



## The comparison of the effects of the natural micronized Progesterone and the Gonadotropin Releasing Hormone (GnRHa) agonist compounds on the rate of bleeding during hysteroscopic myomectomy in the women with abnormal uterine bleeding

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**Article History**

Received: 03 August 2019

Reviewed: 07/August/2019 to 18/September/2019

Accepted: 21 September 2019

Prepared: 25 September 2019

Published: November - December 2019

### Citation

Mehri Jafari Shobeiri, Maryam Pourbarghi Soufiani, Parvin Mostafa Gharabaghi, Manizheh Sayyah Melli, Elaheh Ouladsaheb Madarek, Simin Atashkhoyi, Masome Bakhshandeh, Neda Shoari, Farzane Farhang. The comparison of the effects of the natural micronized Progesterone and the Gonadotropin Releasing Hormone (GnRHa) agonist compounds on the rate of bleeding during hysteroscopic myomectomy in the women with abnormal uterine bleeding. *Medical Science*, 2019, 23(100), 963-971

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## ABSTRACT

**Introduction:** Sub-mucosal myomas are one of the causes of abnormal uterine bleeding. Hysteroscopy is a minimally invasive procedure whereby sub-mucosal myomas can be respected. Various drugs are used to reduce the endometrial thickness and the volume of myoma, which may facilitate the removal of myoma. The aim of this study was to compare the effects of the natural micronized progesterone and GnRHa in controlling the rate of bleeding during hysteroscopy. **Methods:** In this controlled clinical trial study, 50 patients with sub-mucosal myoma were selected, with the myoma diameter of 30 mm or less, and were randomly divided into two equal groups. The first group was admitted at the end of the day of taking the Utrogestan tablet, and the second one was admitted 4 weeks after the second injection of GnRHa, for myomectomy. In both groups, the rate of bleeding during surgery, the success rate of myomectomy, the duration of surgery, the image resolution, the amount of the absorbed fluid, the length of stay in hospital and the drug side effects were compared with Spss20 software used for statistical analysis. **Findings:** In this study, 50 patients were identical in terms of age, the number of gravida, the number of parity and the number of intrauterine myomas. The no bleeding cases were higher in the progesterone group (72%) than in the GnRHa group (16%) ( $P = 0.001$ ). The image resolution of the progesterone group was significantly higher than that of the GnRHa group (88% and 56%,  $P = 0.013$ ). The rate of decline of Hb and Hct after the surgery, the mean duration of surgery, the volume of the absorbed fluid, the change of sodium and potassium were similar in both groups. **Conclusion:** The results of this study showed that the rate of bleeding during surgery was lower and the hysteroscopic image resolution was better in the progesterone group than in the GnRHa group. However, as the duration of treatment with Uterogstan is shorter than GnRHa, and the cost of Uterogstan is lower than that of GnRHa; it is recommended that this drug be used for endometrial preparation to reduce the rate of bleeding during surgery and for more image resolution before hysteroscopic myomectomy.

**Keywords:** Uterine myoma, Hysteroscopy, Progesterone, GnRHa

## 1. INTRODUCTION

Uterine leiomyomas are the most common benign tumors of the uterus. Leiomyomas are benign growth of the myometrial tissue of uterine, which is seen in 70 to 80% of women by the age of 50 years. Depending on their location in the uterus, the myomas are divided into 3 subgroups, including sub-mucosal, intramural and sub-serosal. Sub-mucosal myomas are in contact with or inside the endometrial cavity, thereby causing the uterine cavity to disrupt, and these types of myomas cause abnormal uterine bleeding.

Hysteroscopy is a standard minimally invasive procedure, which can well resect the sub-mucosal myomas and is associated with a rapid recovery after the surgery, and can well relieve the patient symptoms, while the traditional and old treatments of sub-mucosal myomas were hysterectomy or myomectomy. When performing a hysteroscopic myomectomy, the thinning of the endometrium shortens the length of surgery, decreases the fluid absorption and reduces the rate of bleeding during surgery. Therefore, various drugs, such as oral desogestrel in combination with vaginal raloxifene (Cicinelli et al., 2007), oral gestrinone (Triolo et al., 2006) and vaginal danazol (Florio et al., 2012) have been used to prepare the endometrial thickness.

Due to the presence of estrogen and progesterone receptors in myoma tissue, the most effective treatment for endometrial preparation is gonadotropin releasing hormone (GnRH) analogues. It is proven that GnRHa shortens the length of surgery, enhances the visibility of the image, and improves the outcome of hysteroscopic surgery effectively by reducing the size, decreasing the vascularization of myomas, and reducing the endometrial thickness. The use of GnRHa prior to surgery also improved the severe anemia in the patients with abnormal uterine bleeding. However, newer drugs have had therapeutic effects with side effects such as progesterone antagonists, selective progesterone receptor modulators and aromatase inhibitors.

Utrogestan is a natural micronized progesterone compound, which has fewer side effects than the synthetic progesterone. The side effects of the progesterone compounds include dizziness, drowsiness, visual impairments, headache, acne, hives, gastrointestinal disorders and breast pain. The purpose of this drug is to reduce the rate of bleeding and reduce the duration of hysteroscopic myomectomy. Since no study has been performed about using this compound in hysteroscopic surgery, the aim of this study was to investigate the effects of injectable GnRH agonists and the micronized natural progesterone on the rate of bleeding during hysteroscopic myomectomy. The primary outcomes were related to the rate of bleeding during surgery and the hysteroscopic image resolution, and the secondary outcomes were related to the duration of surgery, the hematologic changes after the surgery, and the success in myomectomy.

## 2. METHODS

The present study is a randomized clinical trial study. The study population consisted of patients who were admitted to Alzahra Medical Training Center in Tabriz from October 2016 to March 2018 due to abnormal uterine bleeding with sub-mucosal myoma for hysteroscopic myomectomy. Based on the results of the pilot study in 10 patients for each group, the mean of preoperative Hb in the patient group (progesterone) was  $12.37 \pm 0.43$ , which decreased to  $12.28 \pm 0.41$  after the surgery. However, in the control group, the mean was reduced from  $12.41 \pm 0.49$  to  $11.89 \pm 0.63$ . The mean changes in the patient group ( $0.03 \pm 0.09$ ) were less than in the control group ( $0.52 \pm 0.15$ ). Considering  $\alpha = 0.05$ , power of 80% and difference of 0.15, the number of samples for each group was 20 and overall, 40 samples. 25 samples were included in the study to increase the validity of the study (figure 1).

Inclusion criteria were patients with moderate abnormal uterine bleeding and resistant in reproductive age, with sub-mucosal myoma with diameter of 30 mm or less, and the grade of zero or 1 in transvaginal ultrasound, according to the European Society for Gynaecological Endoscopy (Wamsteker, 1993). Exclusion criteria included the history of heart, liver, kidney, pulmonary and hematologic diseases, hypertension, high triglyceride diabetes, thrombo embolism, uterine and cervical cancer, sub-mucosal Leiomyoma greater than 3 cm, acute genital infection, uterine septum, Pregnant and infertile women, patients in need of transfusions, severe bleeding and taking anticoagulants.

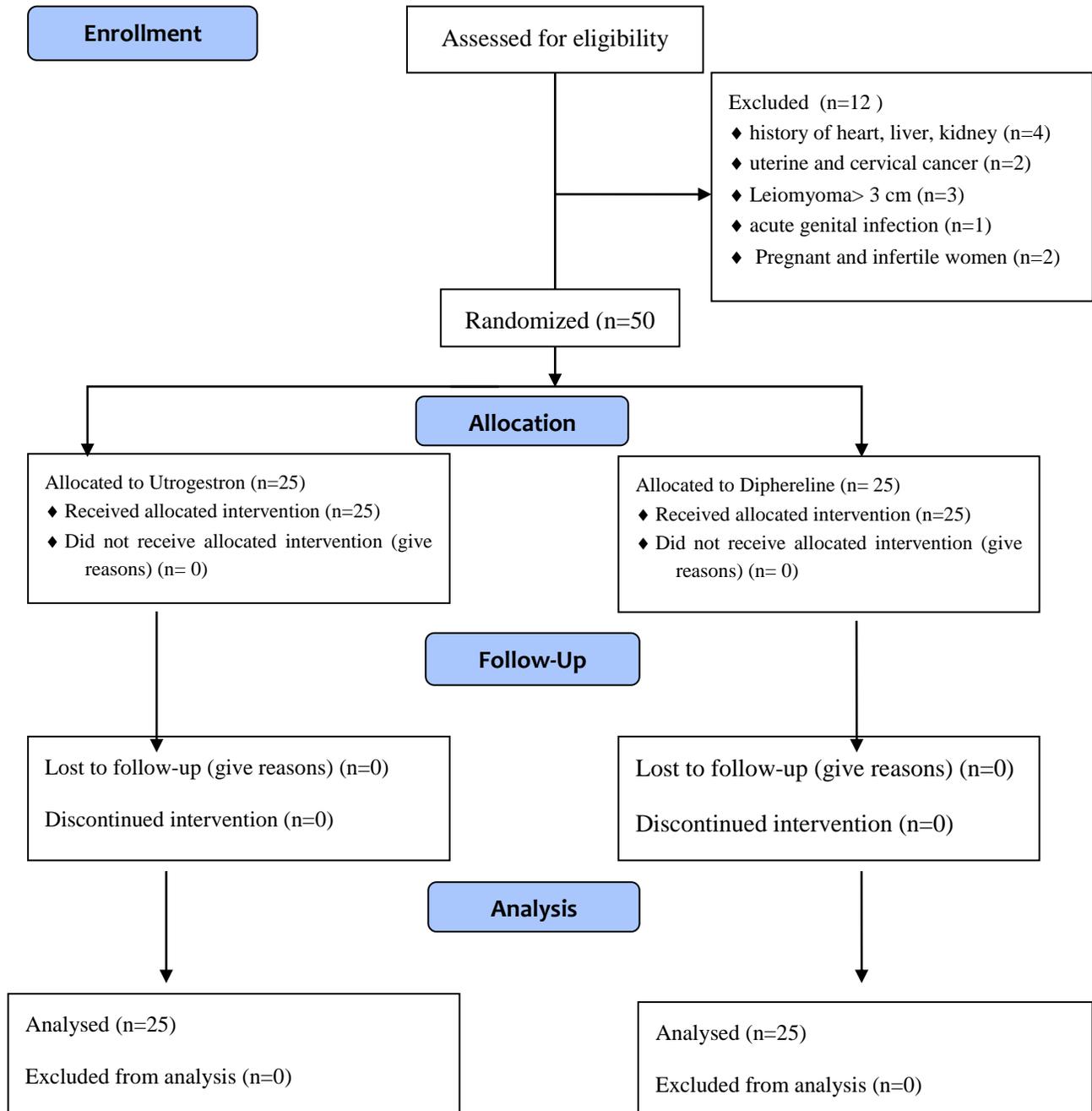
In this study, the patients were divided randomly into two equal groups of 25 people using Dattng CmbH, Tübingen Germany Rand list version software with code 1901365632. The first group (receiving the progesterone capsule) included 25 patients and the second one (intramuscular injection of diphereline ampoule eat a dose of 3.75 mg as a GnRH agonist compound) also included 25 patients. Both groups were matched for age, gravida, parity, and the number of myomas, and the informed consent was obtained from all the patients in both groups.

Transvaginal ultrasound, Pap smear and endometrial pipelle biopsy were performed for all the patients. After the random selection of patients by the respective resident, the first group received 100 mg of the natural micronized progesterone capsule called Utrogestan; from the first day of menstruation, two capsules totaling 200 mg while sleeping 3 hours after the last meal with a glass of water were used for 30 days. In the second group, the intramuscular injection of diphereline ampoule at a dose of 3.75 mg as a GnRH agonist compound on the day 21 of menstruation was used, two doses with a 28 days interval for 2 months before the hysteroscopy. The first group was admitted on the last day of taking the Utrogestan, and the second one was admitted 4 weeks after the second injection of GnRH, for surgery.

In both groups, after the general anesthesia and cervical dilatation to No. 10, a rigid resectoscope with 30 degree lens with Storz Endoscopy Germany monopolar catheter was used. In both groups, the dextrose solution 5% was used as a media to dilate the uterine cavity. The Myomectomy was performed by a gynecologist and a surgeon researcher. In the adjusted information form, all the information required for the study was recorded, so that the information about intra operative variables was recorded by the operating room nurse, and the information about postoperative variables was recorded by the nurse from the surgical ward. The physicians, patients, and nurses in the operating room and the surgical ward were blind to the selected groups.

The rate of bleeding during surgery by using the Visual Analog Scale (VAS), Grade 0 (no bleeding), Grade 1 (mild bleeding), Grade 2 (moderate bleeding), Grade 3 (relatively severe bleeding), Grade 4 (severe bleeding) was determined with the consent of the physician and the operating room nurse. The agreement between the observers (physician and nurse) in measuring the rate of

bleeding during surgery was evaluated using two observers' opinions at 10% of the sample size, and the obtained Kappa Agreement was 80%. In cases where there was no agreement between the physician and the nurse, a third person who was an assistant nurse in the operating room was considered for a definitive opinion.



**Figure 1** CONSORT Flow Diagram

During surgery, the amount of fluid entered into the uterus and the amount of fluid exited of the uterus were measured, and the amount of the absorbed fluid was calculated from the difference of the entered fluid and the exited fluid, after the completion of the myoma resection. When the amount of the absorbed fluid reached 1,500 ml, the surgery was stopped. Success in myomectomy was when the myomas of the endometrial surface to a depth of 1 to 2 mm were separated from the underneath myometer, which was

compared between the two groups. The duration of hysteroscopy was calculated in minutes for both groups, from the entry time of the hysteroscope into the uterus to its exit from the uterus. The image resolution on the monitor was recorded in light and dark. The blood pressure and heart rhythm were monitored during surgery, and a blood pressure drop of 90 mm Hg or less, and an increase in heart rate to 80 beats per minute or more, were considered abnormal. The length of stay of each patient in the hospital was recorded in days.

One hour after patient admission, the side effects of the two medications, including hot flashes, headache, vaginal dryness, joint and muscle stiffness, abnormal bleeding, mood changes and the allergic reaction from the injection site from the patients receiving GnRH, and symptoms of Vertigo, drowsiness, visual disturbances, headache, acne, hives, diarrhea, nausea, vomiting, pain, and breast tenderness of the progesterone receiving group were entered into the information form by the relevant nurse. The levels of Na, K, Hb and Hct were monitored and recorded 6 hours after the surgery.

All patients were assured that their completed information would be kept confidential, and the results would be presented in general. This study was approved by the Ethics Committee of Tabriz University of Medical Sciences with code: REC.TBZMED.IR.703.1396. This study was registered at the clinical trial site with code IRCTID: IRCT20110523006563N3.

### 3. RESULT

The mean age and the standard deviation of patients in the progesterone group was  $45.2 \pm 7.36$  years and its range was 29 to 60 years. The mean gravida of the progesterone group and the GnRHa group were  $3.08 \pm 1.86$  and  $3.06 \pm 1.96$ , respectively. The mean parity of the progesterone group and the GnRHa group were  $2.56 \pm 1.66$ , and  $2.53 \pm 1.63$ , respectively.

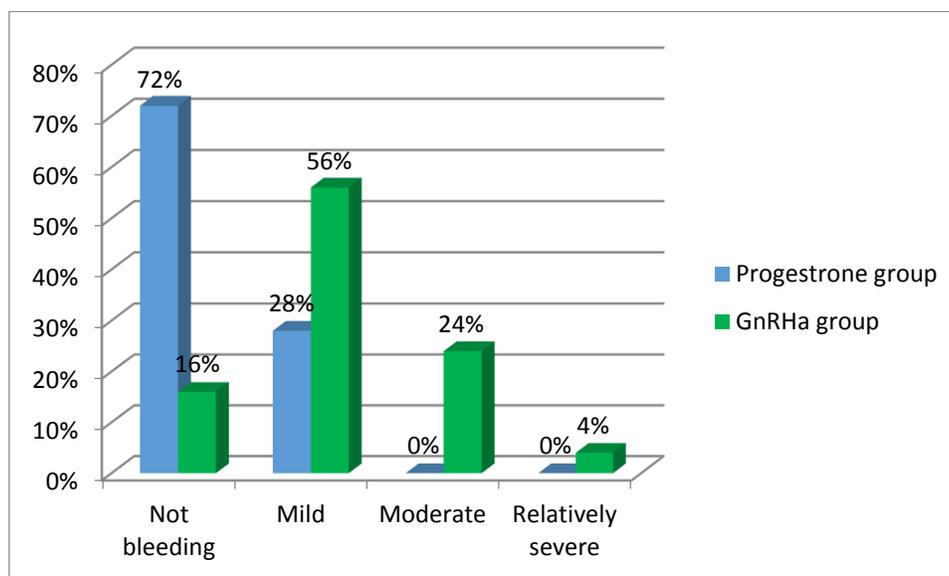
There was no significant difference between the two groups in terms of age, gravida, parity, live birth, the myoma thickness, the number of myomas, the myoma diameter and the bleeding rate during illness (Table 1).

**Table 1** The characteristics of patients in the two study groups

Variable	The progesterone group N=25 SD± Mean	The GnRHa group N=25 SD± Mean	P-Value
Age(year)	2.45± 7.36	44.7 ± 28.1	0.65
Gravidity (n)	8.3± 1.86	3.1 ± 6.96	0.94
parity (n)	2.56± 1.66	2.53±1.63	0.93
The number of myomas (n)	1.32±0.69	1.28 ±0.45	0.81
The maximum of myoma diameter (mm)	19.64 ± 7.08	19.1 ± 6.26	0.78
Endometrial Thickness (mm)	8±3.58	7.08 ± 4.54	0.43

The mean numbers of myomas in the progesterone group and in the GnRHa group were  $1.32 \pm 0.69$  and  $1.28 \pm 0.45$ , respectively. The mean endometrial thickness in the progesterone group and in the GnRHa group were  $8 \pm 3.58$  mm and  $7.08 \pm 4.54$  mm, respectively. The mean maximal diameter of the myoma in the progesterone group and in the GnRHa group were  $19.64 \pm 7.08$  mm, and  $19.1 \pm 6.26$  mm, respectively.

The results showed that in the progesterone group, 18 patients (72%) had no bleeding, and 7 patients (28%) had grade 1 - bleeding, and no patients had more than grade 1 - bleeding. In the GnRHa group, 4 patients (16%) had no bleeding, 14 patients (56%) had grade 1 - bleeding, 6 patients (24%) had grade 2 - bleeding and 1 patient (4%) had grade 3 - bleeding, and no patients had grade 4 - bleeding. Many patients in the progesterone group had no significant bleeding. Mild (grade 1) and moderate (grade 2) bleeding were significantly higher in the GnRHa group, and the difference in the relatively severe bleeding was not significant between the two groups (chart 1 & table 2).



**Chart 1** bleeding during surgery

**Table 2** The comparison of the rate of bleeding and the hemoglobin and hematocrit changes between the two groups

Variable	The progesterone group N=25 SD± Mean	The GnRHa group N=25 SD± Mean	P-Value
Hemoglobin (g / dl) SD± Mean			
Before surgery	12.38 ± 1.51	12.62 ± 1.51	0.57
After surgery	11.55 ± 1.42	11.83 ± 1.42	0.49
The rate of decline	0.84 ± 0.58	0.79 ± 0.57	0.79
Hematocrit (%) SD ± Mean			
Before surgery	38.08 ± 3.72	37.92 ± 3.85	0.87
After surgery	35.25 ± 3.61	35.68 ± 3.77	0.68
The rate of decline	2.83 ± 2.15	2.25 ± 1.84	0.31

**Table 3** The comparison of some variables studied between the two groups

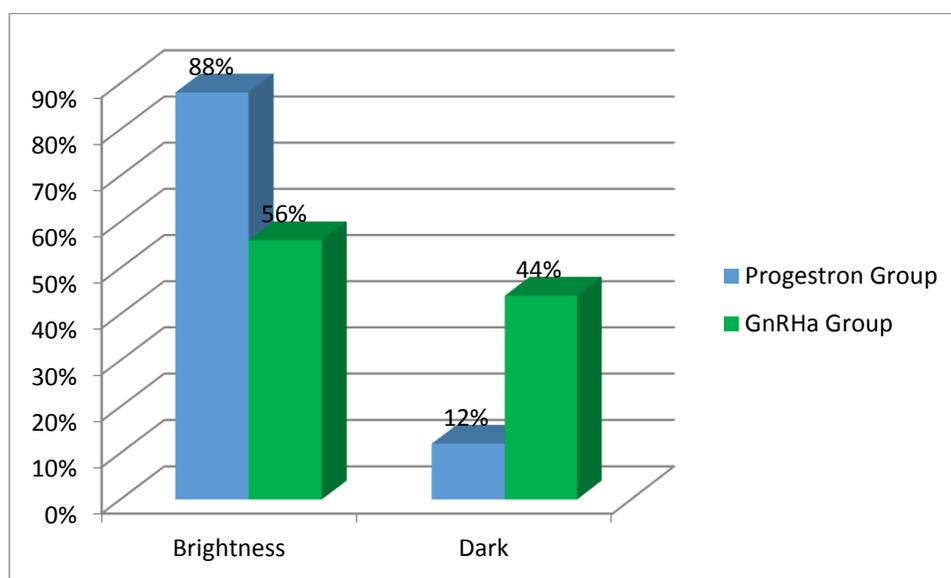
Variable	The progesterone group N=25 SD± Mean	The GnRHa group N=25 SD± Mean	P-Value
Sodium (mEq / l)			
Before surgery	138.44 ± 2.37	138.7 ± 1.89	0.67
After surgery	138.31 ± 3.13	137.92 ± 3.81	0.64
Potassium (mEq / l)			
Before surgery	4 ± 0.36	3.9 ± 2.99	0.27
After surgery	3.99 ± 0.33	3.72 ± 0.35	0.038
Systolic blood pressure (mmhg)	131.96 ± 17.57	129.24 ± 18.47	0.59
Diastolic Blood Pressure (mmhg)	80.52 ± 12.52	80.56 ± 12.92	0.99
The number of heart beats	85.08 ± 12.42	86.24 ± 12.61	0.74

No significant difference was observed between the mean hemoglobin before the surgery in the progesterone group,  $12.38 \pm 1.51$ , and in the GnRHa group,  $12.62 \pm 1.51$ , the mean hemoglobin after the surgery in the progesterone group,  $11.55 \pm 1.42$ , and in the GnRHa group,  $11.83 \pm 1.542$ , the mean of hemoglobin loss after the surgery in the progesterone group,  $0.84 \pm 0.58$ , and in the GnRHa group,  $0.79 \pm 0.57$ , the mean hematocrit before the surgery in the progesterone group,  $38.08 \pm 3.72$ , and in the GnRHa group,  $37.92 \pm 3.85$ , the mean hematocrit after the surgery in the progesterone group,  $35.25 \pm 3.61$ , and in the GnRHa group,  $35.68 \pm 3.77$ , the mean of hematocrit loss after the surgery in the progesterone group,  $2.83 \pm 2.15$ , and in the GnRHa group,  $2.25 \pm 1.84$ , the mean heart rate in the progesterone group,  $85.08 \pm 12.42$ , and in the GnRHa group,  $86.24 \pm 12.61$ , the mean duration of surgery in the progesterone group,  $13.88 \pm 9.54$ , and in the GnRHa group,  $17.16 \pm 9.24$ , the sodium and potassium levels in the serum of patients of the two groups before the hysteroscopy (Table 3).

There was no significant difference between the minimum and maximum serum volume entered, in the progesterone group,  $3076 \pm 2057.76$ , and in the GnRHa group,  $3116 \pm 2046.27$ , the minimum and maximum serum volume exited, in the progesterone group,  $2690 \pm 1868.06$ , and in the GnRHa group,  $2702 \pm 1837.82$ , the minimum and maximum absorbed serum volume, in the progesterone group,  $386 \pm 276.33$ , and in the GnRHa group,  $414 \pm 297.04$ , the myomectomy success rate in the progesterone group, 92% (23 patients), and in the GnRHa group, 96% (24 patients), the observed drug side effects (table 4). The image resolution in the progesterone group was light in 22 cases (88%) and dark in 3 cases (12%) and in the GnRHa group was light in 14 cases (56%) and dark in 11 cases (44%). It was found that the image resolution was significantly better in the progesterone group (chart 2).

**Table 4** The comparison of some variables studied between the two groups

Variable	The progesterone group N=25 SD± Mean	The GnRHa group N=25 SD± Mean	P-Value
The duration of surgery (min)	$13.88 \pm 9.54$	$17.16 \pm 9.24$	0.22
The entered serum volume	$3076 \pm 2057.76$	$3116 \pm 2046.27$	0.94
The exited serum volume	$2690 \pm 1868.06$	$2702 \pm 1837.82$	0.98
The absorbed serum volume	$386 \pm 276.33$	$414 \pm 297.04$	0.73
The myomectomy success rate	92% (23 patients)	96% (24 patients)	0.5



**Chart 2** hysteroscopic vision

#### 4. DISCUSSION

In this study, we compared the effects of the natural micronized progesterone and GnRHa on the rate of bleeding during hysteroscopic myomectomy in 50 patients with abnormal uterine bleeding due to intrauterine myoma.

In examining the results of the study of the rate of bleeding based on VAS, 72% of the progesterone group and 16% of the GnRHa group did not show any bleeding during hysteroscopy, meaning that the incidence of bleeding in the progesterone group was significantly lower than that of the GnRHa group. ( $P = 0.001$ ), and the hemoglobin and hematocrit changes after surgery did not show significant difference between the two groups ( $P = 0.49$ ,  $P = 0.68$ ). The results of the study of Gutmann et al. also showed that the definitive advantage of GnRHa is the correction of anemia, and its potential advantage is a mild decrease in bleeding during surgery, and a nonsignificant decrease in the postoperative hemoglobin (Gutmann et al., 2005). In the study of Fedele et al. that performed on patients undergoing hysteroscopy and myomectomy, the rate of bleeding during surgery in the GnRHa group and in the control group (emergency myomectomy) were reported, 235 mL and 275 mL, respectively, and the results showed that GnRHa failed to reduce the rate of bleeding significantly ( $P > 0.05$ ) (Fedele et al., 1990). In the study of Yu HY et al, it was also reported that the patients who underwent GnRHa before myomectomy had significantly reduced intra operative bleeding, and a decrease in hemoglobin was not observed significantly, and it was concluded that the GnRHa administration can reduce the rate of bleeding (Yu YH et al., 2004). The results of the present study were also consistent with the results of the study of Zullo et al. (Zullo et al., 1998) and Parazzini et al. (Parazzini et al., 1998).

The present study showed that, although the success rate of myoma resection in the use of GnRHa (96%) was higher than that of the progesterone group (92%), it was not statistically significant. In other words, with the two drugs GnRHa and Uterogestan, myomectomy has been successful. According to the results of the study of Monleón Sancho, the success rate of myoma resection with GnRHa was higher than UPA (98% compared to 93%) (Monleón Sancho et al., 2016). According to the results of the study, Fedele et al. Found that in transvaginal ultrasound, after myomectomy in the GnRHa group, in 63% of patients, and in the control group (emergency surgery), in 13% of patients, the myomas were left less than 1.5 cm (Fedele et al., 1990).

In the present study, the duration of hysteroscopy, from its start to the exit of the hysteroscope, in the progesterone group and in the GnRHa group were  $13.88 \pm 9.54$  minutes and  $17.16 \pm 9.24$  minutes, respectively. The results showed no significant difference between the two groups, although the hysteroscopy duration was shorter in the progesterone group. The results of this study are consistent with the results of the study of Monleón Sancho (Monleón Sancho et al., 2016). In the study of Muzii et al., The duration of surgery when using GnRHa was  $15.9 \pm 3.1$  versus  $21.3 \pm 4$  minutes in the control group, which showed a significant difference (Muzii et al., 2010). The duration of myomectomy, in the study of Zullo et al in the GnRHa group and in the control group (surgery before taking the drug) were  $98.5 \pm 26.1$  minutes (significantly higher) and  $113.3 \pm 35.1$  minutes, respectively (Zullo et al., 1998).

The rate of fluid absorption, according to the results of the study of Muzii et al. in the GnRHa group and in the control group were  $378 \pm 137$  ml and  $566 \pm 199$  ml, respectively, and the difference was significant (Muzii et al., 2010). Monleón Sancho et al. showed that there was no significant difference between the two drugs UPA and GnRHa in terms of the fluid deficit (200 cc compared to 350 cc) and the side effects (Monleón Sancho et al., 2016). The results of the present study also showed that the volume of absorbed serum in the progesterone group and in the GnRHa group were  $386 \pm 276.33$  and  $414 \pm 297.04$ , respectively, which showed no significant difference. The results of the present study are in contrast to the study of Triolo et al. (Triolo et al., 2006), who had lower infusion fluid in the use of Gestrinone compared to Danazole.

Our study also showed that if the progesterone be used, the side effects are nausea, vomiting, diarrhea and dizziness, and if the GnRHa be used, the side effects include headache, vaginal dryness, allergies, mood changes, muscle stiffness and hot flashes. The differences between the two groups were not significant in terms of the side effects. According to the results of the study of Triolo et al., The side effects of gestrinone use included headache, swelling, nausea, and weight gain (Triolo et al., 2006). Zullo et al. also reported that there was no significant difference between the GnRHa group and the control group in terms of the side effects (Zullo et al., 1998).

The study of Lethaby et al. showed that there was no significant difference between the two drugs in the duration of hospitalization after surgery in patients receiving GnRHa and Lynestrenol ((Lethaby et al., 2001). In the study of Lethaby et al, the mean duration of hospitalization in patients receiving GnRHa was 1.1 days, which was significantly less than that of the control group (Lethaby et al., 2002). In this study, all patients in both groups had one day of hospitalization. In the present study, the use of Uterogestan compared to GnRHa produced a lighter image resolution that is consistent with the result of the study of Cicinelli et al. (Cicinelli et al., 2007) who used desogestrel.

## 5. CONCLUSION

The results of this study showed that the rate of bleeding during surgery was lower and the hysteroscopic image resolution was better in the progesterone group than in the GnRHa group. However, as the duration of treatment with Uterogstan is shorter than GnRHa, and the cost of Uterogstan is lower than that of GnRHa; it is recommended that this drug be used for endometrial preparation to reduce the rate of bleeding during surgery and for more image resolution before hysteroscopic myomectomy.

### Acknowledgment

We would also like to show our gratitude to the Women's Reproductive Health Research Center, Tabriz University of Medical Sciences for sharing their pearls of wisdom with us during the course of this research.

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