

Analysis of single dose GnRH analog (goserelin acetate – 10.8 mg) treatment in patients with uterin leiomyomatosis treated at the Outpatient Clinic of Endocrine Gynecology of a Tertiary Hospital in Curitiba

Análise do tratamento com dose única do análogo do GnRH (acetato de goserrelina - 10,8 mg) em pacientes com leiomiomatose uterina atendidas no Ambulatório de Ginecologia Endócrina de um Hospital Terciário de Curitiba

Anna Paula Bueno Haurani¹, Ariadne Decarli¹, Patrícia Arenas Rocha¹, Mila Schettini de Andrade¹, Flávia Centenaro de Oliveira¹, Sheldon Rodrigo Botogoski¹

Abstract

Introduction: Leiomyomas are benign tumors that appear in the myometrium and are common in women of childbearing age. They may be asymptomatic or may be associated with pelvic symptoms, such as bleeding and pain. **Objective:** In the present study, we analyzed clinical situations of 64 women with symptomatic uterine leiomyomatosis who underwent treatment with GnRH analogue (gonadotropin releasing hormone agonist) injection, these patients were followed up in 2009-2019. Data were collected from medical records of the Gynecology outpatient clinic of the Santa Casa Hospital in Curitiba. **Material and Method:** It is an observational, retrospective study, with quantitative and qualitative variables. Inclusion criteria were women with ultrasound-proven uterine leiomyomatosis who underwent GnRH analogue treatment. Quantification of uterine volume reduction after GnRH application; assessment of improvement in hematimetric levels; measurement and discrimination of how many patients underwent surgery and correlation with clinical history; the assessment of which surgery was mostly performed and the identification of complaints before and after injection correspond to the objectives found in the current study. **Results:** The use of preoperative GnRH analogue contributed to the improvement of hematimetric indices, in which an average increase of hemoglobin of 20.1% was observed, and pre-application contributed to a reduction of uterine volume by 90.6% of the patients. Thus, a safer surgical scenario was obtained

for the 23 patients who required surgery, whether abdominal or vaginal hysterectomy, or even myomectomy. In accordance with the literary arsenal, this study noted that the main complaints – pre-application of the analogue – were abnormal uterine bleeding and dysmenorrhea; just as the complaint after injection was mainly of hot flashes, that occurs due to the state of hypoestrogenism, caused by the GnRH. **Conclusion:** Considering this evidence, the GnRH analogue has numerous benefits as a therapeutic and preoperative treatment for uterine leiomyomatosis; its adverse effects and high cost, however, contribute to lower accessibility to patients.

Keywords: Leiomyomatosis, Goserelin, Uterine bleeding, Infertility, Pelvic pain, Dysmenorrhea

Resumo

Introdução: Leiomiomas são tumores benignos que surgem no miométrio e são comuns em mulheres em idade fértil. Eles podem ser assintomáticos ou podem estar associados a sintomas pélvicos, como sangramento e dor. **Objetivo:** Neste presente estudo, foram analisadas situações clínicas de 64 mulheres portadoras de leiomiomatose uterina sintomática que foram submetidas ao tratamento com a injeção de análogo de GnRH (agonista do hormônio liberador de gonadotrofina), sendo acompanhadas no período de 2009-2019. **Material e Método:** Os dados foram coletados de prontuários do ambulatório de Ginecologia do Hospital Santa Casa de Curitiba. Trata-se de um método observacional, retrospectivo com variáveis quantitativas e qualitativas. Os critérios de inclusão foram mulheres portadoras de leiomiomatose uterina comprovada por ultrassonografia e que se submeteram ao tratamento com o análogo de GnRH. A quantificação da redução do volume uterino após aplicação do GnRH; avaliação na melhora dos níveis hematimétricos; mensuração e discriminação de quantas pacientes foram

1. Pontifical Catholic University of Paraná (PUCPR). Medicine course. Curitiba – PR – Brazil

Institution: Pontifical Catholic University of Paraná (PUCPR). Medicine. Curitiba – PR – Brazil

Correspondence address: Mila Schettini de Andrade. Rua Doutor Alexandre Gutierrez, 826, sala 1508, Água Verde – 80240-130 - Curitiba – PR – Brazil. E-mail: dramilaschettini@gmail.com

submetidas a cirurgia e correlação com a história clínica; a aferição de qual cirurgia foi mais realizada e a identificação das queixas pré e pós aplicação da injeção correspondem aos objetivos encontrados no atual estudo. **Resultados:** O uso com análogo de GnRH pré-operatório contribuiu para melhora dos índices hematimétricos onde se foi observado um aumento médio de 20,1% de hemoglobina. Além disso, a pré-aplicação colaborou com uma redução de volume uterino em 90,6% das pacientes. Mediante isso, obteve-se um cenário cirúrgico mais seguro para as 23 pacientes que necessitaram de cirurgia, seja via histerectomia abdominal, vaginal ou mesmo miomectomia. Concordante com o arsenal literário, neste estudo observou-se que as queixas principais pré aplicação do análogo foram sangramento uterino anormal e dismenorreia; assim como a queixa pós injeção foi principalmente o fogacho, que ocorre devido ao estado de hipoestrogenismo o qual o GnRH ocasiona. **Conclusão:** À luz dessas evidências, o análogo de GnRH traz inúmeros benefícios, como tratamento terapêutico e pré-operatório da leiomiomatose uterina, porém seus efeitos adversos e seu alto custo contribuem para a menor acessibilidade às pacientes.

Palavras-chave: Leiomiomatose, Gosserrrelina, Sangramento uterino, Infertilidade, Dor pélvica, Dismenorreia

Introduction

Abnormal uterine bleeding (AUB) is a very important complaint present in gynecological consultations. According to its etiology, it can be subdivided following the PALM-COEIN mnemonic classification, and the AUB can be caused by structural causes – polyp, adenomyosis, leiomyoma and malignancy or hyperplasia – or non-structural causes – coagulopathies, ovulatory dysfunction, endometrial causes, iatrogenesis and causes not yet classified⁽¹⁾.

Classified among the structural causes of AUB, uterine leiomyomas (fibroids) are benign tumors formed by uterine smooth muscle cells containing an increased amount of extracellular matrix. They are surrounded by a thin pseudocapsule of areolar tissue and compressed muscle fibers. The fibroids are usually described according to their location⁽²⁻³⁾:

- Intramural: develop within the uterine wall and may be large enough to distort the uterine cavity and the serous surface;
- Submucosal: derive from myometrial cells located just below the endometrium and can often grow into the uterine cavity;
- Subserous: originate from the serous surface of the uterus and may have a wide or pedunculated base and be intraligamentary;
- Cervical: located in the uterine cervix.

About 20 to 30% of women of childbearing age – and more than 40% of women over 40 years old – have

uterine leiomyomatosis, however, only 50% of cases become symptomatic. It is a rare condition before the menopause and usually regresses after menopause. It is estimated that the incidence of diagnosis of leiomyomas is around 12.8 per 1000 women/year, corresponding to 1/3 of hysterectomy indications (approximately 300000/year)⁽⁴⁾.

Factors that affect the risk of developing leiomyomas include^(2,5):

- Parity: pregnancies longer than 20 weeks decrease the chance of fibroid formation. Women with 5 or more children are 4 times less likely to develop fibroids than nulliparous women. This relation, however, can be attributed to the association of infertility with fibroids;
- Oral contraceptives (OC): in general, the use of OC protects against the development of fibroids. Nonetheless, its early usage (between 13 and 16 years), can be correlated with increased risk for fibroid formation;
- Smoking: reduces the risk of developing fibroids through a mechanism not yet understood;
- Diet: consumption of large amounts of red meat is associated with an increased risk of fibroids, while greater consumption of green vegetables decreases it. Still, there is no evidence that dietary interventions offer therapeutic benefits;
- Obesity: women weighing over 70 kg have a 3 times greater risk of developing fibroids than women weighing less than 50 kg;
- Ethnicity: Black women have a 2-3 times greater risk of developing fibroids than white women;
- Family history: patients with first-degree relatives with a history of fibroids have a 2.2 times higher prevalence of developing this disease than individuals in the general population;
- Genetics: the development of fibroids has been linked to specific genotypic alterations, just as fibroids with specific genotypes have particular characteristics. The pathogenesis of leiomyomas is not yet fully enlightened. Although fibroid growth is responsive to gonadal steroids, these hormones are not necessarily responsible for the genesis of the tumors.

Symptoms caused by leiomyomatosis, when present, are related to the number, size, and location of the fibroids. The main clinical manifestations involve increased uterine bleeding, pelvic pain and reproductive dysfunction⁽³⁻⁴⁾.

Uterine bleeding caused by fibroids is characterized by menorrhagia – prolonged menstrual bleeding and excessive blood flow. It is not common to have bleeding situations other than in the menstrual period. Presence and degree of bleeding are defined by the location of the fibroid and its size. Submucosal fibroids

are the ones that most often cause abnormal uterine bleeding. Pain and compression of pelvic structures can also occur and are dependent of location, shape and size of the tumors. Those located anteriorly can compress the bladder and cause urinary symptoms⁽³⁾.

Reproductive dysfunction is another sign related to leiomyomatosis. About 2 to 7% of women under investigation for infertility have uterine fibroids on imaging tests. The risk of infertility increases when the endometrial cavity is distorted by submucosal leiomyomas, while the role of intramurals in infertility is smaller. When the endometrial layer is unaltered, the presence of fibroids does not affect the rate of *in vitro* fertilization⁽⁶⁻⁸⁾.

Patients with uterine leiomyomatosis are at increased risk of obstetric complications, such as miscarriage, previous placental implantation, third trimester bleeding, dysfunctional labor, preterm labor, placental retention and premature rupture of membranes⁽⁸⁾.

The diagnosis of uterine fibroids is usually based on the physical examination finding of an enlarged, mobile, and irregularly contoured uterus on bimanual examination. It may also be a casual ultrasound finding⁽⁹⁾.

Imaging exams are necessary to confirm the diagnosis and define the location of the tumor. Ultrasonography can be performed via transabdominal or transvaginal approach, the former still representing an important diagnostic tool in smaller centers. The transvaginal method has a high sensitivity (95-100%) to detect fibroids in uteri smaller than the equivalent size of a 10-week pregnancy uterus. Locating fibroids in very large uteri or when tumors are multiple can be difficult⁽¹⁰⁾.

Drug treatment for abnormal uterine bleeding is based on the action of hormones and other inflammatory mediators on the endometrium, in addition to hemostatic control of bleeding^(11,12).

GnRH analogues, neuropeptides that regulate pituitary function in women, are considered one of the most effective clinical treatments for fibroids. Initially, they increase the release of gonadotropins, followed by downregulation and desensitization, leading to a state of hypogonadotropic hypogonadism, mimicking a menopausal state. Most women develop amenorrhea and experience a significant reduction (25 to 80%) in uterine size with treatment, with maximum effect within 12 weeks. There may be climacteric symptoms associated with the use of medication, such as loss of bone mass and lipid disorders.

The administration schedules for Goserelin are 3.6 mg monthly, or 10.8 mg quarterly, subcutaneously injected into the abdomen.

Treatment with a GnRH analogue alone should not exceed 6 months, due to the risk of developing

osteoporosis. Patients under clinical treatment for leiomyomatosis with contraindications to curative surgical treatment should be reassessed every 6 months. If patients need to use analogues for more than 1 year, they must be evaluated in a specialized gynecology service. Normally, with the onset of menopause, there is a natural decrease in hormones, with no further need for fibroid treatment^(13,14).

Adverse effects associated with analogue therapy can be minimized by concomitant administration (add-back therapy) of estrogens, progestogens, association of estrogens and progestogens, tibolone and raloxifene. Hormonal therapy with low doses of estrogens maintains amenorrhea and uterine reduction, in addition to preventing the adverse effects of hypoestrogenism.

If there is no response to clinical treatment, the surgical approach must be considered, in which route and type of approach will depend on the number, location, size of uterine myomas and future desire of pregnancy⁽¹⁵⁾.

GnRH analogue usage can be considered before surgery, particularly to enable recovery from the bleeding and reduction in volume. The use of GnRH analogues is recommended for three months and surgery should be scheduled before menstruation returns⁽¹⁶⁾.

When myomectomy is not possible or when there is no desire to preserve fertility, hysterectomy is indicated to control abnormal uterine bleeding resulting from leiomyomatosis. It can be performed through vaginal, laparoscopic or laparotomic approaches⁽¹⁷⁾.

Objectives

Main objective

To evaluate the response to the treatment of uterine leiomyomatosis with the use of GnRH analogue (Goserelin Acetate 10.8 mg) by patients followed up at the Gynecology Outpatient Clinic of Hospital Santa Casa de Curitiba, from 2009 to 2019.

Specific objectives

1. Quantify the reduction in uterine volume of patients undergoing treatment;
2. Estimate the improvement of hematimetric levels with the use of medication;
3. Identify the pre-treatment and post-treatment complaints presented by patients;
4. Analyze how many patients underwent surgery and correlate with corresponding clinical history;
5. Evaluate which surgery was mostly performed.

Material and Method

This is an observational, retrospective study, with quantitative and qualitative variables, which resulted from a process of analyzing medical records.

The research was based on the analysis of manual medical records according to the objectives of the study, complementing with data from the electronic medical records of the Gynecology Outpatient Clinic of Hospital Santa Casa de Curitiba, from February to August 2019.

The medical records of 93 patients diagnosed with uterine leiomyomatosis followed up at the Gynecology Outpatient Clinic of Hospital Santa Casa de Curitiba, from June 2009 to September 2019, were evaluated. Of these, 64 met the inclusion criteria.

Patients with an ultrasound diagnosis compatible with uterine leiomyomatosis who underwent treatment with GnRH analogue (Goserelin Acetate 10.8 mg) were included in the study.

Patients with other pelvic diseases (such as adenomyosis and endometriosis), those who used more than one dose of medication and patients with incomplete medical records were excluded of the analysis.

During the period of the present study, the information obtained from the medical records of the Gynecology outpatient clinic was distributed in a Microsoft Excel® spreadsheet, which included the following variables: age, pre-treatment complaints, pre-treatment uterine volume, pre-treatment hemoglobin (Hb), post-treatment complaints, post-treatment uterine volume, post-treatment Hb, post-treatment surgery and type of surgery performed.

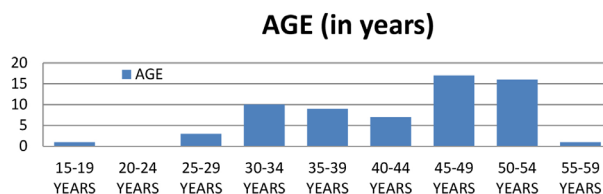
Quantitative variables were described using mean, median, minimum, and maximum values and standard deviation statistics. Qualitative variables were summarized, considering frequencies and percentages. To evaluate the association between two qualitative variables, Chi-Square and Fisher's Exact tests were used. P-values under 0.05 indicated statistical significance.

The present study was approved by the Ethics and Research Committee of the Hospital Santa Casa de Misericórdia of Curitiba, under the Certificate of Presentation of Ethical Appreciation number 46204521.2.0000.0020.

Results

The sample consisted of 64 patients, with a mean age of 43 years, with a minimum age of 18 and a maximum of 55 years. Of these, 53.1% of the sample were patients over 45 years (Graph 1).

The selected patients were asked about their main complaints at the time of the first consultation, when



Graph 1 - Age (in years) of patients

serum Hb dosage and a recent transvaginal ultrasound (performed within the last six months of the consultation date) were also requested.

Regarding the complaints presented in the pre-application of the injection of the GnRH analogue, of the 64 women evaluated: 58 (90.6%) complained of abnormal uterine bleeding, 17 (26.6%) reported dysmenorrhea, 8 (12.5%) reported increased abdominal volume, 12 (18.8%) had the desire to have future pregnancies.

After an average of three months of the GnRH analogue application (Goserelin Acetate 10,8 mg – single dose), they were reassessed and questioned about uterine bleeding pattern and occasional complaints after using the medication. A new serum Hb dosage and a new transvaginal ultrasound were also requested at this time.

As for uterine bleeding after application of the GnRH analogue, 21 (32.8%) maintained the AUB complaint and 43 (67.1%) denied new episodes of bleeding after using the medication (post-application amenorrhea). As for side effects, 22 (34.3%) reported hot flashes related to the application of the GnRH analogue.

Analyzing the correlation between the report of amenorrhea after the application of the GnRH analogue and age, it was observed that, of the 31 women over 45 years old, 24 (77.4%) of them developed amenorrhea, while in the 33 aged 45 years old or less, 19 (57.6%) reported the finding ($p = 0.091$).

When analyzing the variables age and complaint of hot flashes, of the 31 women over 45 years old, 15 (48.4%) reported the symptom, whereas, of the 33 aged 45 years old or less, 7 (21.2%) complained of hot flashes ($p = 0.022$), as shown in Table 1.

According to laboratory analysis, after applying

Hot flashes complaint	Age (in years)			
	≤ 45 years old		> 45 years old	
	n	%	n	%
No	26	78.8%	16	51.6%
Yes	7	21.2%	15	48.4%
Total	33	100.0%	31	100.0%

Table 2

Hematimetric levels (g/dL) pre- and post-application of the GnRH analogue

Variable	n	Mean	Median	Minimum	Maximum	Standard deviation
Pre Hb	64	11.3	11.8	5.3	15.1	2,3
Post Hb	64	13.1	13.1	9.0	16.3	1.4
Increase of Hb (%)	64	20.1%	11.2%	-6.3%	150.9%	28.2%

the GnRH analogue, 57 (89.1%) had an increase in serum Hb, corresponding to a 20.1% increase in Hb when compared to the previous measurement, with the mean and deviation standard pre- and post-medication respectively being (Pre Hb: 11.3 ± 2.3 g/dL; Post Hb: 13.1 ± 1.4 g/dL). As for the 7 (10.9%) who presented Hb reduction, all had serum levels above 12.5 mg/dL and remained within the reference value (12 to 16 g/dL), not representing any clinical significance.

Regarding the ultrasound analysis, with assessment of uterine volume, of the 64 women who participated in the study, 58 presented a reduction in uterine volume (90.6%), while 6 showed an increase (9.4%). The average reduction in uterine volume was of 48.8%, with the minimum reduction corresponding to 37.6% of the total volume, and the maximum corresponding to a reduction of 86.3% of it.

Between volume reduction and AUB after application of the GnRH analogue, out of the 58 women who presented volume reduction, 41 (70.7%) did not present AUB post-medication. Whereas, out of 6 women who had no reduction in uterine volume, 3 (50%) had AUB post-application and 3 (50%) developed amenorrhea, with a p-value = 0.366 (Table 3).

Table 3

Relationship between reduction in uterine volume (cm³) and AUB after the application of the GnRH analogue.

AUB POST	Uterine volume reduction			
	No		Yes	
	n	%	n	%
No	3	50.0%	41	70.7%
Yes	3	50.0%	17	29.3%
Total	6	100.0%	58	100.0%

The patients were monitored accordingly and 23 (35,9%) underwent surgery. Of these, 10 (15.6% of the total) underwent total abdominal hysterectomy, 12 (18.7% of the total) underwent myomectomy, and 1 (1.5% of the total) underwent vaginal hysterectomy.

Among the 12 (18.8%) patients with desire of future pregnancy: 11 (91.6%) had a reduction in uterine volume after application of the GnRH analogue and only 1 (8.3%) had an increase. All these patients underwent surgery (myomectomy).

When relating age and surgical procedures, it was noted that, out of 31 patients over 45 years old, 25 (80.6%) did not undergo surgery. Whereas, of the 33 women aged 45 or less, 17 (51.5%) underwent surgery (p = 0.007), as shown in Table 4.

Table 4

Relationship between the variables age (in years) and surgical procedures

Underwent Surgery	Age (in years)			
	≤ 45 years old		> 45 years old	
	n	%	n	%
No	16	48.5%	25	80.6%
Yes	17	51.5%	6	19.4%
Total	33	100.0%	31	100.0%

Comparing the variables reduction in uterine volume and surgery, of the 6 women who did not obtain a reduction in uterine volume after application of the GnRH analogue, 5 (83.3%) underwent surgery. On the other hand, of the 58 women who obtained uterine reduction, 40 (69.0%) did not undergo surgery, obtaining a p-value of 0.020, as shown in Table 5.

Table 5

Relation between the variables reduction in uterine volume (cm³) and surgery

Underwent Surgery	Reduction of uterine volume (cm ³)			
	No		Yes	
	n	%	n	%
No	1	16.7%	40	69.0%
Yes	5	83.3%	18	31.0%
Total	6	100.0%	58	100.0%

Among the 20 (31.2%) patients who complained of abnormal uterine bleeding after medication, 14 (70.0%) underwent surgery (p = 0.001), as shown in Table 6.

Discussion

The characterization of the sample – women with a mean age of 43 years – corroborates with data from literature, which demonstrate that most patients af-

Table 6

Relationship between AUB post-application of GnRH analogue and surgery

Underwent Surgery	AUB post			
	No		Yes	
	n	%	n	%
No	35	79.5%	6	30.0%
Yes	9	20.5%	14	70.0%
Total	44	100.0%	20	100.0%

ected by uterine leiomyomatosis are within this age range^(2,4).

During their first consultations, patients mostly presented the complaints of AUB (90.6%), dysmenorrhea (26.6%), increased abdominal volume (12.5%) and desire for pregnancy (18.8%). Such data also agree with literature, which states that the main manifestations related to uterine myomatosis are uterine bleeding, pelvic pain, and reproductive dysfunction^(3,5).

The treatment chosen was a single application of 10.8 mg of the GnRH analogue goserelin acetate, since it was believed that this form of administration provided better treatment results. In the present study, we observed a mean uterine volume reduction of 48.8%, in accordance with the study carried out at the Hospital de Clínicas de São Paulo. In this hospital, a comparative study of different administration schemes of goserelin acetate was carried out, in which one group received 3.6 mg monthly for three months, and the other group received a single dose of 10.8 mg. The results obtained were favorable to the single-dose 10.8 mg goserelin acetate regimen, with a mean uterine volume reduction of 54%, while in the group that used monthly GnRH analogues, the obtained mean of reduction was of 43%⁽¹¹⁾.

The main adverse effect reported by patients was the complaint of hot flashes (34.5%), in agreement with literature, which reports that among the main adverse effects of GnRH analogues are those related to hypoestrogenism. When using a single dose of goserelin acetate, there hot flashes are reported as the main adverse effect when compared to others (osteoporosis, genital atrophy, depression, and insomnia)⁽¹⁴⁾.

When comparing the age of patients with complaint of hot flashes, it was shown that most patients who reported this symptom were over 45 years, which may justify an already lower ovarian reserve before the study, with greater sensitivity to the effects of medication. These data showed statistical relevance in our study ($p = 0.022$), but there is still not enough data in literature to reinforce this analysis.

Regarding the evaluation of hematimetric indices and the use of the GnRH analogue, 89.1% of patients

showed an increase in Hb, with an average of 20.1% (2.2 mg/dL) increase over pre-application values. The data are consistent with a randomized, double-blind, multicenter clinical trial that evaluated a dose of goserelin (10.8 mg) or placebo associated with ferrous sulfate. This study showed that after 12 weeks, serum Hb concentration was significantly higher in the goserelin group than in the placebo group (1.17 g/dL), and that there was a significant increase of more than 2 g/dL in Hb dosage⁽¹⁸⁾.

Another randomized clinical trial evaluated goserelin with and without the coadministration of ferrous sulfate, compared with ferrous sulfate alone in premenopausal patients with anemia and AUB caused by leiomyomatosis. Goserelin therapy improved hematologic parameters, with the increase in Hb being higher when compared to ferrous sulfate therapy alone⁽¹⁹⁾.

Among the patients studied, 35.9% underwent surgery. Correlating the results of this study and literature data, surgeries were safer after the application of the GnRH analog: its preoperative use is associated with a decrease in uterine size, an increase in serum concentrations of Hb and hematocrit, a reduction of bleeding during surgery and shorter time of surgery⁽²⁰⁻²¹⁾.

Of the total number of patients in the study, 18.8% had the desire to become pregnant as their main motivation for treatment. Of these patients, only one did not present reduction of uterine volume, and all were submitted to surgery (myomectomy). The ideal technique to perform infertility-related myomectomy should be the least aggressive one, with good results and low sequelae rate. According to the literature, the approach that fulfills this is the use of GnRH analogues and a subsequent surgical approach⁽²²⁻²³⁾.

A study comparing patients submitted directly to myomectomy to a group that received preoperative GnRH analogue demonstrated a decrease in uterine volume: $473 \pm 88 \text{ cm}^3$ of initial volume in the group that use of GnRH analogues to $396 \pm 79 \text{ cm}^3$, while in the group that underwent myomectomy directly, the volume was $458 \pm 92 \text{ cm}^3$. There was also less blood loss ($171.8 \pm 70.9 \text{ mL}$ versus $232.1 \pm 68.1 \text{ mL}$), higher Hb rates ($12.2 \pm 1.1 \text{ gm/dL}$ versus $11.4 \pm 1.3 \text{ gm/dL}$) and shorter surgical time ($98.5 \pm 26.1 \text{ minutes}$ versus $113.3 \pm 35.1 \text{ minutes}$) in the group that used the analogue⁽¹⁵⁾.

In the UK, a randomized study that reinforces these results was conducted with 247 patients who underwent total abdominal hysterectomy. 123 of the women analyzed had been previously treated with a GnRH analogue (goserelin acetate 10.8 mg). The patients who underwent surgery showed a significant reduction in uterine volume and myomas, as well as a significantly higher mean increase in Hb values – since entering the preoperative period – in the group

that underwent prior treatment with the analogue (1g/dL versus 0.3 g/dL in the group that did not use the GnRH analogue). There was also a tendency toward surgical facility and reduced blood loss in these cases. In addition, patients treated with the GnRH analogue required shorter hospital stay⁽²⁴⁾.

Similarly, a meta-analysis published in 2011 evaluated the comparison of surgical conditions in patients who had previously used a GnRH analogue with a control group. There was significant variation in perioperative blood loss between the group of patients (mean of 60 mL), with a difference in postoperative Hb of 1.15 mg/dL, with no divergence regarding serum iron. In this meta-analysis, there was no significant discrepancy in surgical time between groups⁽¹⁴⁾.

On the other hand, a cost-effectiveness analysis by a New Zealand group found no benefit in using preoperative therapy with GnRH analogues. The additional cost for a hysterectomy was of 1,190.00 New Zealand dollars (NZD), while the cost to prevent an abdominal procedure or perform it prior to GnRH analog use was of 4,577.00 NZD⁽²³⁾.

In this study, when correlating age over 45 years and surgery, it was observed that most patients in this group (80.6%) did not undergo surgery, while in the group of women aged 45 years or less, 51.5% of patients underwent surgery ($p = 0.007$). Thus, this indicates that women who are closer to menopause can benefit from the treatment of the GnRH analogue, with chances of avoiding exposure to a possible surgery, since during menopause there will be a natural decrease of hormones, with no need for additional treatment⁽¹⁴⁾.

Conclusion

It can be concluded from this study that uterine leiomyomas affect a large proportion of women during the menacme, especially above 40 years of age. Most of the symptoms associated with uterine leiomyomas are related to AUB, dysmenorrhea, and infertility.

The decrease in uterine volume was one of the main advantages identified in the treatment of uterine leiomyomatosis with GnRH analogue: 90.6% of patients achieved a reduction in uterine volume, with a mean reduction of 48.8% of the total volume.

Amenorrhea occurs in most patients, and the improvement in hematimetric levels is significant. An average increase of 20.1% in Hb was obtained pre- and post-application of the GnRH analogue. For patients who present anemia, this treatment is a good option.

With improvement in hematimetric levels and reduction of uterine volume, a better clinical scenario was reached for patients who required surgery, thus presenting better surgical conditions.

The use of GnRH analogue is an ally and a good option for treatment of uterine leiomyomatosis and also as a pre-surgical treatment. The adverse effects are mainly related to hot flashes, and in this study, patients older than 45 years presented a higher rate of this complaint.

Patients who desired future pregnancies were all submitted to myomectomies. With the reduction of the uterine volume due to GnRH analogue, surgeries became less aggressive, with chances of better results and lower sequelae rate, increasing the possibility of a future pregnancy. Consequently, the use of GnRH analogues and the subsequent surgical approach constituted a safer method for these patients.

Most patients over 45 years did not undergo surgery and presented persistent amenorrhea after treatment. Thus, these patients can benefit from the use of the GnRH analogue alone, having good chances of avoiding exposure to surgery, since during menopause there will be a natural decrease of hormone production, without need for further treatment.

Nevertheless, the adverse effects and the high cost make the use of the GnRH analogue still restricted and less accessible to many patients.

References

1. 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. *Int J Gynecol Obstet*. 2011; 113(1):3–13.
2. ACOG. Practice bulletin clinical management guidelines for obstetrician-gynecologists - alternatives to hysterectomy in the management of leiomyomas. *Obstet Gynecol*. 2009;113(6):1405–13.
3. Donnez J, Dolmans M. Uterine fibroid management: from the present to the future. 2016; *Hum Reprod Update*. 2016; 22(6):665–86.
4. Boclin K de LS, Faerstein E. Prevalência de diagnóstico médico auto-relatado de miomas uterinos em população brasileira: Padrões demográficos e socioeconômicos no Estudo Pró-Saúde*. *Rev Bras Epidemiol*. 2013; 6(2):301–13.
5. Banu NS, Manyonda IT. Myometrial tumours. *Curr Obstet Gynaecol*. 2004; 14(5):327–36.
6. Mukhopadhyaya N, Pokuah Asante G, Manyonda IT. Uterine fibroids: impact on fertility and pregnancy loss. *Obstet Gynaecol Reprod Med*. 2007;17(11):311–7.
7. Farquhar C, Arroll B, Ekeroma A, Fentiman G, Lethaby A, Rademaker L, et al. An evidence-based guideline for the management of uterine fibroids. *Aust N Z J Obstet Gynaecol*. 2001;41(2):125–40.
8. Moghissi K. A clinician's guide to the use of gonadotropin-releasing hormone analogues in women. *Medscape Womens Health*. 2000; 5:5.
9. Borsari R, Bozzini N, Junqueira CR, Soares JM, Hilário SG, Baracat EC. Genic expression of the uterine leiomyoma in reproductive-aged women after treatment with goserelin. *Fertil Steril*. 2010; 94(3):1072–7.
10. Bassaw B, Mohammed N, Jaggat A, Singh-Bhola M, Ramkissoon A, Singh P, et al. Experience with a gonadotrophin-releasing

- hormone agonist prior to myomectomy--comparison of twice- vs thrice-monthly doses and a control group. *J Obstet Gynaecol J Inst Obstet Gynaecol*. 2014; 34(5):415-9.
11. Bozzini N, Messina M, Borsari R, Hilário S, Pinotti J. Comparative study of different dosages of goserelin in size reduction of myomatous uteri. *J Am Assoc Gynecol Laparosc*. 2004; 11(4):462-3.
 12. Islam MS, Protic O, Giannubilo SR, Toti P, Tranquilli AL, Petraglia F, et al. Uterine leiomyoma: available medical treatments and new possible therapeutic options. *J Clin Endocrinol Metab*. 2013; 98(3):921-34.
 13. Lethaby AE, Vollenhoven BJ. An evidence-based approach to hormonal therapies for premenopausal women with fibroids. *Best Pract Res Clin Obstet Gynaecol*. 2008; 22(2):307-31.
 14. Chen I, Motan T, Kiddoo D. Gonadotropin-releasing hormone agonist in laparoscopic myomectomy: systematic review and meta-analysis of randomized controlled trials. *J Minim Invasive Gynecol*. 2011; 18(3):303-9.
 15. Sharma M, Buck L, Mastrogamvrakis G, Kontos K, Magos A, Taylor A, et al. Cost effectiveness of pre-operative gonadotrophin releasing analogues for women with uterine fibroids undergoing hysterectomy or myomectomy. *BJOG*. 2003; 110(7):712.
 16. Gerris J, Degueldre M, Peters AA, Romao F, Stjernquist M, al-Taher H. The place of Zoladex in deferred surgery for uterine fibroids. Zoladex Myoma Study Group. *Horm Res*. 1996; 45(6):279-84.
 17. Muneyyirci-Delale O, Richard-Davis G, Morris T, Armstrong J. Goserelin acetate 10.8 mg plus iron versus iron monotherapy prior to surgery in premenopausal women with iron-deficiency anemia due to uterine leiomyomas: results from a Phase III, randomized, multicenter, double-blind, controlled trial. *Clin Ther*. 2007; 29(8):1682-91.
 18. Benagiano G, Kivinen ST, Fadini R, Cronjé H, Klinton S, van der Spuy ZM. Zoladex (goserelin acetate) and the anemic patient: results of a multicenter fibroid study. *Fertil Steril*. 1996; 66(2):223-9.
 19. Hudecek R, Ivanová Z, Smerdová M, Pánková S, Krajčovicová R. Effect of GnRH analogues pre-treatment on myomectomy outcomes in reproductive age women. *Ces Gynekol*. 2012; 77(2):109-17.
 20. Nikolov A, Karag'ozov I. [A comparative efficacy study of the preoperative use of GnRH agonists in women with uterine fibromyomas]. *Akush Ginekol (Sofia)*. 1999; 38(4):38-42.
 21. Petta CA, Aldrighi JM. Qual é a técnica ideal de miomectomia em infertilidade? *Rev Assoc Méd Bras*. 2000; 46(4):289-301.
 22. Mavrelou 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(9):2264-9.
 23. Lethaby A, Vollenhoven B, Sowter M. Efficacy of pre-operative gonadotrophin hormone releasing analogues for women with uterine fibroids undergoing hysterectomy or myomectomy: a systematic review. *BJOG*. 2002; 109(10):1097-108.
 24. Vercellini P, Trespidi L, Zaina B, Vicentini S, Stellato G, Crosignani PG. Gonadotropin-releasing hormone agonist treatment before abdominal myomectomy: a controlled trial. *Fertil Steril*. 2003; 79(6):1390-5.

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