentes em português.

Seleção dos estudos Os critérios de inclusão foram ensaios clínicos controlados que avaliaram o tratamento com GnRH-a antes da ressecção histeroscópica de miomas submucosos. Quatro ensaios clínicos foram incluídos na meta-análise

Coleta de dados Dois autores revisores extraíram os dados, sem modificarem os dados originais, usando a forma acordada. Nós resolvemos as discrepâncias através de discussão ou, se necessário, consultando um terceiro autor.

Síntese dos dados A meta-análise incluiu um total de 213 mulheres e não demonstrou diferença estatisticamente significativa no uso de GnRH-a comparado com o grupo controle para ressecção completa de mioma submucoso (risco relativo [RR]: 0.94. índice de confiança [IC] 95%: 0.80–1.11); tempo cirúrgico (diferença de média [MD]: - 3.81; IC95%: -3.81–2.13); absorção de fluidos (MD: - 65.90; IC95%: - 9.75–2.13); ou complicações (RR 0.92; IC95%: 0.18–4.82).

Conclusão A presente revisão sistemática não suporta o uso pré-operatório rotineiro de GnRH-a antes de miomectomia histeroscópica. No entanto, não é possível determinar sua inferioridade quando comparado aos outros métodos devido à heterogeneidade dos estudos existentes e ao pequeno tamanho da amostra.

Palavras-chave
- mioma
- análogo GnRH
- submucoso
- histeroscopia
- ressecção histeroscópica

Introduction

Uterine myomas are the most common benign tumor of the female genital tract.[1] Myomas could be classified into subserous, intramural, and submucous types according to their location in the uterus. Clinical presentation of the submucous myoma includes menorrhagia, metrorrhagia, dysmenorrhea, infertility, and repeated abortion.[2,3]

The surgery goal is the complete removal of the fibroid – reducing the chance of recurrence and regrowth.[3] Submucous fibroids distort the endometrial cavity and typically cause heavy or irregular menstrual bleeding.[4] The advantages of hysteroscopic resection of submucous myomas are reduced trauma, shorter hospitalization and recovery times, as well as decreased risk of adhesion formation. Gonadotropin-releasing hormone analogues (GnRH-a) have been used preoperatively before hysteroscopic myomectomy to decrease the size and vascularization of the myomas (therefore rendering surgery faster), but robust evidence to support this practice is weak.[5]

Fibroid growth is stimulated by estrogen. Gonadotropin-hormone releasing analogues induce a state of hypoestrogenism that shrinks fibroids, but has undoubtedly unpleasant side effects such as hot flushes and night sweats.[6,7]

The available literature on the issue of medical treatment before hysteroscopic resection is scanty, mainly consisting of uncontrolled and relatively small and nonrandomized trials, which are in contrast with each other and possibly biased.[7]

A Cochrane review evaluated the role of preoperative medical therapy before surgery for uterine fibroids. They compared GnRH-a, progestin, selective progesterone receptors modulators (SPRMs), selective estrogen receptor modulators (SERMs), dopamine agonists, estrogen receptor antagonists and placebo before myomectomy and hysterectomy. They did not specifically compare GnRH-a and placebo prior to hysteroscopic resection of submucous fibroid.[6]

In 2014, a systematic review comparing GnRH-a and no treatment before hysteroscopic resection of submucous fibroids found no significant benefit of preoperative GnRH-a before hysteroscopic resection of submucosal myomas. It used two randomized controlled trials (RCTs) for the meta-analysis.[8,9] Since then, other trials were conducted.

As the majority of previous studies of use of GnRH-a preoperatively for hysteroscopic resection of submucous fibroids have been relatively small and not randomized, our objective was to analyze the use of GnRH-a in the reduction of submucous fibroid as a facilitator for surgical hysteroscopy from published clinical trials and to compare its efficacy with other methods.

Methods

Search Strategy

The review protocol was established by two investigators (Corrêa T. H. and Caetano I. M.) prior to commencement and two authors (Corrêa T. H. and Caetano I. M.).identified trials by searching independently the literature in electronic databases. We used the following sources for the identification of trials: Pubmed, Scielo, LILACS, EMBASE, Scopus, the PROSPERO International Prospective Register of Systematic Reviews and Cochrane Central Register of Controlled Trials, between 1980 and June 2019. We also screened the reference lists of identified articles for additional studies, according to the review eligibility criteria.

The review was based only on published literature. The following Medical Subject headings (MeSH terms) and all combinations of these words were used: *fibroid*, *GnRH analogue*, *submucous*, *histeroscopy*, *histeroscopic resection* and their correspondents in Portuguese, *mioma*, *análogo GnRH*, *submucoso*, *histeroscopia* and *ressecção histeroscópica*. We restricted our search to papers published in the English and Portuguese languages. Agreement regarding potential relevance was reached by discussion with a third reviewer (Santos Filho A. S.) and the full text of all relevant trial reports identified through the searching activities described above was reviewed.

Primary and secondary outcomes were defined before data extraction. The primary outcome was complete resection of the fibroid. The secondary outcomes were operating time, complications (excessive intraoperative bleeding, uterine perforation, bowel injury), fluid absorption and adverse effects.

Study Selection

The review was undertaken by two reviewers (Corrêa, T.D and Saraiva, P. H. T.). The search strategy described previously was employed to obtain titles, and, where possible, abstracts of studies that were potentially relevant to the review. The titles and abstracts were screened by Corrêa, T.D and Saraiva, P. H. T., who discarded studies that were clearly ineligible but aimed to be overly inclusive rather than risk losing relevant studies. Copies of the full articles were obtained. Both reviewers independently assessed whether the studies met the inclusion criteria. Disagreements were resolved by referring to a third reviewer (Santos Filho A. S.) for discussion. Further information was sought from the authors whose papers contained insufficient information to make a decision about eligibility.

The inclusion criteria were: controlled trials that evaluated the GnRH-a treatment before hysteroscopic resection of submucous myomas. The exclusion criteria were: observational studies, review or retrospective studies, articles published outside the period described and those with non-hysteroscopic myomectomy.

Data Extraction and Risk of Bias Assessment

We designed a form to extract data. For eligible trials, the two reviewers independently abstracted data for each eligible study using a standardized electronic data abstraction form. Data elements included the following: trial identifiers; study methods (including enrollment and withdrawal numbers); patient characteristics; interventions; outcomes; and comments. We reported the results of trial selection using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (►**Fig. 1**).

We performed an assessment of all RCTs using the Cochrane 'risk of bias' tool according to the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[10] Two review authors (Corrêa, T.D and Saraiva, P. H. T.) worked independently to assess each element of potential bias listed below as high (any nonrandom process), low (any truly random process), or unclear risk of bias.

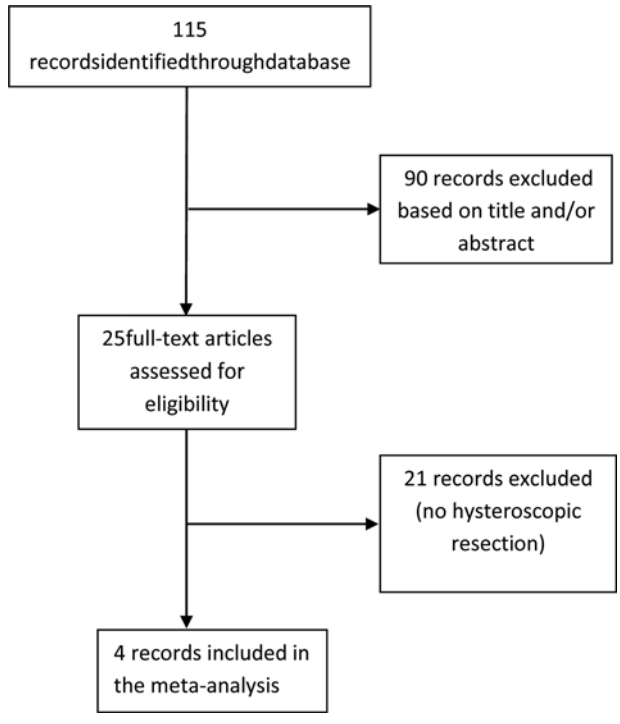

Fig. 1 Flow diagram of identified studies.

Disagreements were resolved by discussion or by involving a third assessor.

The Cochrane tool for assessing risk of bias was used, which included the following domains: selection bias (random sequence generation and allocation concealment); performance bias (blinding of participants and personnel); detection bias (blinding of outcome assessment); attrition bias (incomplete outcome data); reporting bias (selective reporting); other bias (checking for bias due to problems not covered by others above).

Data Analysis

Data was entered into Review Manager 5.3 software (The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark)[11] and checked for accuracy. For continuous outcomes, we recorded the mean, standard deviation (SD) and total number of participants in both the treatment and control groups and performed analyses using the mean difference (MD) with 95% confidence intervals (CIs). For dichotomous outcomes, we recorded the number of events and the total number of participants in both the treatment and control groups and reported the pooled risk ratio (RR) with a 95% CI. We used the Mantel–Haenzel method for combining dichotomous variables and inverse variance method for continuous variables.

The meta-analysis was reported following the PRISMA statement. The comparisons made among these publications were between GnRH-a and no-GnRH-a or placebo.

Heterogeneity between studies was tested with the I^2 Index. An $I^2 > 50\%$ was interpreted as moderate heterogeneity, and $I^2 > 80\%$ was considered considerable. A random-effects model was used for this meta-analysis to produce an overall summary, when we detected a substantial statistical heterogeneity, sufficient to expect that the underlying treatment effects differed between trials and an average treatment effect across trials was considered clinically meaningful. When heterogeneity was $< 50\%$, we used the fixed-effects model.

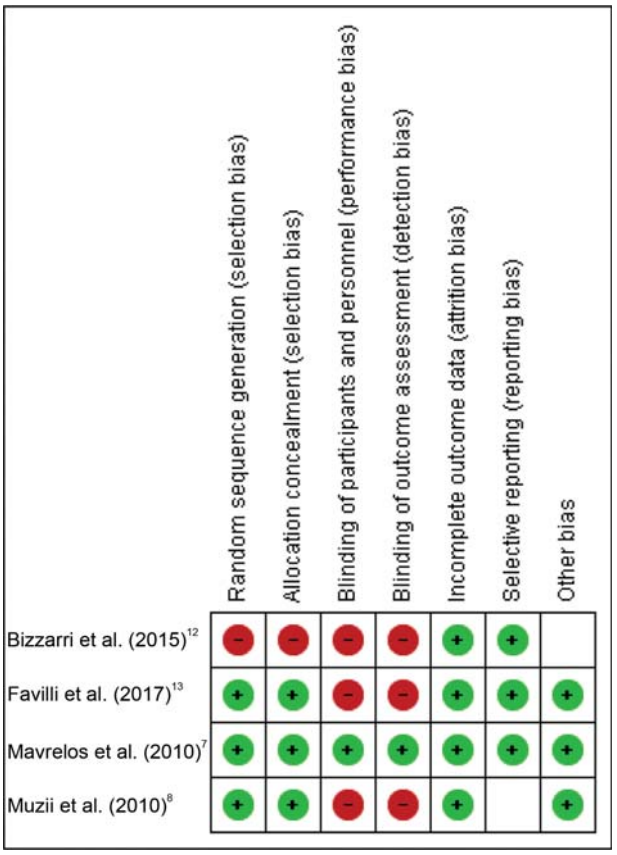

Fig. 3 Summary of risk of bias for each trials. Minus sign: high risk of bias; plus sign: low risk of bias; blank space or question mark: unclear risk of bias.

Results

Study Selection and Study Characteristics

►**Fig. 1** shows the flow diagram (PRISMA template) of information through the different phases of the review.

A total of 115 articles were found, and the ones which did not meet the criteria of the present study were excluded. A total of 25 studies were screened; 21 including nonhysteroscopic resection were excluded. Four clinical trials were

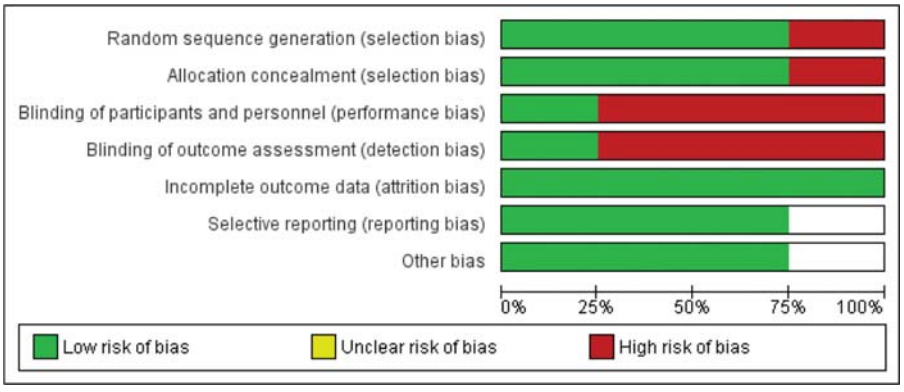

Fig. 2 Summary of risk of bias for all trials. Risk-of-bias graph about each risk-of-bias item presented as percentages across all included studies.

therefore included in the meta-analysis. Two studies are unpublished, planned or ongoing. At least 10 trials for inclusion in a meta-analysis were not identified, so we did not explore potential publication bias (small trial bias) by generating a funnel plot and using a linear regression test. The overall risk of bias is shown on ►**Figs. 2** and **3**.

Muzii et al[8] is a multicenter randomized controlled trial of 39 women with abnormal uterine bleeding caused by submucous fibroids (1 or 2 submucous fibroids and size between 10 mm and 35 mm) and scheduled for hysteroscopic resection. The recruited women were randomized into two groups: women who received GnRH-a (triptorelin 3.75 mg) for 8 weeks prior to surgery, and women who received no treatment prior to surgery. The authors followed up women at 1, 3, 6 and 12 months. In that cohort, no patients presented G2 myomas, but only G1 and G0, and the main outcome was the duration of the procedure in minutes.

Mavrelos et al[7] performed a double-blinded placebo-controlled trial at a single center in London and 47 women were analyzed with submucous fibroids (single or multiple fibroids of any size) on ultrasound requiring hysteroscopic resection. They were randomized in two groups: women who received preoperative GnRH-a (3.6 mg goserelin) for 12 weeks prior to planned surgery, and women who received placebo (identical injections; 5 ml of 1% lignocaine) for similar duration prior to surgery. After resection of the fibroid, women of both groups were reviewed in the clinic 6 weeks after the procedure.

Bizzarri et al[12] is a single-center nonrandomized controlled trial involving 46 subjects with premenopausal women with FIGO type 0, 1 or 2 myomas with diameter between 20 and 35 mm conducted in Genova.[13] Treatment allocation was decided on the basis of patient preferences, who were informed of the potential benefits and adverse effects of each

Box 1 Descriptive Data of the Included Trials

	Muzii et al. (2010)[8]	Mavrelos et al. (2010)[7]	Bizzarri et al. (2015)[12]	Favilli et al. (2017)[14]
Study location	Rome	London	Genova	Rome
Number of centers	3	1	1	1
Sample size	39	47	46	99
Lost to follow-up	0	7	3	15
Intervention	Preoperative GnRH analogues for 8 weeks Control: no preoperative GnRH	Preoperative GnRH analogues for 12 weeks Control: placebo (5ml of 1% lignocaine)	Preoperative GnRH analogues for 12 weeks Control: no preoperative GnRH	Preoperative GnRH analogues for 12 weeks Control: no preoperative GnRH
Medication and route of administration	Triptorelin 3.75 mg intramuscular injection	Goserelin 3.6 mg Subcutaneous injection	Triptorelin 3.75 mg intramuscular injection	Triptorelin 375 mg intramuscular injection
Outcomes	Duration of the procedure in minutes, fluid absorption, difficulty of the operation, surgeon satisfaction with the procedure, intra- and postoperative complications, postoperative pain, patient satisfaction	Completeness of fibroid resection. Duration of the TCRM, fluid deficit recorded at TCRM, resolution of symptoms postoperatively, number of subsequent fibroid related operations.	Assess the incidence of incomplete resection in the study groups. Surgical and hysteroscopy time, volume of absorbed fluid, complications, operative difficulty, postoperative patient pain and satisfaction, changes in myoma volume caused by hormonal therapies.	Assess if cold loop hysteroscopic myomectomy in a single surgical procedure was facilitated by preoperative GnRH analogue administration. Distension liquid absorption, duration of the procedure
Inclusion criteria	Submucous myomas diagnosed by transvaginal ultrasonography, with a diameter between 10 and 35 mm, and a grade G0 or G1 according to the European Society for Gynecological Endoscopy classification	History of heavy and/or irregular menstrual periods and diagnosis of a Type I or Type II submucous fibroid on ultrasound	Premenopausal women with FIGO type 0, 1 or 2 myomas with diameter between 20 and 35 mm.	Women with a diagnosis of a single submucous myoma without any other intracavitary pathology and a grade G0, G1 or G2 according to the European Society for Gynecological Endoscopy classification
Exclusion criteria	Present or past history of cancer, preoperative clinical suspicion of associated multiple or large polyps (sonographic estimate being $>$ 20 mm in largest diameter), planned associated nonhysteroscopic surgical procedures, or $>$ 2 myomas requiring hysteroscopic resection.	Not reported	Associated polyps or other pathologies requiring hysteroscopic treatment (such as uterine septa), previous incomplete myoma resection, associated nonhysteroscopic surgical procedures, $>$ 2 myomas requiring hysteroscopic resection.	Patients with multiple myomas, endometrial polyps, scheduled combined surgical procedures (hysteroscopy with laparoscopy), a present or past history of cancer, ongoing pregnancy, and a postmenopausal status.

Abbreviation: TCRM, transversal resection of myoma.
Data are presented as total number (number in the GnRH analogue group versus number in the control group).

Table 1 Primary and secondary outcomes

	Muzii et al. (2010)[8]	Mavrelo et al. (2010)[7]	Bizzarri et al. (2015)[12]	Favilli et al. (2017)[14]	Total	I^2	RR or MD (95% CI)
Sample size	39 (20 vs 19)	47 (24 vs 23)	43 (20 vs 23)	84 (42 vs 42)	213	–	–
Complete resection of the fibroid	20/20 (100%) vs 19/19 (100%)	14/24 (58.3%) vs 16/23 (69.5%)	20/20 (100%) vs 22/23 (95.6%)	31/42 (73.8%) vs 39/42 (92.9%)	85/106 (80.2%) vs 96/107 (89.7%)	74%	0.90 (0.81 to 1.00)
Operating time	M 15.9 (SD 3.1) vs M 21.3 (SD 4)	M 30.1 (SD 11.7) vs M 33.8 (SD 22.7)	M 26.4 (SD 6.4) vs M 36.7 (SD 8.4)	M 26.62 (SD 15.308) vs M 20.71 (SD 15.052)	–	82%	−3.81 [−9.75 to 2.13]
Complications*	2/20 (10%) vs 1/19 (5.2%)	1/21 (4.8%) vs 2/19 (10.5%)**	0/20 (0%) vs 0/23 (0%)	0/42 (0%) vs 0/42 (0%)	3/103 (2.9%) vs 3/103 (2.9%)	0%	0.92 [0.18 to 4.82]
Fluid absorption	M 378 (SD 137) vs M 566 (SD 199)	M 662.5 (SD 668.3) vs M 568.75 (SD 785.8)	M 340 (SD 112) vs M 457 (SD 139)	M 135.85 (SD 217.2) vs M 62.44 (SD 130.66)	–	85%	−65.90 [−207.79 to 75.99]

Abbreviations: CI, confidence interval; M, mean; MD, mean difference; RR, relative risk; SD, standard deviation.
Data are presented as total number (number in the GnRH analogue group versus number in the no-GnRH analogue group) with percentage.
*Complications (excessive intraoperative bleeding, uterine perforation, bowel injury).
**1 woman in the placebo group had abdominal myomectomy and 3 women were not operated. In the GnRH analogue group, 1 woman had abdominal myomectomy, 1 had allergic reaction and 1 was not operated.

hormonal therapy. Patients underwent either direct surgery (group S) or received a 3-month preoperative treatment with: triptorelin (3.75 mg intramuscular injection every 28 days; group T), letrozole (2.5 mg/day; group L) or ulipristal acetate (UPA) (5 mg/day; group U). For our meta-analysis, we considered only data of groups S and T.

Favilli et al[14] performed a single-center randomized controlled trial at Rome with 99 participants, who had the diagnosis of a single submucous myoma without any other intracavitary pathology. Patients were analyzed according to the type of myoma, G0, G1 or G2, according to the European Society for Gynecological Endoscopy classification.[14,15] Women were randomly assigned to non-pharmacologic treatment or preoperative GnRH-a treatment, where three injections of triptorelin 3.75 mg were given 28 days apart. Afterwards, they were submitted to a cold loop hysteroscopic myomectomy. Further details are provided in ►**Box 1**.

Synthesis of Results

►**Table 1** shows the pooled results for the primary and the secondary outcomes.

Although the studies have similar outlines, their results were different. Muzii et al[8] demonstrated that the use of medical treatment before hysteroscopic resection of G0–G1 10–35 mm myomas is associated with shorter operative times, less fluid absorption, and better surgeon satisfaction, with similar patient satisfaction and reduction of symptoms, compared with no preoperative medical treatment. According to these findings, Bizzarri et al[12] presented that preoperative treatment with triptorelin decreases the hysteroscopy time and the volume of fluid absorbed during hysteroscopic resection of uterine submucosal myomas with diameter between 20 and 35 mm (FIGO type 0, 1 or 2). On the other hand, Mavrelos et al[7] do not support routine administration of GnRH-a before transcervical resection of fibroid as they did not identify any benefit in such treatment (Complete resection: 58.3% in the GnRH-a group versus 69.5% in the no-GnRH-a; relative risk [RR]: 0.79; 95% confidence interval [CI]: -0.55–1.13). Favilli et al[14] showed that GnRH-a administration does not facilitate the completion of cold loop hysteroscopic myomectomy in a single surgical procedure in G2 myomas (according to the European Society for Gynecological Endoscopy classification), and it is correlated with a longer duration of the surgery.[14,15] Considering side effects, in the trial by Muzii et al,[8] patients in the GnRH pretreatment group experienced hot flushes (80% mild and 20% moderate), which were, in any case, well tolerated. Bizzarri et al[12] demonstrated that three patients interrupted the hormonal therapy because of adverse effects and requested to undergo immediate surgery, and patients treated with triptorelin and letrozole reported some adverse effects. However, they did not specify the side effects or the group to which they belong.

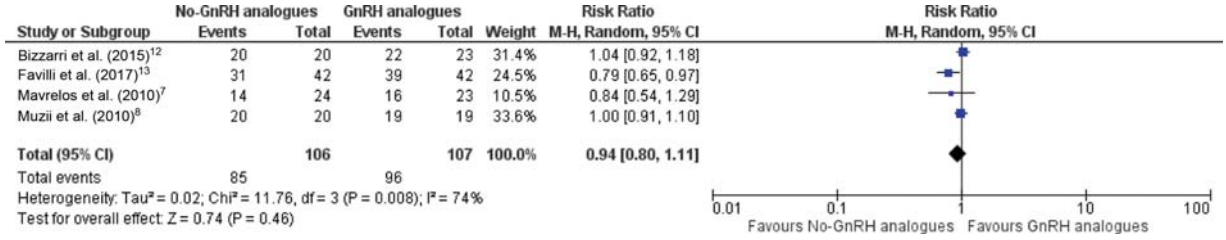

Fig. 4 Meta-analysis of included studies, for complete resection of submucous myoma.

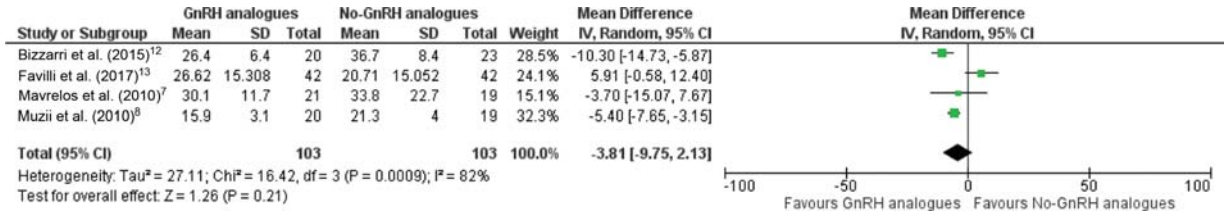

Fig. 5 Meta-analysis of included studies, for operative time (in minutes).

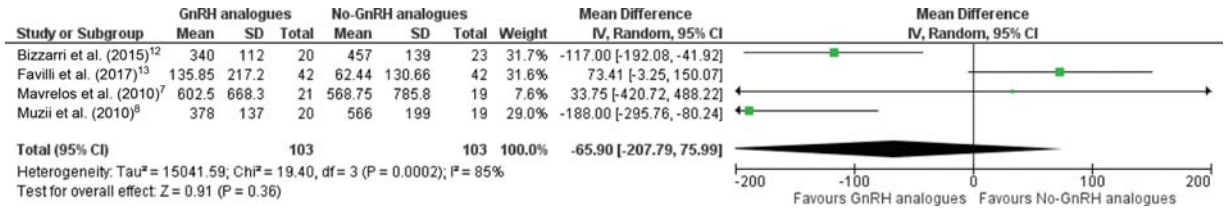

Fig. 6 Meta-analysis of included studies, for fluid absorption (in mL).

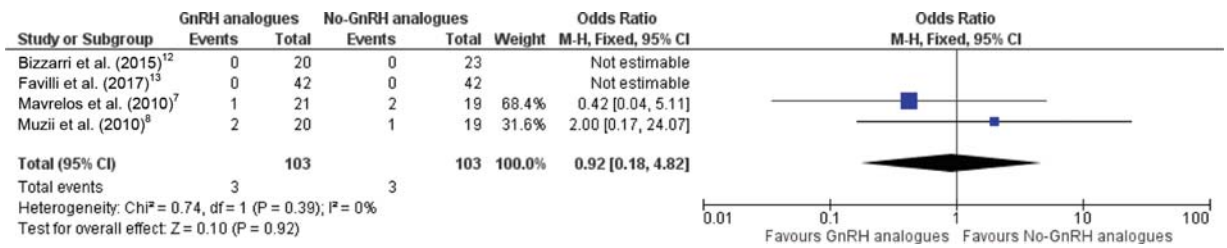

Fig. 7 Meta-analysis of included studies, for complications (excessive intraoperative bleeding, uterine perforation, bowel injury).

Meta-Analysis

The meta-analysis was done as specified in the protocol. The meta-analysis showed no statistically significant differences in the use of GnRH-a compared with the control group (RR: 0.94; 95%CI: 0.80–1.11) for complete resection of submucous myoma, as exposed in ►**Fig. 4**.

Considering the secondary outcomes, the meta-analysis showed no statistically significant difference in the use of GnRH-a compared with the group that did not use the GnRH-a when considering operative time (mean difference [MD]: -3.81; 95%CI: -3.81–2.13), fluid absorption (MD: -65.90; 95%CI: -9.75–2.13) or complications (RR 0.92; 95%CI: 0.18–4.82), as exposed in ►**Figs. 5**, **6** and **7**.

Discussion

Main Findings

The meta-analysis obtained after analysis and comparison of results from 4 clinical trials – Mavrelos et al,[7] Muzii et al,[8] Bizzarri et al[12] and Favilli et al[14]–including a total of 213 women, showed that there was no statistically significant difference between the group that used GnRH-a and the group that did not use it. Therefore, with regard to the primary outcome evaluated, that is, complete resection of submucous myoma, the use of GnRH-a was not effective. Our meta-analysis included level 1 data from 4 appropriately powered, well-designed clinical trials. Pooled data available to date point to a lack of efficacy of the GnRH-a pretreatment before myomectomy resection.

We also searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports and found 2 studies.

Comparison with the Existing Literature

The present meta-analysis showed no advantage of administering GnRH-a preoperatively before hysteroscopic resection of fibroids over no GnRH-a preoperatively, in accordance

with Mavrelos et al,[7] Muzii et al[8] and Bizzarri et al.[12] Favilli et al[14] revealed a significantly longer duration of surgery and a greater number of repeated procedures in the GnRH-a group when compared with the control group. It is possible that Favilli et al[14] found a different result because they used electrical powered loop for the resection of the intracavitary component of the myoma and a cold loop for the cleavage plane between the myoma and the pseudocapsule and the detachment of the intramural portion of the myoma from its pseudocapsule. The other clinical trials used exclusively electrical powered loop.

Our data supports earlier findings of a meta-analysis of 2 trials, including 86 women with submucous fibroids, when preoperative GnRH-a were not more effective than placebo/no treatment in terms of symptom relief, complications and ease of surgery. However, our study did not show benefit of GnRH-a therapy in terms of reduction in both operating time and fluid absorption, as shown in the previous meta-analysis.[9]

Fluid volume depends directly on the duration of the procedure. Another rationale for the administration of preoperative GnRH-a is a reduction of fluid deficit. A study found that preoperative administration of GnRH-a is associated with reduced fluid deficit. However, the criteria for GnRH-a administration were not listed and the operating surgeon was not blinded to the treatment, which may have introduced an element of bias.[16] Muzii et al[8] and Bizzarri et al[12] revealed that the procedure was faster in the intervention group. Therefore, they also revealed that the intervention group had less fluid absorption.

The four clinical trials had different criteria used to establish the end of the procedure.[7,8,12,14] Favilli et al[14] conducted the only clinical trial that used clearly vision of the pseudocapsule in the uterine cavity as the criterium to stop the procedure. The use of GnRh-a decreases myoma size, but at the same time causes an alteration to the structure of the pseudocapsule, masking the correct cleavage plan between the myoma and its pseudocapsule.[17] It is possible that it prolonged the procedures in the intervention group conducted by Favilli et al.[14]

As we already know, theoretically, GnRH-a pretreatment may render surgery easier, by means of a reduction of the myoma size and vascularization and possibly a thinning of the endometrium. Additional advantages of a preoperative treatment are the correction of anemia, if present, and the possibility of performing surgery at any time, because the patient is amenorrheic, with clear organization benefits.[5] A meta-analysis of RCTs comparing GnRH-a administration before abdominal myomectomy showed that women in the treatment group had significantly higher preoperative hemoglobin concentration compared with the control group. Similar benefits are also likely to occur in women scheduled for hysteroscopic surgery.[6]

On the other hand, a retrospective study affirmed that the preoperative treatment with GnRH-a can be associated with a prolonged operative time, because the step of the cervical dilation can be more uncomfortable in a hypoestrogenic patient.[18]

In contrast, a controlled study of 53 patients found that preoperative GnRH reduced operative time and the volume of distension medium used.[19] However, it is unclear from the published paper whether the treatment and control groups were balanced in terms of the morphological characteristics of the fibroids submitted to hysteroscopic resection. Moreover, they did not include women with fibroids > 3 cm in diameter, which is the group of women that we would expect to derive the maximum benefit from preoperative GnRH-a.[19]

Considering surgery complications, the meta-analysis revealed that there was no statistic difference in patients who received GnRH-a preoperatively when compared with patients who did not, in accordance with Mavrelos et al[7] and with Muzii et al.[8] The other two clinical trials used for the meta-analysis did not use the complication rates as an outcome of the study.

In the RCT conducted by Mavrelos et al,[7] one procedure was abandoned because of excessive bleeding and one was abandoned because of a fluid deficit of 1.5 L.[7] One woman who received GnRH-a suffered a uterine perforation and bowel injury that necessitated laparotomy and repair. Two women in the placebo group suffered excessive intraoperative bleeding, which was controlled by the insertion of a Foley catheter in one and by cervical suture in the other case. In the RCT conducted by Muzii et al,[8] no cases of uterine perforation or fluid overload occurred in either group. Minimal complications recorded were three cases of minor cervical tears (not requiring any suture placement), two of which occurred in the GnRH-a group.

Strengths and Limitations

One of the strengths of the present review is that we followed the Cochrane Handbook of Systematic Review for Intervention closely in conducting the present review.[10] Our meta-analysis included all studies published to date on the topic and included > 200 women. Intent-to-treat analysis was used and publication bias could not be assessed given the small (< 10) number of studies included.

We encountered a high heterogeneity in the meta-analysis of the primary outcome for complete resection of submucous myoma (74%), operative time (82%) and fluid absorption (85%). On the other hand, for complications, heterogeneity was low (0%).

Only 4 trials were included in the meta-analysis. The small number of available studies and the variation of their sample size could have decreased the forcefulness of the meta-analysis with an increased chance of bias. Other limitations of our study are intrinsic to the limitations of the included RCTs. Just one of the included studies was double-blind – Mavrelos et al.[7] Bizzarri et al[12] was a non-randomized controlled trial. Since the patients and the surgeons were not blinded, performance and detection biases could possibly creep in.

Furthermore, the outcome assessment for intraoperative parameters, such as complete resection of fibroid, depends on the experience of the surgeon. Ideally, a total resection should be confirmed by ultrasound and by the symptomatology of the patients during follow-up visits. Thus, studies should include and report ultrasound findings and follow-up of the patients to

avoid biases. In our review, the included studies did not give ultrasound details in the postoperative period and long-term follow-up in descriptive manner, but Favilli et al[14] reported an outpatient diagnostic hysteroscopy 2 months after the surgical procedure. Taking in consideration that the visualization of the myoma fovea could be "subjective" and at risk of bias, a diagnostic hysteroscopy has more diagnostic power than ultrasound regarding the follow-up of residual myomas.[14]

Muzii et al[8] and Bizzarri et al[12] evaluated, respectively, myomas between 10 and 35 mm and 20 and 35 mm. Hysteroscopic resection of large fibroids may involve increased perioperative complications and/or require more than one procedure for symptomatic relief.[20]

The size of the submucous myoma may contribute to determine if the myomectomy is preferable through hysteroscopy or laparotomy. As discussed above, GnRH-a reduces the size of the myoma. A potential use of GnRH-a is to reduce the size of larger myomas and change the access way of the myomectomy – from laparotomy to hysteroscopy – reducing trauma, hospitalization and recovery times, as well as decreasing the risk of adhesion formation.

Implications

From the data obtained by the present meta-analysis, it is observed that the GnRH-a is not effective as a pretreatment in the hysteroscopic resection of submucous fibroid, as the proportion of patients undergoing complete resection of fibroids was not affected by preoperative administration of GnRH-a. Thus, there is still insufficient evidence to support the use of this tool in practice as an attempt to reduce the incidence of surgical complications. Moreover, it might be beneficial when administered preoperatively in anemic patients.

Conclusion

From the analyzed studies, we can conclude that the preoperative use of GnRH-a seems to show a lack of efficacy to support a routine use prior to hysteroscopic resection of submucous fibroids. However, it is not possible to determine its inferiority when compared with the other methods due to the heterogeneity of existing studies and the small sample size. Future studies should preferably be blinded and define the completeness of fibroid resection – assessment of the surgeon, clinical profile of the patient pre- and postsurgery, preoperative and intraoperative effects, ultrasound follow-up and reduction in the size of larger myomas, which could possibly change the access way of the myomectomy - from laparotomy to hysteroscopy. More studies are necessary to evaluate the use of GnRH-a with this specific purpose.

Contributors

All of the authors contributed with the project and data interpretation, the writing of the article, the critical review of the intellectual content, and with the final approval of the version to be published.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Okolo S. Incidence, aetiology and epidemiology of uterine fibroids. Best Pract Res Clin Obstet Gynaecol. 2008;22(04):571–588. Doi: 10.1016/j.bpobgyn.2008.04.002
2 Narayan R, Rajat Goswamy K. Treatment of submucous fibroids, and outcome of assisted conception. J Am Assoc Gynecol Laparosc. 1994;1(4 Pt 1):307–311. Doi: 10.1016/s1074-3804(05)80793-5
3 Pritts EA. Fibroids and infertility: a systematic review of the evidence. Obstet Gynecol Surv. 2001;56(08):483–491. Doi: 10.1097/00006254-200108000-00022
4 Clevenger-Hoeft M, Syrop CH, Stovall DW, Van Voorhis BJ. Sonohysterography in premenopausal women with and without abnormal bleeding. Obstet Gynecol. 1999;94(04):516–520. Doi: 10.1016/s0029-7844(99)00345-2
5 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. Hum Reprod. 1998;13(09):2592–2597. Doi: 10.1093/humrep/13.9.2592
6 Lethaby A, Puscasiu L, Vollenhoven B. Preoperative medical therapy before surgery for uterine fibroids. Cochrane Database Syst Rev. 2017;11:CD000547. Doi: 10.1002/14651858.CD000547.pub2
7 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. Hum Reprod. 2010;25(09):2264–2269. Doi: 10.1093/humrep/deq188
8 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. Fertil Steril. 2010;94(04):1496–1499. Doi: 10.1016/j.fertnstert.2009.05.070
9 Kamath MS, Kalampokas EE, Kalampokas TE. Use of GnRH analogues pre-operatively for hysteroscopic resection of submucous fibroids: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2014;177:11–18. Doi: 10.1016/j.ejogrb.2014.03.009
10 Higgins JP, Green S, Eds. Cochrane handbook for systematic reviews of interventions. Chichester: John Wiley & Sons; 2017
11 Review Manager (RevMan). Version 5.3 [software]. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014
12 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. Eur J Obstet Gynecol Reprod Biol. 2015;192:22–26. Doi: 10.1016/j.ejogrb.2015.06.018
13 Munro MG, Critchley HOD, Fraser IS; FIGO Menstrual Disorders Working Group. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. Fertil Steril. 2011;95(07):2204–2208, 2208.e1–2208.e3. Doi: 10.1016/j.fertnstert.2011.03.079
14 Favilli A, Mazzon I, Grasso M, Horvath S, Bini V, Di Renzo GC, Gerli S, et al. Intraoperative effect of preoperative gonadotropin-releasing hormone analogue administration in women undergoing cold loop hysteroscopic myomectomy: a randomized controlled trial. J Minim Invasive Gynecol. 2018;25(04):706–714. Doi: 10.1016/j.jmig.2017.11.011
15 Wamsteker K, Emanuel MH, de Kruif JH. Transcervical hysteroscopic resection of submucous fibroids for abnormal uterine bleeding: results regarding the degree of intramural extension. Obstet Gynecol. 1993;82(05):736–740
16 Emanuel MH, Hart A, Wamsteker K, Lammes F. An analysis of fluid loss during transcervical resection of submucous myomas. Fertil Steril. 1997;68(05):881–886. Doi: 10.1016/s0015-0282(97)00335-x

17 De Falco M, Staibano S, Mascolo M, et al. Leiomyoma pseudocapsule after pre-surgical treatment with gonadotropin-releasing hormone agonists: relationship between clinical features and immunohistochemical changes. Eur J Obstet Gynecol Reprod Biol. 2009;144(01):44–47. Doi: 10.1016/j.ejogrb.2009.02.006

18 Campo S, Campo V, Gambadauro P. Short-term and long-term results of resectoscopic myomectomy with and without pretreatment with GnRH analogs in premenopausal women. Acta Obstet Gynecol Scand. 2005;84(08):756–760. Doi: 10.1111/j.0001-6349.2005.00690.x

19 Perino A, Chianchiano N, Petronio M, Cittadini E. Role of leuprolide acetate depot in hysteroscopic surgery: a controlled study. Fertil Steril. 1993;59(03):507–510. Doi: 10.1016/s0015-0282(16)55790-2

20 Bradley LD. Uterine fibroids (leiomyomas): hysteroscopic myomectomy [Internet]. 2019 [cited 2019 Apr 10]. Available from: https://www.uptodate.com/contents/uterine-fibroids-leiomyomas-hysteroscopic-myomectomy