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**Original Research Article**

# Letrozole versus dienogest in endometrioma recurrent after surgery: a randomized controlled trial

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## ABSTRACT

**Background**: Letrozole is a third-generation aromatase inhibitor. As there is aberrant aromatase production by endometriotic stromal cells and the growth and regression of endometriosis is estrogen-dependent, the use of letrozole to reduce the size and symptoms of endometrioma especially in recurrent cases is a promising medical intervention. Dienogest is a fourth-generation progestin which is being used for the treatment of endometriosis due to its antiproliferative and antiangiogenic properties on endometrial tissue. The present study was conducted to compare the effects of letrozole and dienogest on endometrioma recurrent after surgery.
**Methods:** This randomized controlled study was conducted on 38 women having recurrence of endometrioma after surgery. They were randomly assigned to receive either letrozole (2.5 mg daily) or dienogest (2 mg once daily) for 6 months. Size of the endometrioma was measured by transvaginal ultrasound and the pain (dysmenorrhoea) was measured on a visual analog scale (VAS) of 0-10, prior to treatment and after 3 and 6 months of treatment.
**Results:** The mean size of endometrioma was reduced from a baseline of 6.06±2.40 cm to 5.23±1.37 cm and to 4.59±1.25 cm after 3 and 6 months of treatment with letrozole. While with dienogest the reduction was from a baseline of 6.67±1.31 cm to 4.83±1.50 cm and to 3.80±1.34 cm after 3 and 6 months of treatment. The difference between the two groups was not statistically significant but dienogest yielded better result in terms of effect size. Decrease in pain (dysmenorrhoea) was highly significant with both the drugs.
**Conclusions:** In terms of reduction of the size of endometrioma, dienogest yields better results than letrozole. Both the drugs are highly effective in alleviating pain (dysmenorrhoea).

**Keywords:** Endometrioma, Endometriosis, Letrozole, Dienogest

## INTRODUCTION

Endometriosis is an estrogen-dependent, chronic, inflammatory disease, prevalent worldwide in women of reproductive age and beyond. It affects roughly 10% (190 million) of reproductive age women and girls globally and the prevalence rises to 50% in infertile women.[1] Characterized by the growth and proliferation of endometrial glands and stroma outside the uterine cavity, it is responsible for chronic pelvic pain, dysmenorrhea, dyspareunia, chocolate cyst or endometrioma and subfertility. Endometrioma or the formation of a cyst within the ovary with ectopic endometrial tissue lining is one of the most common (17%-44%) manifestations of endometriosis.[2] Management of endometrioma includes surgical and medical treatment, taking into consideration the symptoms, desire for childbearing, lesion size and ovarian reserve. The recurrence rate after surgical management is 12-30% over a period of 2-5 years follow up,[3] and it may be higher if we take into consideration the

asymptomatic cases.[4] Excising endometrioma decreases ovarian reserve and compromises both natural and assisted fertility.[5-7] Leaving endometriomas in place prior to IVF increases the risk of pelvic infection and contamination of the culture system and thereby compromises the success of this expensive procedure.[8]As the management of the recurrent endometriomas by surgical intervention is becoming controversial, the reduction in the volume of the endometrioma and relief of pain by medical management is becoming a more acceptable choice of treatment.

Dienogest is a fourth-generation progestin with potent oral progestational activity without any systemic androgenic activity.[9] The effects of dienogest on endometriosis are not only antiovulatory activity, but also a direct effect on proliferation or cytokine production in stromal cells from eutopic and ectopic endometrial tissues.[10,11] Dienogest was found to significantly decrease the volume of the endometrial implants and dienogest 2 mg daily received approval for the treatment of endometriosis in the European Union in 2009.[11,12] Park et al demonstrated that dienogest administered for prolonged period is highly effective in preventing recurrence after surgery, reducing endometriosis-associated pain, and decreasing the size of recurrent endometrioma.[1]

Aromatase inhibitors (AI) have the ability to work both at the ovary and locally in the endometriotic tissue. Other medical therapies only inhibit estrogen production from the ovaries but not in endometriotic implants.[12] A systematic review assessing the efficacy of aromatase inhibitors (AIs) in treating pain symptoms caused by endometriosis concluded that AIs effectively reduce the severity of endometriosis-related pain symptoms.[13] Letrozole has been used in combination with steroid analogs to treat endometriosis for quite some time now. But we found no study so far on the use of letrozole alone for reducing the size of endometrioma. Letrozole does not inhibit hypothalamo-pituitary axis and subsequent ovulation and so may be suitable for women who wish pregnancy. Use of letrozole alone to reduce the size and associated pain of endometrioma appears to be a promising alternative to dienogest. With this background the present study was designed to compare the role of letrozole and dienogest in women with recurrent endometrioma.

## METHODS

The open label parallel design randomized controlled trial was conducted in the Department of Reproductive Endocrinology and Infertility of Bangabandhu Sheikh Mujib Medical University from March, 2021 to February, 2022. The participants were women, age between 18-40 years, with sonographically diagnosed endometrioma (>3 cm) recurrent after surgery, associated with dysmenorrhea. The exclusion criteria were sonographic features suggestive of other benign or malignant ovarian cyst, use of investigational drugs or hormones concomitant or in past 30 days and known case of pulmonary, cardiac, renal or hepatic disease. The study was approved by institutional review board. Informed consent was taken from each participant.

The participants were randomized into experimental and comparator groups. The experimental group A was given letrozole (Letrol 2.5 mg tablet, Renata Pharmaceuticals Limited, Dhaka) daily for 6 months. The comparator group B was given dienogest (Dinogest 2 mg tablet, Beximco Pharmaceuticals Limited, Dhaka) daily for 6 months. Primary outcome was change in the size and pain at the end of the 3rd and the 6th month. The size of recurrent endometrioma maximum transverse diameter assessed by transvaginal ultrasound. The pain of dysmenorrhea was scored on VAS. Secondary outcome was change in the serum Ca 125 levels.

The criteria for the diagnosis of endometrioma at transvaginal sonography was unilocular or multilocular cystic structures with diffuse low level internal echoes, with or without internal septations, surrounded by echogenic capsule or thickened nodular walls. Recurrence was defined as the presence of endometrioma more than 2 cm in size, detected by ultrasonography after previous surgery for endometrioma. The measurement of the larger one was taken when endometrioma was bilateral. The VAS is a validated, subjective measure for acute and chronic pain.[15] Scores were recorded by making a hand written mark on a 10 cm line that represented a continuum between “no pain” and “worst pain”. Patients were asked to put a tick mark on the scale according to their pain. In this scale, 0 meant no pain, and 10 meant ‘worst pain imaginable’. Cancer antigen 125 (CA-125) is a glycoprotein biomarker. Serum Ca-125 was measured from blood sample by automated analyzer Atellica, Siemens Germany.

Random sequence generation was done by computer generated random numbers. Permuted block randomization was done with stratification for age. Random allocation of treatment was done by someone not involved with the care of the patients. Allocation concealment was done by sequentially numbered sealed opaque envelops; each had a card inside labeled with an alphabet representing the intervention type. Allocation was never changed after opening the closed envelops. All data were collected by the principal investigator. There was no blinding.

Sample size of participants was calculated as 41 in each group, for a power of 0.80, a significance level of 0.05 and an effect size of 0.95. Statistical analyses were carried out by the SPSS program for Windows, version 22.0 (SPSS, Chicago, IL). The data were tested for homogeneity prior to analysis. The mean ± SD values or median, interquartile range were calculated as appropriate for outcome variables. Data was tested using the parametric tests such as unpaired t test, paired t-test, non-parametric test as Mann Whitney U test and Chi-square test as appropriate. $P<0.05$ was considered as statistically significant.

## RESULTS

This prospective comparative study was conducted in the Department of Reproductive Endocrinology and Infertility, Bangabandhu Sheikh Mujib Medical University, Dhaka from March 2021 to February 2022. A total 51 cases of recurrent endometrioma were screened for the study. Initially 44 patients met the inclusion criteria as well as gave consent, so they were recruited, randomized and received interventions. Finally, a total of 38 patients completed the study. Table 1 shows that 51 cases of recurrent endometrioma were screened for the study. Finally, 17 patients in letrozole group and 21 patients in Dienogest group completed the study.

**Table 1: Recruitment, intervention and participant flow.**

| Variables | N | |
|---|---|---|
| **Screened/ assessed for eligibility** | 51 | |
| **Excluded** | | |
| Not meeting inclusion criteria | 06 | |
| Declined to participate | 01 | |
| **Randomized and received intervention, (n=44)** | Group I, letrozole | Group II, dienogest |
| **Received intervention** | 21 | 23 |
| **Completed** | 17 | 21 |
| **Not completed** | 4 | 2 |
| Non compliance | 1 | 0 |
| Lost to follow up | 3 | 2 |

Table 2 and 3 describes the socio demographic and clinical characteristics of the study participants. Regarding demographic variables, there was no significant difference between group I and group II ($p<0.05$).

Table 3 and 4 show that the decrease in cyst size over 3 months and 6 months is significant ($p<0.05$) in Letrozole group and highly significant ($p<0.001$) in Dienogest group. Mean reduction at end point 6 months is more than that at end point 3 months. Overall, the mean reduction over 6 months is larger in the dienogest group (2.52±1.10 cm vs 1.65±1.23 cm). Cohen'sd is the effect size (standardized mean difference) used to indicate the magnitude of difference. It tells how large that effect is, while a p-value only tells if there is an effect. A value of 0.8 or more represents a large effect size. The effect size was also measured in terms of percentage reduction in the size of endometrioma. Table 5 shows that percentage reduction in cyst size is greater in dienogest group both after 3 months and 6 months of treatment. Difference is not significant after 3 months, but significant after 6 months ($p<0.05$).

Regarding the effects on pain, VAS score has dropped from baseline to after 3 months and then continued to drop lower than 2 after 6 months in both groups. Table 6 and 7 show that reduction of VAS score after 3 and 6 months of treatment were statistically highly significant in women given letrozole as well as dienogest. Table 8 compares the reduction in VAS score for pain over 3 months and 6 months between group I (Letrozole) and group II (Dienogest). Though not significant by p value, the effect size of dienogest over 6 months (Cohen's d 4.50) was larger than that of letrozole (Cohen's d 2.23).

**Table 2: Baseline sociodemographic characteristics of study participants, (n=38).**

| Variables | Group I (Letrozole), (n=21) | | Group II (Dienogest), (n=21) | | P value |
|---|---|---|---|---|---|
| | N | % | N | % | |
| **Age (years)** | | | | | |
| 18-30 | 10 | 58.82 | 16 | 76.19 | 0.074$^{ns}$ |
| 31-40 | 07 | 41.17 | 05 | 23.80 | |
| **Age (years), mean±SD** | 29.59±4.01 | | 27.48±4.65 | | |
| Range (min-max) | 23-36 | | 20-35 | | |
| **Occupation** | | | | | |
| Housewife | 12 | 64.07 | 17 | 80.95 | 0.357$^{ns}$ |
| Others | 05 | 35.29 | 04 | 19.04 | |
| **Living area** | | | | | |
| Urban | 13 | 76.47 | 14 | 66.66 | 0.383$^{ns}$ |
| Rural | 04 | 23.52 | 07 | 33.33 | |
| **Household income (monthly) (taka)** | | | | | |
| <30,000 | 10 | 58.80 | 11 | 52.40 | 0.473$^{ns}$ |
| ≥30,000 | 7 | 41.20 | 10 | 47.60 | |
| **Seek fertility treatment** | | | | | |
| Type of infertility | 14 | 82.35 | 20 | 95.23 | 0.226$^{ns}$ |
| Primary | 09 | 52.94 | 15 | 71.42 | |
| Secondary | 05 | 29.41 | 05 | 23.80 | |
| **Years of infertility** | 6.17±3.39 | | 4.38±3.28 | | 0.108$^{ns}$ |

Continued.

| Variables | Group I (Letrozole), (n=21) | | Group II (Dienogest), (n=21) | | P value |
|---|---|---|---|---|---|
| | N | % | N | % | |
| **Time interval to diagnosis of recurrence from previous surgery (Years)** | 2.93±1.28 | | 2.81±1.23 | | 0.778[ns] |
| **Previous surgery** | | | | | |
| Laparoscopy with ovarian cystectomy | 07 | 41.17 | 09 | 42.85 | 0.590[ns] |
| Laparotomy with ovarian cystectomy | 10 | 58.82 | 12 | 57.14 | |
| Bilateral endometrioma | 15 | 88.23 | 15 | 71.42 | 0.195[ns] |
| Unilateral endometrioma | 02 | 11.76 | 06 | 28.57 | |
| **Clinical** | | | | | |
| VAS for pain (Dysmenorrhoea) | 6.06±2.40 | | 6.67±1.31 | | 0.164[ns] |
| **Sonographic** | | | | | |
| Mean of maximum diameter of endometrioma (cm) | 6.24±1.21 | | 6.32±1.56 | | 0.801[ns] |
| Range (cm) | 4.00-8.80 | | 4-10.50 | | |
| **Laboratory** | | | | | |
| Serum Ca125 (U/ml) | 70.64 | | 59.10 | | 0.622[1] |
| Median, range | 20-232.3 | | 8.70-104.5 | | |

1=Non parametric test. Nonparametric test was done to analyze the data which have non-normal distribution.

**Table 3: Mean reduction in size of endometrioma at 3 and 6 months after treatment in group I (Letrozole), (n=17).**

| Variables | Size (mean of max diameter) of endometrioma (cm) | Mean reduction ± SD, paired difference | 95% CI of difference | | P value | Cohen's d |
|---|---|---|---|---|---|---|
| | | | Lower | Upper | | |
| **Baseline** | 6.24±1.21 | | | | | |
| **After 3 months** | 5.23±1.37 | 1.01±1.02 | 0.485 | 1.53 | 0.001[s] | 0.987 |
| **After 6 months** | 4.59±1.25 | 1.65±1.23 | 1.02 | 2.28 | 0.000[s] | 1.34 |

Paired t-test, s= significant.

**Table 4: Mean reduction in size of endometrioma at 3 and 6 months after treatment in group II (dienogest) (n=21).**

| Variables | Size (mean of max diameter) of endometrioma (cm) | Mean reduction ± SD, paired difference | 95% CI of difference | | P value | Cohen's d |
|---|---|---|---|---|---|---|
| | | | Lower | Upper | | |
| **Baseline** | 6.32±1.56 | | | | | |
| **After 3 months** | 4.83±1.50 | 1.49±0.78 | 1.132 | 1.848 | 0.000[s] | 1.89 |
| **After 6 months** | 3.80±1.34 | 2.52±1.10 | 2.017 | 3.024 | 0.000[s] | 2.28 |

s=significant

**Table 5: Percentage reduction in cyst size compared between letrozole and dienogest group.**

| Variables | Letrozole (mean ± SD) | Dienogest (mean ± SD) | P value | Cohen's d |
|---|---|---|---|---|
| **Percentage reduction in the cyst size from baseline to after 3 months (%)** | 15.27±15.78 | 24,22±2.29 | 0.057[ns] | 0.632 |
| **Percentage reduction in the cyst size from baseline to after 6 months (%)** | 25.32±16.05 | 40.09±13.74 | 0.004[s] | 0.988 |

Independent sample t test, ns=not significant, s= significant.

**Table 6: Decrease in mean VAS score from baseline to observations after 3 months and 6 months follow up in group I (letrozole), paired t test.**

| VAS score, (n=17) | Mean difference ± SD | 95% CI of difference | | P value | Cohen's d |
|---|---|---|---|---|---|
| | | Lower | Upper | | |
| **After 3 months** | 3.64±1.86 | 2.686 | 4.608 | 0.000[s] | 1.95 |
| **After 6 months** | 4.94±2.22 | 3.799 | 6.083 | 0.000[s] | 2.23 |

s=significant

**Table 7: Decrease in mean VAS score from baseline to observations after 3 months and 6 months follow up in group II (Dienogest), paired t test.**

| VAS score, (n=21) | Mean difference ± SD | 95% CI of difference | | P value | Cohen's d |
|---|---|---|---|---|---|
| | | Lower | Upper | | |
| **After 3 months** | 4.00±0.949 | 3.56 | 4.43 | 0.000[s] | 4.21 |
| **After 6 months** | 5.71±1.27 | 5.13 | 6.29 | 0.000[s] | 4.50 |

s=significant.

**Table 8: Comparison of change in VAS score for pain in group I (Letrozole) and group II (Dienogest), unpaired t test.**

| Variables | Mean difference ± SD | 95% CI of difference | | P value (significance of difference) | Cohen's d |
|---|---|---|---|---|---|
| | | Lower | Upper | | |
| **After 3 months** | 0.352±0.467 | 0.594 | 1.30 | 0.455[ns] | 0.75 |
| **After 6 months** | 0.773±0.573 | 0.389 | 1.936 | 0.186[ns] | 1.35 |

ns=not significant

**Table 9: Comparison of mean reduction of Ca 125 in group I (Letrozole) and group II (Dienogest) after 6 months, non-parametric test.**

| Variables | Group I (Letrozole), (n=17) | Group II (Dienogest), (n=21) | Test | Sig. |
|---|---|---|---|---|
| **Mean reduction of Ca 125 (U/ml)** | 10.7 (6.3-13.0) | 16.7 (10.0-32.6) | Independent samples Mann-Whitney U test | 0.026[1] |

Non-parametric test was done for the data as this has non-normal distribution, 1= significant.

**Table 10: Side effects associated with group I (letrozole) and group II (dienogest), (n=50).**

| Variables | Group I (Letrozole), (n=17) | | Group II, (Dienogest) (n=21) | |
|---|---|---|---|---|
| | N | % | N | % |
| **Irregular bleeding** | 11 | 64.70 | 12 | 57.14 |
| **Nausea vomiting** | 2 | 11.0 | 0 | 0.0 |
| **Leg cramp** | 2 | 11.0 | 1 | .04 |
| **Acute abdominal pain** | 2 | 11.0 | 0 | 0.0 |
| **Back pain** | 1 | 05.0 | 2 | 09.0 |
| Hot flush | 1 | 06.0 | 0 | 0.0 |
| Headache | 0 | 0 | 0 | 0 |
| Decrease libido | 0 | 0.0 | 0.0 | 0.0 |

Table 9 shows that the reduction of Ca 125 from baseline to after 6 months is more in women having dienogest than in women having letrozole and the difference is significant (<0.05). Table 10 shows that irregular bleeding was the most troublesome and commonly encountered side effect in both groups.

## DISCUSSION

This randomized controlled trial was carried out with an aim to evaluate and compare the effects of letrozole and dienogest on the size of endometrioma and associated pain (dysmenorrhea) recurrent after surgery. The findings were that dienogest yielded better results than letrozole in reducing the size of endometrioma after 3 and 6 months of treatment though the mean difference was not statistically significant. Both the drugs were highly effective in alleviating associated pain.

The existing studies regarding the therapeutic application of aromatase inhibitors for endometrioma used an additional hormonal drug. There are very few studies on the letrozole alone in alleviating pain of endometriosis. Our study is to assess the efficacy of letrozole in reducing the size of endometrioma. In our study the mean size of endometrioma continued to reduce through 3 and 6 months of treatment, but it was less than that achieved in the previous studies using additional drugs, which are discussed here.

Ansary et al showed that the percentage reduction in mean diameter of endometrioma by daily administration of letrozole, 2.5 mg combined with norethisterone 5 mg for 3 and 6 months was 19.72% and 40.59% respectively. Agarwal et al treated endometrioma with daily administration of letrozole 5 mg (double the dose we used) along with norethindrone acetate 5 mg.[17] They had a higher (50%) reduction in maximum diameter at the end

of three months. So, the effect of letrozole on the size of endometrioma appears to be dose dependent.

Taniguchi et al achieved a 37.2% reduction by using only norethisterone.[18] Taniguchi et al reported a 40% of reduction in endometrioma volume by using oral contraceptives (drosperinone 3 mg plus ethinyl estradiol 20 microgram) alone for 6 months.[18] Letrozole combined with norethisterone may be more efficacious than letrozole or norethisterone alone in reducing the volume of endometriotic cysts. Seal et al reported the case series of 5 women who took letrozole (2.5 mg), plus 0.15 mg desogestrel, and 0.03 mg of ethinyl estradiol, for 6 months.[19] Disappearance of ovarian endometrioma and reduction in pelvic pain was seen in all cases at the end of 6 months. These findings favor the use of letrozole in combination with progestin suppression provided by combined oral contraceptive pills.

Use of letrozole has been associated with development of ovarian cysts.[20,21] Our study as well as other studies did not reveal any evidence of ovarian cyst formation.[19,22] Remorgida et al and Abushahin et al excluded women with chocolate cyst prior to the intervention, provided the drugs following surgery and did not categorize the cysts as simple or endometriotic but all women of our study and the studies of Seal et al and Ferrero et al had documented presence of the endometrioma, which may prevent the appearance of functional cysts.[20-22]

Our study found that the endometrioma size reduction was more with dienogest than with treatment by letrozole. Cyst size reduction greater than 40% was achieved with dienogest for 6 months. Efficacy of dienogest at a dose of 2 mg/day has been proven in multiple studies. Aizzi reported a reduction of mean diameter of endometrioma from 5.45 cm baseline to 3.1 cm in twenty women treated with dienogest for 3 months.[23] By the end of the 6$^{th}$ month's treatment, only 2 patients had residual cysts. Park et al[1] showed that by treatment with dienogest the size of endometrioma was significantly reduced at 12 months (30.9 versus 20.8 mm) and 18 months (20.5 versus 14.7mm). Muzzi et al reported of a 40% reduction in diameter after 6 months of treatment with dienogest.[24] All the results are consistent proving the efficacy of dienogest in reducing size of endometrioma.

Mandy treated a total of 20 premenopausal women with letrozole 2.5 mg for 6 months and found mean VAS dropped from 6.1 to 4.[25] In our study, with administration of letrozole the mean pain score dropped from 6.06 to 4.00 after 3 months and reached 1.12 after 6 months. So, the reduction over 6 months was higher. Pain perception varies with population which may explain this difference. It is apparent from our study and study by Mandy and case reports of Takayama et al, Razzi et al, Fatemi et al, Hefler et al, Verma and Konje that letrozole alone can cause significant improvement in pain score.[25-30] But Ferrero et al did a comparative study on norethisterone versus letrozole plus norethisterone alone and observed no significant difference in the amelioration of pain symptoms, questioning the additional effect of letrozole on the pain reduction provided by norethisterone alone. [22]

Our study found dienogest as a better option for pain relief. Uludag et al, Vignali et al as well as Muzzi et al found a significant improvement in pain score 6 months after treatment with dienogest.[24,31,32]

Our study found that the reduction of Ca 125 from baseline to after 6 months was more in women having dienogest than in women having letrozole and the difference was significant (<0.05). This finding may be a reflection of the anti-inflammatory effect exerted by dienogest.

We did the estimation of effect size. Effect size is not the same as statistical significance. Smaller p values do not necessarily imply the presence of larger or more important effects but the effect size tells us about the magnitude of treatment effects.[33] Effect size was greater in respect of both size and pain reduction with dienogest.

In our study, side effects in both groups were mild and did not require withdrawal of any participant. Irregular bleeding was the most common complaint. Chandra et al reported irregular bleeding in 15.8% women having dienogest.[34] In the study of Uludag et al, the most common side effect was menstrual irregularities.[31] The irregular bleeding is a type of breakthrough bleeding explained by hormonal imbalance that can be stabilized with short course of estradiol valerate. The incidence of irregular bleeding was much more in our study (64.7% with letrozole and 57.4% with dienogest). This may be explained by the younger age women in our study.

Letrozole may stimulate available antral follicles and induce pregnancy. There was pregnancy in women with adenomyosis receiving daily 2.5 mg letrozole for 6 months.[35] Our study did not result in any pregnancy in the letrozole arm. Disturbed tubo-ovarian relation resulting from surgery or endometriosis may be responsible.

The clinical significance of the study findings is that letrozole should be administered with other progestins or in a double dose to have an enhanced effect. The use of letrozole in women who wishes pregnancy will ameliorate pain but compromise the reduction in endometrioma. Because few data are available on long-term efficacy and safety of letrozole it should be administered only short term in women or be combined with calcium and vit D to prevent osteoporosis from possible hypoestrogenic effect.

***Limitations***

The study was done with a small sample size over a short period of time, the study population recruited form one selected center thus challenging the external validity of study findings. Data collection and follow up was challenging due to COVID-19 situation. Selection bias was eliminated by random allocation and allocation

concealment, but their absence of blinding of participants and personnel dispensing the drugs, absence of blinding of outcome assessment and outcome data was incomplete as there was drop out of participants in both arms.

## CONCLUSION

For reduction of the size of endometrioma, dienogest yields better results than letrozole though mean difference in changes is not statistically significant. Both the drugs are highly effective in alleviating associated dysmenorrhoea. Letrozole at a dose of 2.5 mg daily is a good option for pain reduction but not a better option than dienogest for reducing the size of recurrent endometrioma. Further research is needed on higher doses and regimens of letrozole, with or without combinations to determine the optimal medical treatment of recurrent endometrioma.

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