

## **Uterine resectoscopic myomectomy with and without microrelin pretreatment: a single-blinded randomized clinical trial.**

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### **Abstract**

**Study objective:** To assess the outcomes of surgery in the group of patients who were submitted to pre-operative GnRH agonists in comparison with those who received no medication. The levels of gonadotropin hormones (LH and FSH) and estradiol, which were measured 2 and 12 weeks after treatment, were also compared between two groups.

**Design:** Single-blinded randomized clinical trial.

**Design classification:** Canadian Task Force Classification I.

**Setting:** University hospital.

**Patients:** A total of 60 patients participated in this clinical trial. Inclusion criteria were: age between 18-50 y (premenopausal women).

**Interventions:** Sixty patients were assigned randomly to intervention and control group. Intervention group received three doses of monthly intramuscular injections of Microrelin 3.75 mg (a sustained release formulation of triptorelin) before hysteroscopic myomectomy and control group received no medications. Uterine resectoscopic myomectomy was performed in both groups.

**Measurements and main results:** Operation characteristics including operation time and amount of absorbed fluid were measured. Level of difficulty and satisfaction from surgeon's view were assessed based on Visual Analog Scale (VAS). Serum levels of LH, FSH and estradiol were measured at the baseline and after 2 and 12 weeks in both groups. A total of 60 patients participated in this clinical trial. The sizes of myomas were significantly reduced in microrelin group in comparison with control group (33% reduction,  $p < 0.0001$ ). The administration of Microrelin led to significant reduction of estradiol, LH and FSH levels after 12 weeks. However a transient flare-up in the level of estradiol was detected after 2 weeks. The satisfaction level from operation from surgeon's view was significantly higher ( $p = 0.01$ ) and the level of difficulty was lower in Microrelin group ( $p = 0.049$ ). No significant difference in haemoglobin drop after operation was detected between two groups.

**Conclusion:** Our study showed that pretreatment with Microrelin before uterine resectoscopic myomectomy could lead to less surgical difficulties and subsequently lower operation time. The amount of haemoglobin (as an indicator of blood loss) was not affected with this intervention. Our study supports the beneficiary influence of GnRH agonists in outcomes of myomectomy.

**Keywords:** GnRH agonist, Myoma, Myomectomy, Clinical trial.

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### **Introduction**

Uterine leiomyomata are the most frequent benign tumour of uterus and is considered to be the most common cause of uterine surgery [1,2]. It has been previously reported that pretreatment with Gonadotropin Releasing Hormone (GnRH) analogs reduces the size of myomas and facilitate hysteroscopic surgery [3,4]. However, the numbers of randomized clinical trial confirming this beneficiary effect of GnRH analogs are so restricted. Some studies have supported the advantages of administration of GnRH analogs before

operation since these medications have the potential to decrease the volume of distension fluid and the overall surgical time, but some other literatures have shown that these analogs may increase the recurrence of myomas because they make small myomas less visible during the surgery [5,6].

The growth of leiomyomas are stimulated by sex steroid hormones and therefore prescription of GnRH agonists leads to suppression of pituitary ovarian function which helps to temporary control of bleeding and correction of iron deficiency anaemia [2,7,8]. However, as these analogs may sometimes

make the enucleation of myomas more difficult no definite recommendation of their administration has been made so far.

The purpose of this study was to evaluate and compare the clinical and surgical outcomes of uterine resectoscopic myomectomy with and without pretreatment with GnRH analogs. Here, we also tried to compare the difficulty of the operation with assessing the volume of the absorbed fluid and total operation time and also the level of satisfaction from surgeon's view with and without pretreatment with GnRH analog.

## Materials and Methods

### Study design and participants

This investigation is a single-blinded randomized clinical trial with registration number: IRCT201408133950N3. Participants were premenopausal women selected for hysteroscopic myomectomy due to different complains related to uterine myomas.

**Inclusion criteria:** Age between 18-50 y (premenopausal women), patients who are candidate for surgical myomectomy, existence of myomatous uterus with sub-mucosal, intracavitary myomas or myomas with less than 50% invasion into myometrium, less than 2 myomas with size range of 2-4 cm, using non-hormonal contraception methods and Body Mass Index (BMI) between 18 and 30.

**Exclusion criteria:** Previous history of endometrial, cervical or breast cancer, previous history of endometrial atypical hyperplasia or adenocarcinoma, history of severe coagulopathy, previous consumption of GnRH agonists to treat myomas, pregnancy, history of osteoporosis, liver dysfunction, alcohol consumption, drug abuse and necessity for urgent operation. Patients with a trial of embolization therapy in the preceding 2 y were excluded from the study.

62 patients referred to gynaecology clinic were selected based on the inclusion and exclusion criteria and were randomly assigned to intervention and control group by using Permuted Balanced Block Randomization method. Adequate information about the trial was given to each patient before enrolment and written consent was obtained from each patient. The study was approved by the ethics committee of Tehran University of Medical Sciences. Data were collected from Jan to Dec 2014. Two patients refused to continue due to personal reasons, therefore 60 patients were finally allocated into intervention and control groups, 30 participants in each (Figure 1).

### Intervention

Treatment group received 3.75 mg Microrelin (provided by Pooyesh Daru Corporation). Myomectomy was performed in both groups using monopolar resectoscope system. Procedures were scheduled in the early follicular phase for patients

allocated to the control group and in the third or early fourth week after the second GnRH administration in the treatment group. Resectoscopic resection was done in both groups using the slicing technique with a transcervical 9 mm, 0° fore oblique view, operative resectoscope, equipped with a unipolar electro-surgical loop (KARL STORZ GmbH and Co., Germany).

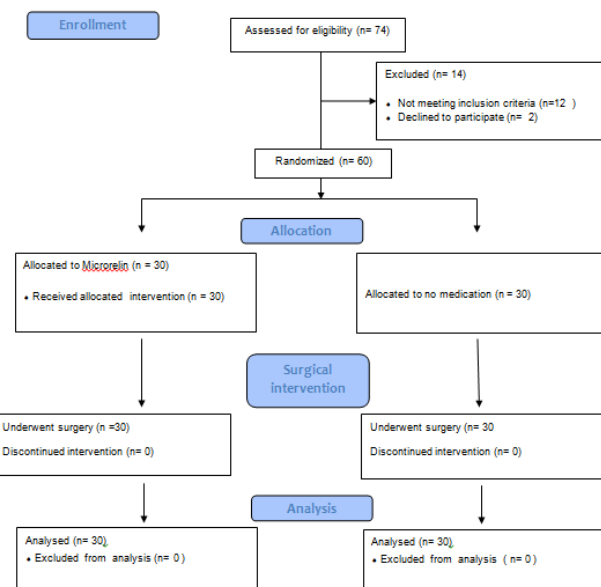


Figure 1. Flow diagram.

### Measurements

Patient's baseline characteristics including age, parity and history of reproductive disorders were indexed during face-to-face interviews. The sizes of myomas were measured at the baseline (before treatment with GnRH analog) and before operation by ultrasound, which was performed by a single expert of radiology. Total surgical time and operation time were measured. The amount of absorbed fluid was calculated by reduction of the amount of fluid in the suction instrument from the total administered fluid. Circulatory estradiol, Luteinizing Hormone (LH) and the Follicle Stimulating Hormone (FSH) were measured at the baseline and then 2 and 12 weeks after administration of first dose of Microrelin.

Serum levels of LH and FSH were measured with immunometric ELIZA kit with detection range of 0.5 mIU/ml to 200 mIU/ml for LH and 0.6-100 mIU/ml for FSH. Estradiol parameter assay kit with sensitivity of 12.1 pg/mL was used to measure serum level of estradiol. The level of satisfaction from operation and the difficulty of the surgery were assessed according to surgeon's view and were rated based on Visual Analog Scale (VAS) with the score range of 1-10.

Both the surgeon and the radiologist reporting the size of myomas before the treatment and the operation were not aware of the patient's allocated groups.

**Statistical analysis**

All statistical analyses were performed using SPSS software, version 18.0 (SPSS Inc., Chicago IL, USA). Categorical values are reported by percentages and continuous data are expressed by mean ± standard deviation (SD). One-way analysis of variance (ANOVA) with test for linearity was used to compare means between groups. Pearson chi-square test was used to compare categorical data and Independent t-test with confidence interval of 95% was used to compare quantitative value of both groups. The value of p<0.05 was considered statistically significant.

**Results**

All patients were nulliparous. Table 1 shows the baseline characteristics of the patients in this clinical trial. The mean age in the Microreltin group was 32.10 ± 2.7 and 31.94 ± 2.4 in control group. No significant difference in the mean age was observed between two groups (p=0.82). History of reproduction disorders was detected in 9 (29%) patients in Microreltin group and in 8 (25.8%) participants in control group. Myomas were matched according to their topography in two groups. Cumulative topographic scores according to STEPW were 0.96 and 1.07 in agonist and control group respectively (p=0.12). There was no significant difference in the mean of pretreatment size of myomas between two groups (2.8 ± 0.79 cm and 1.9 ± 1.02 cm in the Microreltin and control groups, respectively). There was no statistically significant difference between the mean numbers of myomas between two groups. The mean size of myomas was significantly reduced in the Microreltin group in comparison with control group

(P<0.0001). The mean size of myomas before operation was 1.9 ± 1.02 cm (range: 1.6-3.1 cm) in intervention group and 2.8 ± 0.79 (range: 2.4-3.4) in control group which illustrate the significant reduction of the size of the myomas with Microreltin administration.

**Table 1.** Baseline characteristics of the subjects in two groups.

Category	Microreltin Group (n=30)	Control Group (n=30)	p value
Age <sup>a</sup>	32.10 ± 2.7	31.94 ± 2.4	0.82
History of reproductive disorders <sup>b</sup>	9 (29%)	8 (25.8%)	0.13
Myoma pretreatment size <sup>a</sup>	2.8 ± 0.79	1.9 ± 1.02	0.62
Number of leiomyomata <sup>a</sup>	1.3 ± 0.2	1.3 ± 0.4	0.55
Myoma topographic score <sup>c</sup>	0.96	1.07	0.12
Hemoglobin <10 g/dl the day before operation <sup>b</sup>	3 (9.6%)	4 (12.9%)	0.06

<sup>a</sup>mean ± SD; <sup>b</sup>frequency (%); <sup>c</sup>STEPW scoring system.

The laboratory measurements showed haemoglobin (Hb) less than 10 g/dl in three (9.6%) patients in the Microreltin group and four (12.9%) in control group at the day before surgery. The day after operation, low levels of Hb (below 10 g/dl) were detected in 4 and 5 patients (12.9% and 16.1%) in intervention and control groups, respectively (Table 2). In the Microreltin group, the total surgical time was significantly lower (22.5 ± 3.1 min in the Microreltin group and 28.3 ± 3.7 min in control group) (Table 2).

**Table 2.** Comparison of surgical outcomes between the two groups.

Outcome	Microreltin Group	Control Group	p value
Operation time <sup>a</sup>	16.4 ± 2.5 b	22.1 ± 2.4	0.0001
Total Surgical Time <sup>a</sup>	22.5 ± 3.1	28.3 ± 3.7	0.0001
Administered Fluid <sup>c</sup>	3398 ± 229	4100 ± 408	0.163
Absorbed Fluid <sup>c</sup>	374 ± 45	486 ± 65	0.045
Level of Satisfaction <sup>d</sup>	8.4 ± 0.6	7.8 ± 1.0	0.012
Level of difficulty <sup>d</sup>	4.6 ± 1.8	6.0 ± 2.9	0.049
Hemoglobin<10 g/dl at the day after operation <sup>e</sup>	4 (12.9)	5 (16.1%)	0.43

<sup>a</sup>Minutes; <sup>b</sup>Mean ± SD; <sup>c</sup>milliliters; <sup>d</sup>VAS: Visual Analog Scale (1-10); <sup>e</sup>frequency (%).

There was no significant difference in the levels of estradiol, LH and FSH at the baseline between two groups. However, concentrations of circulatory estradiol and LH were significantly reduced after 12 weeks of treatment with Microreltin in comparison with control group (P<0.0001). Similarly, the significant reduction of FSH occurred after 12 weeks in the Microreltin group in comparison with control group. (p<0.0001, Table 3).

The satisfaction level from operation from surgeon’s view was significantly higher in the Microreltin group. Satisfaction level was measured based on VAS (scale: 1-10) and was 8.4 ± 0.6 in the Microreltin group and 7.8 ± 1.0 in the control group (p=0.01). Surgeon’s viewpoints about the difficulty level of the operation were also indexed based on VAS and was significantly lower in the treatment group (4.6 ± 1.8 and 6.0 ± 2.9).

2.9 in the Microrelin and control groups, respectively. (p=0.049, Table 2).

**Table 3.** The amount of change in serum hormone levels after 2 and 12 weeks in the Microrelin group.

Serum hormone level	Baseline	Week 2	Week 12	p value <sup>a</sup>
Serum estradiol level <sup>b</sup>	67.66 10.23	± 75.87 10.94	± 16.79 ± 8.56	<0.0001 <sup>c</sup>
Serum LH level <sup>d</sup>	6.77 ± 2.11	7.74 ± 2.95	2.05 ± 0.67	<0.0001
Serum FSH level <sup>d</sup>	6.74 ± 2.32	7.02 ± 2.65	2.95 ± 0.64	<0.0001

<sup>a</sup>Significance of difference between baseline and week 12; <sup>b</sup>pg/ml; <sup>c</sup>Comparison using paired t-test; <sup>d</sup>mIU/ml

### Discussion

Although the advantages of administration of GnRH agonists before laparoscopic or abdominal excision of intramural or subserosal myomas have been demonstrated, still prescription of these agents has not been definitively recommended [9]. Dubuisson et al. showed that preoperative GnRH analogue results in a softening of the uterine myomas and facilitates morcellation [10]. However, Campo et al. illustrated that the operative time in patients who have received preoperative GnRH was higher than those who received no medication [9]. The results of Campo’s study are in controversy with our outcomes. Our investigation revealed significant reduced operation time and lower difficulty level from surgeon’s view in the group of patients submitted to preoperative GnRH therapy. Some other investigations have also reported that administration of preoperative GnRH analogs results in a more difficult identification of the cleavage plane and thus makes the surgical time longer [11-13]. In controversy with these reports, Perino et al. showed a decreased surgical time, bleeding, and volume of distension fluid for those patients to whom GnRH analogs had been administered in comparison to control group who received no medication which is in line with our results [5]. According to Campo et al. study in 2005, the cervical dilatation is harder and more time-consuming among those patients submitted to pre-operative GnRH analogs [13]. So, the reason for these reported controversies in surgical time can be differences in measuring surgical time (whether they have considered the duration of anaesthesia and cervical dilatation time or not). In fact, it seems that GnRH analogs reduce the size of myomas and thus facilitates surgical process and decreases the amount of bleeding. On the other hand, when considering the time that is required for cervical dilatation or the time that consumes in exploring the small-sized myomas for enucleating, pre-operative administration of GnRH analogs does not seem to be advantageous. In controversy with these results, our investigation showed reduced operation time both the surgical duration and total operation duration. Other operation features such level of satisfaction was significantly higher among the GnRH group compared with the control group.

Similar with previous reports that have shown that pre-operative GnRH agonist increase the difficulties to identify and dissect the cleavage plan between leiomyoma and its pseudocapsule [14,15]. Vercellini et al. demonstrated that treatment with a GnRH agonist before abdominal myomectomy has no significant effect on intraoperative blood loss [16]. Here, we did not measure the volume of blood loss but the frequency of low Hb level (lower than 10 g/dl) the day before and the day after operation showed no significant difference between the Microrelin and control group. Our results are in line with Vercellini’s reports and it seems that pre-operative treatment with GnRH agonists does not have a beneficiary effect in reducing blood loss [16].

Uterine myomas are estrogen dependent tumours. Both receptors of estrogen and progesterone have been identified in these tumours [17]. Moreover, the estrogen secreted by myomas may reach a concentration to support its own growth [18]. It has been shown that GnRH agonists reduce estrogen levels to those occurring after menopause or after surgical oophorectomy [19]. In the present study we demonstrated an average reduction of 77% (16.7 pg/ml) in circulatory estradiol level after 12 weeks. GnRH agonists which initially stimulate the pituitary gland but continuous administration inhibits the secretion of gonadotropins as a result of receptor desensitization and/or down-regulation. Our investigation showed an increased level of estradiol after 2 weeks of treatment with GnRH agonists which is a result of the initial stimulation of pituitary glands. Similar to our results, Parsanezhad et al. demonstrated raised levels of estradiol after 2 weeks of GnRH analog administration [20]. The same phenomenon of hormone flare-up was also reported by Harding et al. who also demonstrated the probability of ovarian enlargement, especially when GnRH agonists are started at the early follicular phase [21]. Although increased levels of estradiol with treatment initiation can result in myoma growth, these consequences are usually transient. However, Friedman reported a case of rapid uterine enlargement during the first seven days of the administration of GnRH agonists [22].

In conclusion, our study shows that pretreatment with GnRH agonist before uterine resectoscopic myomectomy leads to less surgical difficulties and subsequently lower operation time. This study shows an average reduction of 33% (from 2.8 cm to 1.9 cm) in the sizes of uterus myomas with administration of GnRH agonist. Although, GnRH analogs led to more favourable surgery characteristics, the amount of Hb (as an indicator of blood loss) was not affected with this intervention.

### Conclusion

In the present study, we tried to evaluate the effect of the administration of GnRH agonists (Microrelin 3.75 mg) on outcomes of resectoscopic myomectomy among premenopausal women with uterine myomas. A significant reduction of the mean myoma size (33%) was reached in the Microrelin group which, as a result, led to more favourable surgical outcomes. The duration of operation and the level of surgery difficulty from surgeon’s viewpoints were significantly

lower in the Microrelin group. Moreover, the administration of these agents was associated with significant reduction in estradiol, LH and FSH levels after 12 weeks, though initially, a transient increase in these levels were detected by the end of the second week due to flare-up effect. Our study supports the beneficiary influence of GnRH agonists in the short-term. Longer follow-up studies, nonetheless, are required to evaluate long-term outcomes and the rate of recurrence.

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