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COMPARISON OF GONADOTROPIN RELEASING HORMONE AGONISTS (GNRHA) VS AROMATASE INHIBITORS ON VOLUME OF UTERINE LEIOMYOMAS IN PREMENOPAUSAL WOMEN

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ABSTRACT

Among the most prevalent yet poorly understood female health issues is uterine leiomyomas. In order to preserve fertility and avoid or delay surgical intervention, medical treatments are typically considered first-line. Therapeutic benefits of GnRH antagonists, aromatase inhibitors, progestin, and selective progesterone receptor modulators have been studied for the treatment of irregular uterine bleeding and the reduction of fibroid volume. To compare the effect of gonadotropin-releasing hormone agonist (leuprolide acetate) vs. Aromatase inhibitor (Letrozole) on volume of uterine leiomyoma in pre-menopausal women with leiomyomas. Randomized Controlled Trial. The study was conducted at Obstretrics and Gynaecology Department of Tertiary Care Hospital of Lahore i.e, Lady Willingdon Hospital Lahore. The study duration was six months. Patients were split into two groups of 31 using a lottery system; Group-A and Group-B. Group-A received aromatase inhibitor (letrozole) tablets and long-acting GnRHa (leuprolide acetate) injections (Group-B). The Aromatase Inhibitor (Tab letrozole). Every participant was given a set of standard measurements. All ultrasound examinations and analyses were carried out by a trained sonologist, who most often used a transvaginal probe. Once the myoma was located, its volume was determined utilising a step-by-step planimetry approach and a unified piece of software. Mean values were determined from measurements taken at the beginning of treatment and again at weeks 4, 8, and 12. Statistical analysis showed no significant difference among Leuprolide acetate treatments after 12 weeks of administration, (10.42 vs. Letrazole's 9.95, p=0.626) and Letrazole (22.44 vs. Letrazole's 22.95, p=0.692) in terms of myoma volume reduction. Both groups had a drop in volume, but there were no statistically significant differences between treatments. Results of this study demonstrate no significant difference for leuprolide acetate and Letrozole on volume reduction of uterine leiomyoma in pre-menopausal women.

Keywords: Pre-menopausal, Uterine, Leiomyoma, Gonadotropin-releasing hormone agonist, Leuprolide acetate, Aromatase inhibitor, Letrozole

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INTRODUCTION

Between 25 and 50 percent of reproductive-aged women develop uterine leiomyomas (fibroids), and the majority of these cases (more than 50 percent) do not cause any symptoms [**1**]. In therapeutic settings where symptoms drive presentation Menstrual bleeding that is excessive or protracted, pelvic pain, or abdominal pressure feelings are common indications. It is possible that fibroids play a role in infertility and miscarriage, however it is unclear whether or not this is a direct result of fibroid disease [**2**].

Most pharmaceutical therapies for symptomatic uterine fibroids have only a short-term impact, and some have substantial costs and side effects. Among these are selective oestrogen receptor modulators [SERM], danazole, gestrinone, anti-progestogens, and aromatase inhibitors, as well as agonists and antagonists of gonadotropin-releasing hormone [**3, 4**]. Although gonadotropin-releasing hormone agonists (GnRHa) can reduce leiomyoma size by about 50% in 3 months, their use is limited because of their high cost, need for parenteral administration, and

association with oestrogen flare and hypo-estrogenism, which can cause symptoms such as hot flashes, vaginal dryness, and bone resorption [**5**].

Because of their mode of action, aromatase inhibitors were thought to be safer alternatives to the GnRH inhibitor (leuprolide acetate) which also accounts for their quick effect, lower risk of adverse events, compliance, oral administration, price, absence of preliminary estrogen flare and hypo-estrogenism, and disrupted reversal of symptoms after discontinuation of treatment. Aromatase inhibitors have been found in multiple studies to reduce leiomyoma size and associated symptoms [**6**]. Aromatase inhibitor use is associated with an increased risk of ovarian cyst development. Fibroids can be treated with aromatase inhibitors, although low doses (2.5mg/day) may be all that is needed to avoid changing gonadotropin levels and so lessen the likelihood of ovarian cyst formation [**7, 8**]. Furthermore, additional conservative methods have been established, including myolysis, ultrasound thermoablation, uterine artery embolization, and uterine artery ligation [**9, 10**].

However, there is a small risk of premature ovarian failure and uterine synechia with uterine artery embolization, making it an effective approach to treat fibroid only in women who do not wish to have children in the future [**11, 12**]. There are fewer serious problems with UAE compared to surgery, but this comes at the tradeoff of a higher chance of needing future intervention [**13**]. Myomectomy and hysterectomy are two of the most common surgical procedures. Though hysterectomy is medically considered a cure, it is obviously not acceptable to women who hope to have children in the future. By contrast, myomectomy is a large operation that has a significant risk of mortality and complications, even in advanced medical care systems [**14**].

Exception of GnRHa, which is used as a perioperative adjunct for patients who are anaemic, none of the aforementioned medications gained sufficient popularity due to concerns about efficacy and safety. By suppressing ovarian hormone release, long-acting GnRHa causes amenorrhea and a smaller uterus. Growth of leiomyomas can be slowed by using the aromatase inhibitor letrozole, according to in vitro and clinical research. After 8 weeks of treatment, aromatase inhibitor dramatically reduces myloma volume, according to these trials, with no serious adverse effects [**15**].

The purpose of this research is to examine whether premenopausal women with leiomyomas respond better to a GnRH agonist or an aromatase inhibitor in terms of volume reduction. In the academic literature, this topic receives insufficient attention. To add insult to injury, we were unable to locate a single local trial that examined the efficacy of these two medications in the treatment of leiomyoma. Therefore, we intend to perform this study so that we may gather evidence for the local community and, ultimately, adopt a more effective medicine in terms of better tolerance with less side effects, quick commencement of action with less risks of recurrence, lack of first oestrogen flare and loss of bone mineral density, adherence with easy administration of drug, and being less expensive in low resource setups. Having this information will help us better care for premenopausal women who have been diagnosed with leiomyoma, as well as inform the development of local recommendations for this care [**16, 17**]. In general, it is hypothesized that in premenopausal women with uterine leiomyoma, aromatase inhibitors are more effective than Gonadotropin-Releasing Hormone Agonists (GnRHa) at shrinking the tumour. Therefore, this research work aimed to compare the effect of gonadotropin-releasing hormone agonist (leuprolide acetate) vs. Aromatase inhibitor (Letrozole) on volume of uterine leiomyoma in pre-menopausal women with leiomyomas.

MATERIAL AND METHODS

Study Design and Setting

Randomized Controlled Trial (RCT). The study was carried out in the Obstetrics and Gynecology Department of Lady Willingdon Hospital Lahore, which is a Tertiary Care Hospital.1 year beginning on the date that the synopsis was approved.

Sample Size and Sampling Technique

Assuming a 33.2% drop in total myoma volume in the GnRHa group and a 9.3% decrease in the aromatase inhibitor group, we will select a sample size of 62 patients (31 patients in each group) to conduct our study. The sampling technique was nonprobability convenient sampling

Inclusion and Exclusion Criteria

The inclusion criteria were Women who have not yet entered menopause (those aged 18–42). Being 5-10 centimeters in diameter with a single uterine myoma of any form. Symptoms include pelvic pain and pressure, abnormal bleeding from the uterus, and infertility that cannot be explained. On the contrary, the exclusion criteria were Women with uterine myoma who have had an estrogen or progesterone implant within the past three months and who have been receiving treatment for uterine myoma for at least one month. Women who have had significant medical issues in the past or who have had previous medical treatment. Has undergone therapy for leiomyomata through surgery.

Data Collection Procedure

Indoor and outdoor patients presenting to lady Willingdon hospital and fulfilling our study criteria was included after taking approval from hospital

ethical committee, demographic history and informed consent. Patients were randomly allocated into 2 groups using lottery method; Group-A and Group-B; each having 31 patients. They were treated with aromatase inhibitor (Tab letrozole) (Group-A) and long-acting GnRHa (injection leuprolide acetate) (Group-B). Aromatase inhibitor (Tab letrozole) was purchased locally and administered orally (2.5 mg/d), regardless of the day of menstrual period. The GnRH agonist (Injection leuprolide acetate) was purchased locally and was administered IM in a dose of 3.75 mg monthly, starting after complete pre-treatment workup. All subjects underwent baseline measurement. An expert sonologist performed all ultrasound scans and analysis preferably using a transvaginal probe. After identification of the myoma, its volume was calculated with a stepwise planimetry method using an integrated software program. Measurements were performed at baseline and during treatment at weeks 4, 8 and 12 and mean values were calculated.

Statistical Analysis

The software used to enter and analyze the data was SPSS 26.0. We used frequency and percentages to depict qualitative characteristics like gender, place of myoma, symptoms, etc. Age, myoma size, and number of myomas were some of the quantitative factors that were displayed as mean±SD. Student's t-test was used to examine the two groups' mean differences in the reduction of myoma volume caused by GnHRa and aromatase. The cutoff for significance was set at p0.05.

RESULTS

The mean age of women in Groups A and B was 32.35±4.37 and 33.32±3.92 years, respectively. The histogram for the age of patients in the study groups is presented in **Fig 1**.

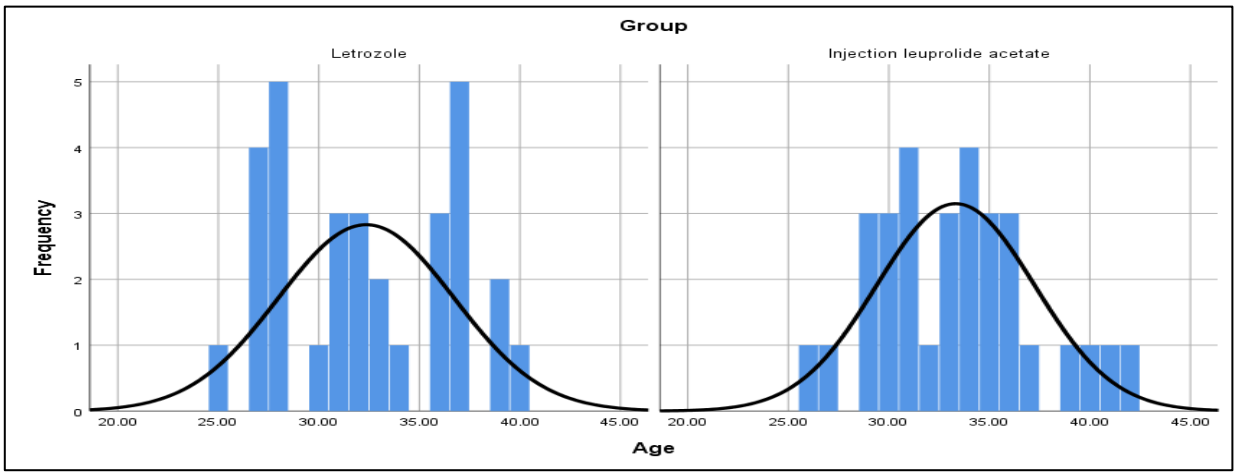

Figure 1: Histogram for age of patients in study group.

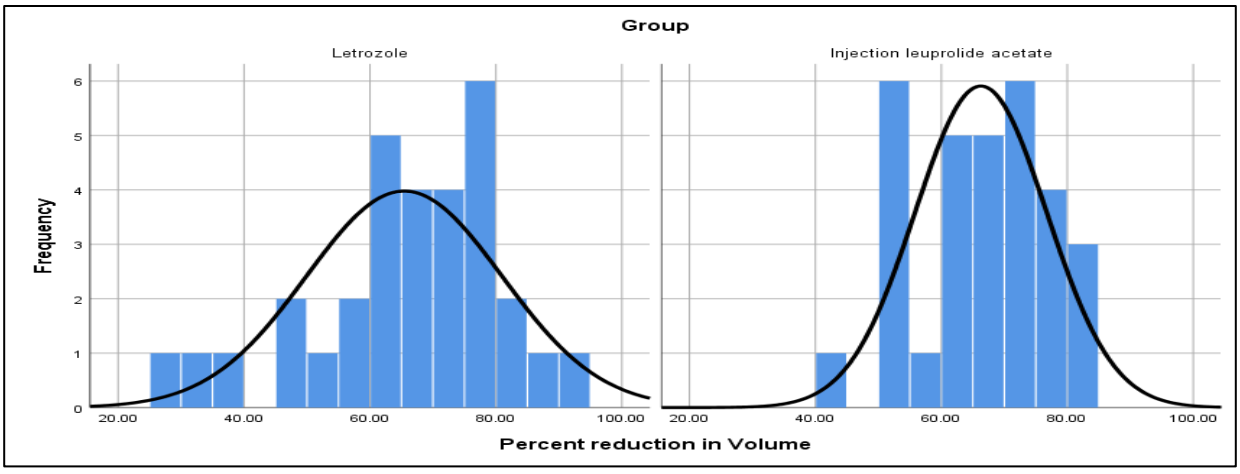

Figure 2: Histogram for percentage reduction in volume of myoma before and after treatment in study groups.

Table 1: Treatment groups and site in treatment groups.

Site	Treatment Groups		Total
	Group-A	Group-B	
Intramural	5(16.13%)	8(25.81%)	**13**
Myometrial	9(29.03%)	12(38.71%)	**21**
Submucosal	3(9.68%)	2(6.45%)	**5**
Subserosal	14(45.16%)	9(29.03%)	**23**
Total	**31**	**31**	**62**

Group A: Aromatase inhibitors (injection leuprolide acetate); Group B: Gonadotropin-releasing hormone agonist (Letrozole)

Table 2: Volume of myoma before treatment and at different treatment stages and percentage reduction in volume of myoma before and after treatment in study groups.

Vol. of Myoma	Group	N	Mean ± SD	95% CI	Minimum	Maximum	*P* value
Before treatment	A	31	31.28±6.76	28.80041 to 33.75959	21.50	48.96	0.327
	B	31	29.87±4.18	28.33676 to 31.40324	21.78	40.88	
4^{th} week	A	31	22.44±4.67	20.72703 to 24.15297	15.18	26.40	0.692
	B	31	22.95±5.40	20.96926 to 24.93074	14.40	39.52	
8^{th} week	A	31	14.01±6.47	11.63678 to 16.38322	0	26.00	0.832
	B	31	13.67±6.03	11.45818 to 15.88182	0	26.46	
12^{th} week	A	31	10.42±4.37	8.817071 to 12.02293	4.00	21.12	0.626
	B	31	9.95±3.14	8.798239 to 11.10176	5.46	18.56	
% reduction	A	31	65.43±15.54	59.72988 to 71.13012	27.17	91.01	82.31
	B	31	66.27±10.46	62.43324 to 70.10676	40.80	82.31	

Group A: Aromatase inhibitors (injection leuprolide acetate); Group B: Gonadotropin-releasing hormone agonist (Letrozole)

As presented in **Table 1**, in Group-A 5(16.13%) women had leiomyomas in intramural regions, 9(29.03%) in the myometrial region, 3(9.68%) in the submucosal region and 14(45.16%) women location of leiomyomas was subserosal. On the contrast, in Group B, 8(25.81%) women had leiomyomas in the intramural region, 12(38.71%) in the myometrial region, 2(6.45%) in the submucosal region, and 9(29.03%) in the subserosal region. Likewise, the volume of myoma before treatment and at different treatment stages and the percentage reduction in the volume of myoma before and after treatment in study Groups are presented in **Table 2**. Before treatment mean volume of leiomyomas in Group-A and B was 31.28±6.76 and 29.87±4.18, respectively. At this point, no significant difference was seen for volume between groups. i.e., p-value=0.327. The mean volume of myoma at 4th week in Group-A and B was 22.44±4.67 and 22.95±5.40. No significant difference was seen in mean volume between groups. i.e., p-value=0.692. In the 8th week, no significant difference was seen for the mean volume of myoma between groups. i.e. (Group-A: 14.01 vs, Group-B: 13.67, p-value=0.832). In the 12th week, no significant difference was seen for the mean volume of myoma between groups. i.e. (Group-A: 10.42 vs. Group-B: 9.95, p-value=0.626). Before treatment and after treatment from the 4th week till the 12th week no significant difference was seen in the number of myomas in treatment groups. The histogram for the percentage reduction in the Volume of myoma before and after treatment in study Groups is depicted in **Fig 2**.

DISCUSSION

The strategy for treating uterine myomas usually relies on the severity of symptoms, size and location of the myoma, patient's age, proximity of menopause, and patient's desire for pregnancy.

Approximately 40% of patients need medical/surgical intervention [**18**]. In this study, we compare the effect of gonadotropin-releasing hormone agonist (leuprolide acetate) vs. Aromatase inhibitor

(Letrozole) on the volume of uterine leiomyoma in pre-menopausal women with leiomyomas. Results of this study showed no significant difference between Leuprolide acetate and letrazole for volume reduction of myoma at 4th (leuprolide acetate: 22.44 vs. letrazole: 22.95, p-value=0.692), 8th (leuprolide acetate: 14.01 vs. letrazole: 13.67, p-value=0.832) and at 12th week (leuprolide acetate: 10.42 vs. letrazole: 9.95, p-value=0.626) post-treatment. Volume reduction was seen in both treatment groups but no statistically significant difference was obtained between groups. Percentage reduction in the volume of myoma before and after treatment showed that in the letrazole group reduction of volume was higher as compared to Leuprolide acetate but the difference is not statistically significant. i.e., Leuprolide acetate: 65.43% vs. letrazole: 66.27%, p-value=0.804

Similar to this study Ahmed m. Badawy in his study reported that aromatase inhibitors are as effective as gonadotropin-releasing hormone agonists in reducing adenomyoma volume and improving symptoms [**19**].

Mohammad Ebrahim Parsanezhad in his study reported greater myoma volume reduction with letrozole as compared to GnRh. i.e. 45.6% vs. 33.2% [**20**]. Percentage reduction in the volume of myomawas higher in both treatment groups as compared to Mohammad Ebrahim Parsanezhad findings.

Duhan et al. found a significant decrease in myoma volume after 12 weeks of treatment with letrozole 2.5 mg/day (52.5% on average) [**21**]. Percent decrease in myoma volume in this study was higher after 12 weeks of treatment. Koskas and Derrien study showed that Letrozole is as effective as GnRH agonists in reduction of fibroid size with less hot flush and the use of GnRH agonist is effective to decrease of uterine bleeding and correction of hemoglobin level, also add-back therapy with tibolone seems to reduce the hypoestrogenism symptoms of GnRH agonists [**22**].

Contrary to above mentioned studies Sanam Moradan in his study evaluated the effectiveness of the combination of GnRH agonists + aromatise inhibitor on the uterine fibroids. As per his findings the mean fibroid size reduced from 15.05 ± 57.20 cm to 13.56 ± 39.39 cm (p-value = 0.012) and fibroid volume reduced from 72.78 ± 110.6 to 50.96 ± 64.2 (p-value = 0.116).

Despite studies have reported better efficacy and higher reduction of volume for Letrozole a Cochrane review published in 2013 on aromatase inhibitors used for the management of uterine leiomyomas reported that there was insufficient evidence to support the use of aromatase inhibitors in the treatment of women with uterine fibroids (Song, Lu et al. 2013).Aromatase inhibitors contribute to the alleviation of symptoms and are considered to have little influence on the hormonal state of the whole body compared to GnRH agonists, causing no change in E2, T, FSH, and LH values in blood.

Therefore, for short-term use, aromatase inhibitors should preclude the side effects of low estrogen levels. At present, its use is limited. Long-term use of aromatase inhibitors (>24 weeks) with the consequent hypo-estrogenaemia could result in bone turnover, loss of bone mineralization, increased fracture risk and the need for add-back therapy [**23**]. However, the treatment course was not long in the present study

As a class of medication, GnRH agonist (leuprolide acetate) has historically been considered the most effective pre-surgical therapy for symptomatic leiomyoma. They induce a pre-menarchal state notable for hypoestrogenism, by downregulation of the hypothalamic-pituitary-ovarian axis, amenorrhea, improvement in symptoms (namely, AUB-HMB/IMB), and rapid reduction in leiomyomata volume. That being said, the benefits achieved come with an unavoidable side effect profile to include vasomotor symptoms, vaginal dryness, sleep disturbances, myalgia, arthralgia, mood-swings, and potential cognitive impairment [**24**].

On a molecular level, GnRH agonists decrease the expression of factors important for fibroid growth to include Transforming Growth Factor-Beta, Epidermal Growth Factor, and Insulin-like Growth Factor. Further data from our laboratory has shown reduction of the extracellular components collagen - 1, fibronectin, and versican with leuprolide acetate treatment [**25**].

According to the aforementioned research, uterine myomas may be effectively reduced in volume with the help of an aromatase inhibitor, and the results corroborate previous findings on letrozole's efficacy, safety, and absence of serious adverse effects in this respect. However, as was previously mentioned, findings vary in terms of the extent of efficacy; this may be related to between-study difference in patients' specific physical features, genetic variables, and severity of illness upon admission.

CONCLUSION

In conclusion, our randomized controlled trial at Lady Willingdon Hospital's Obstetrics and Gynecology Department compared leuprolide acetate and letrozole in reducing uterine leiomyomas in pre-menopausal women. Group A received aromatase inhibitor (letrozole) tablets for six months, while Group B received long-acting GnRHa (leuprolide acetate) injections and letrozole tablets. We measured myoma volumes using ultrasounds by a competent sonologist throughout the trial. The two therapy

groups reduced myoma volume similarly after 12 weeks of treatment, according to statistical analysis. Leuprolide acetate and letrozole reduced uterine leiomyoma volume similarly in pre-menopausal women. Leuprolide acetate and letrozole may be effective treatments for uterine leiomyoma volume reduction, according to our data. There is no statistically significant difference between these treatments, thus physicians and patients may have more freedom to choose depending on preferences, tolerances, and clinical concerns. This knowledge can also help healthcare providers and patients make informed decisions about uterine leiomyomas that preserve fertility and relieve symptoms. Our study helps explain various therapy possibilities, but patient responses may vary, and more research is needed to determine long-term outcomes, side effects, and other aspects. This study sheds light on the treatment of uterine leiomyomas in pre-menopausal women, highlighting the necessity to personalize treatment to each patient's needs.

REFERENCES

1. Yu O, D Scholes, R Schulze-Rath, J Grafton, K Hansen, SD Reed. A US population-based study of uterine fibroid diagnosis incidence, trends, and prevalence: 2005 through 2014. American journal of obstetrics and gynecology 219(6); 591: 2018.
2. Zepiridis LI, GF Grimbizis, BC Tarlatzis. Infertility and uterine fibroids. Best Practice & Research Clinical Obstetrics & Gynaecology 34; 66-73: 2016.
3. Smart OC, JT Hindley, L Regan, WG Gedroyc. Gonadotrophin-releasing hormone and magnetic-resonance–guided ultrasound surgery for uterine leiomyomata. Obstetrics & Gynecology 108(1); 49-54: 2006.
4. Sohn GS, S Cho, YM Kim, CH Cho, MR Kim, SR Lee. Current medical treatment of uterine fibroids. Obstetrics & gynecology science 61(2): 192-201, 2018.
5. Hodgson R, PB Chittawar, C Farquhar. GnRH agonists for uterine fibroids. The Cochrane Database of Systematic Reviews 2017(10), 2017.
6. Lewis TD, M Malik, J Britten, AM San Pablo, WH Catherino. A comprehensive review of the pharmacologic management of uterine leiomyoma. BioMed research international 2018.
7. Doherty L, L Mutlu, D Sinclai, H Taylor. Uterine fibroids: clinical manifestations and contemporary management. Reproductive sciences 21(9): 1067-1092, 2014.
8. Vilos GA, C Allaire, PY Laberge, N Leyland, AG Vilos, A Murji, I Chen. The management of uterine leiomyomas. Journal of Obstetrics and Gynaecology Canada 37(2): 157-178, 2015.
9. Kashani BN, G Centini, SS Morelli, G Weiss, F Petraglia. Role of medical management for uterine leiomyomas. Best Practice & Research Clinical Obstetrics & Gynaecology 34: 85-103, 2016.
10. Zupi E, G Centini, L Sabbioni, L Lazzeri, IM Argay, F Petraglia. Nonsurgical alternatives for uterine fibroids. Best practice & research Clinical obstetrics & gynaecology 34: 122-131, 2016.
11. Czuczwar P, A Stępniak, W Wrona, S Woźniak, P Milart, T Paszkowski. The influence of uterine artery embolisation on ovarian reserve, fertility, and pregnancy outcomes–a review of literature. Menopause Review/Przegląd Menopauzalny 15(4): 205-209, 2016.
12. Donnez J, MM Dolmans. Uterine fibroid management: from the present to the future. Human reproduction update 22(6): 665-686, 2016.
13. Stępniak A. Uterine artery embolization in the treatment of symptomatic fibroids–state of the art 2018. Menopause Review/Przegląd Menopauzalny 17(4): 141-143, 2018.
14. Alkatout I, L Mettler, V Günther, N Maass, C Eckmann-Scholz, M Elessawy, M Anapolski. Safety and economical innovations regarding surgical treatment of fibroids. Minimally Invasive Therapy & Allied Technologies 25(6): 301-313, 2016.
15. Prakash R, S Pandey, I Chawla. Effects of letrozole on patients with symptomatic leiomyoma in the reproductive age women. International Journal of Reproduction, Contraception, Obstetrics and Gynecology 6(5): 2017.
16. Chabbert-Buffet N, N Esber, P Bouchard. Fibroid growth and medical options for treatment. Fertility and sterility 102(3): 630-639, 2014.
17. Usluogullari B, CZ Duvan, CA Usluogullari. Use of aromatase inhibitors in practice of gynecology. Journal of ovarian research 8: 1-7, 2015.
18. Moroni R, C Vieira, RA Ferriani, FJ Candido-dos-Reis, L Brito. Pharmacological treatment of uterine fibroids. Annals of medical and health sciences research 4(3): 185-192, 2014.
19. Badawy AM, AM Elnashar, AA Mosbah. Aromatase inhibitors or gonadotropin-releasing hormone agonists for the management of uterine adenomyosis: a randomized controlled trial. Acta Obstetricia et Gynecologica Scandinavica 91(4): 489-495, 2012.
20. Parsanezhad ME, M Azmoon, S Alborzi, A Rajaeefard, A Zarei, T Kazerooni, V Frank, EH Schmidt. A randomized, controlled clinical trial comparing the effects of aromatase inhibitor (letrozole) and gonadotropin-releasing hormone agonist (triptorelin) on uterine leiomyoma volume and hormonal status. Fertility and sterility 93(1): 192-198, 2010.
21. Duhan N, S Madaan, J Sen. Role of the aromatase inhibitor letrozole in the management of uterine leiomyomas in premenopausal women. European Journal of Obstetrics & Gynecology and Reproductive Biology 171(2): 329-332, 2013.
22. Moradan S. Gonadotropin-releasing hormone agonist plus aromatase inhibitor in the treatment of uterine leiomyoma in near menopause patient: a case series study. Journal of Menopausal Medicine 24(1): 62-66, 2018.
23. Lønning PE, HP Eikesdal. Aromatase inhibition: clinical state of the art and questions that remain to be solved. Endocrine-related cancer 20(4): R183, 2013.
24. Bulletin AP. Alternatives to hysterectomy in the management of leiomyomas. Obstet Gynecol 112(2 Pt 1): 387-400, 2008.
25. Malik M, J Britten, J Cox, A Patel, WH Catherino. Gonadotropin-releasing hormone analogues inhibit leiomyoma extracellular matrix despite presence of gonadal hormones. Fertility and sterility 105(1): 214-224, 2016.