

Pharmacological Treatment of Uterine Fibroids Prior to Surgery

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Abstract

Introduction: The uterine fibroid represents the most frequent benign tumor in women of reproductive age and the most frequent indication for hysterectomy worldwide. Sometimes medical treatment of uterine fibroids is desirable or necessary in order to improve the woman's clinical condition while surgical scheduling. In this review we assess the effect of pharmacological therapies on pre-operative, peri-operative and post-operative clinical outcomes of patients having hysterectomy or myomectomy due to uterine fibroids.

Method: Searches were conducted in MEDLINE, Pubmed, Wiley Online Library, the Cochrane Database, Directory of Open Access Journals and Google Scholar.

Results: There is wide evidence that Gonadotropin Release Hormone-agonists, Selective Progesterone Receptor Modulators and tranexamic acid reduce uterine bleeding, correct preoperative anemia, decrease fibroid size and reduce endometrial thickness and vascularization. They also improve patient's pre-surgical condition, enhance the visibility and reduce fluid absorption during operative hysteroscopy.

Conclusion: Clinicians can expect an improvement of patient's clinical condition and fibroid parameters by a pharmacological therapy prior to myomectomy or hysterectomy. This medical therapy can improve the safety of the planned surgery, enhances the chance to follow guidelines and recommendations for myoma resection and vaginal hysterectomy, and permits patients to reach their preferences towards uterine preserving therapies.

Keywords: Uterine fibroid, Myoma, Leiomyoma, Therapeutics, Review

Introduction

Uterine fibroid (UF) represents the most frequent benign tumor in women of reproductive age, related with high health care costs. In the USA, the disease has an estimated prevalence between 20 and 40%, and an estimated annual incidence of 0.92%. Although patients wait an average of 3,6 years before seeking treatment, in the year following the diagnosis, 94% of cases have at least one diagnostic or therapeutic procedure [1,2], and 41% saw more than 2 health care providers for diagnosis [3]. The direct and indirect costs of this attention oscillate between 5.89 to 34.37 billion dollars annually, reaching around half of the treating costs of diabetes mellitus. Thus, the economic impact of uterine fibroids is actually higher than breast, colon or ovarian cancer [4].

Surgery is the main treatment of UF, being the most frequent indication in 30% of all hysterectomies worldwide. In turn, hysterectomy is the second most common gynecological surgery after Caesarean section. For example, among 600000 hysterectomies performed each year in the USA, 200000 are due to fibroids [5], and 25% of American women over age 45 has had an hysterectomy [6,7-10]. In addition, data from the National Danish Hysterectomy Register reported that 16-18% of all hysterectomies performed during 1998 to 2006 presented complications, being perioperative bleeding the most frequent [11,12].

In this context, the need for safe and effective therapies to enhance results for patients having UF remains a reality. After decades of Gonadotropin Release Hormone-agonist (GnRH-a), there is growing evidence that other molecules like tranexamic acid and Selective Progesterone Receptor Modulators (SPRM), are alternative options for women who desire to preserve the uterus. Also they could improve the woman's clinical conditions, acting as an adjuvant therapy prior to UF resection or hysterectomy. Therefore, in this review we assess the evidence of available medical treatments on pre-

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operative, peri-operative and post-operative clinical outcomes of patients having hysterectomy or myomectomy due to uterine fibroids, to determinate which benefits could be expected when a pharmacological therapy is administrated prior to UF surgery.

Results

Evidence from studies comparing administration of GnRH-a versus placebo, or versus No- treatment [13], has shown that GnRH-a administration prior to hysterectomy produces an improvement of clinical parameters: increase in hemoglobin (Hb) and hematocrit levels; significant reduction of both uterine and fibroid volume; reduction in time of surgery; reduction of intraoperative blood loss; reduction of blood transfusion events; less stay-in hospital time; less vertical abdominal incision, and more vaginal surgery.

On the contrary, no significant differences in most of these clinical parameters were found when GnRH-a was administered prior to myomectomy, except a significant increase in the postoperative Hb-level [13,14-17]. Besides this effect, it is also reported that GnRH-a produces a more difficult cleavage plane during an abdominal myomectomy, extending the operation time [13-17]. But this time is significantly reduced when hysteroscopic resection is performed [18]. However, the difficulty of UF resection is not associated with differences in the pain-visual analogue scale [13].

Regarding total uterine and fibroid volume, different studies show reduction of the uterine volume with pre-surgical administration of GnRH-a, ulipristal acetate (UPA), raloxifene, fulvestrant or mifepristone [19,20]. Nonetheless, pre-surgical treatment with leuprolide acetate has a significantly greater reduction in uterine volume (-47% reduction), compared to either 5 mg of UPA (-20% reduction), or 10 mg of UPA (-22% reduction) [21]. Furthermore, UPA improves HB levels at different doses (5 or 10 mg) [21].

When fibroid volume reduction is evaluated, there are no significant differences between GnRH-a, cabergolin, raloxifene or UPA, but GnRH-a treatment is associated with a significantly greater fibroid reduction than any doses of fulvestrant [19,21-24].

Additionally, UPA is non-inferior to GnRH-a in controlling uterine bleeding, or in quality of life parameters, measured in a specific fibroid symptom questionnaire. Similarly to GnRH-a, uterine bleeding is controlled in more than 90% of patients receiving preoperatively a three-month course of UPA, but UPA controls bleeding faster than GnRH-a (5-7 day vs. 21 days). A subsequent correction of anemia is observed with both treatments [21,25,26]. Headache, sleep problems, hot flushes and bone sensitivity are more likely with GnRH-a therapy [13,19-24].

Regarding tranexamic acid, a recent randomized controlled trial with patients who received an hysterectomy for benign pathology demonstrate that, preoperative treatment with this drug significantly reduces the overall total blood loss, the incidence of substantial blood loss, and the need for reoperations owing to postoperative hemorrhage [27].

In relation to SPRMs, placebo-controlled experiments show good clinical results with most of them, especially with UPA [24,26,28-30]. Prior to surgery, administration of UPA (5 or 10 mg), or mifepristone (50 mg every other day), increases Hb level

by almost 1g/dl [26,29]. Bleeding reduction (less than 75 units by PBAC), is significantly higher in women receiving presurgical treatment with UPA than placebo [26]. UPA shows greater reductions in uterine fibroids than other SPRM, but asoprisnil 10 mg is not superior to placebo. Another small study, comparing menstrual blood loss at the baseline and at the end of treatment, shows that asoprisnil is associated with significant reduction of menstrual bleeding prior to surgery, with no changes seen in the placebo group [28]. Furthermore, one trial found that UPA, either 5 mg or 10 mg, significantly increases woman's quality of life, reduces dysmenorrhea and other UF-related symptoms [25].

Respecting side effects of SPRMs such as UPA (5 or 10 mg), asoprisnil (10 or 25 mg) or CDB-2914 (10 or 20 mg), diverse studies show that none of these drugs induce breast cancer, endometrial hyperplasia, fibroid protrusion, meno-metrorrhagia or ovarian hemorrhage [25,28,29]. Although almost 70% of patients exhibit changes in their endometrium at the end of treatment, which are described as progesterone receptor modulator (PRM)-associated endometrial changes (PAECs). These changes have proved to be benign and reversible, as they disappear two months after the end of therapy [21,25,31,32].

In contrast to the positive results obtained with GnRH-a, SPRMs and tranexamic acid, there is no evidence of a difference in preoperative Hb, postoperative Hb or fibroid volume in patients who received misoprostol prior to surgery [29]. Additionally, there is a lack of evidence about the role of mifepristone in decreasing myoma volume [33]. Additionally, two recent Cochrane Reviews found no evidence to support the use of herbal preparations or aromatase inhibitors as medical therapy treating UF [34,35].

Discussion

Surgical management of UF has a crucial role in the management of uterine fibroids [36,37], but frequently it is not accepted by patients. Moreover, hysterectomy is associated with significant morbidity, mortality, and economic burden on the health care system, making the personal, social and economic impact of UF considerable. Specifically, American women expressed they would like to have access to treatments that preserve the uterus (51%), preserve fertility (43% of women aged <40 years), and that do not involve invasive surgery (79%) [3]. However, sometimes is not possible to fulfill the patient's desire when she presents with severe UF-related symptoms, or with secondary health problems, like anemia or rapid growing myomata. Especially, anemia itself constitutes a risk for the surgery. As an example, in a cohort study of 227425 patients with major non-cardiac surgery, mortality and morbidity rates were significantly higher in women with anemia (69229 cases), even with a mild-degree preoperative anemia [38,39]. Therefore, sometimes considering an adjuvant therapy prior to surgery is desirable, or even necessary, in order to improve the woman's clinical condition while surgical scheduling [14,40-43].

In this review we found wide evidence that pre-surgical use of pharmacological treatments, either GnRH-a, SPRMs or tranexamic acid, are of clinical benefit when used prior to myomectomy or hysterectomy. These substances reduce uterine bleeding, correct preoperative anemia [11,18,44,45], decrease fibroid size [40,45,46], and reduce endometrial thickness and vascularization, improving visibility and reducing fluid absorption during operative hysteroscopy [40,45,46]. Besides

their benefits, all mentioned substances are associated with a tolerable side-effects rate, and fewer post-surgical complications [13,14,19-24,25,44].

Considering that a UF is more or less a sphere (volume: $4/3 \pi R^3$), a 30% reduction in its diameter equates to an approximately 65% reduction in volume. An intuitive explanation for less midline incision, more vaginal surgery and less difficult surgery is associated with the preoperative treatment of myomata. Presurgical administration of GnRH-a is associated with a significant increase in the time to undertake laparoscopic myomectomy (18 to 45 minutes), because the fibroid capsule becomes soft, less evident and may be missed, and consequently the excision may be appreciated as more difficult [15-17]. It is known that surgical approach for benign indications frequently is surgeon-dependent [13,14]. Here, the ability and experience of surgeons could introduce a bias when analyzing such a subjective appreciation, especially when operative difficulty is rated by the operating surgeon himself.

Therefore, in the present review we have used surrogate parameters as indirect indicators of surgical difficulty to evaluate whether the use of a preoperative pharmacological treatment could make UF surgery safer, such as: operating time, total blood loss, post-operative hemoglobin concentration, peri and post surgical complications. This analysis is limited by quality of the evidence, due to limitations of placebo-controlled studies, and the low quantity of head-to-head trials.

Conclusion

Clinicians can expect an improvement of patient's clinical condition and fibroid parameters by prescribing a pharmacological therapy prior to myomectomy or hysterectomy. Most of these substances have the potency to improve the safety of the planned surgery to enhance the chance to follow guidelines and recommendations for myoma resection and vaginal hysterectomy, and to permit patients to achieve uterine preserving therapies.

Conflict of Interest

All authors declare that they do not have any potential conflict of interest relevant to this article.

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

Supplementary Material

None.

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