The Use of Gonadotropin-Releasing Hormone Analogues in Fibroid Surgery: A Prospective Comparative Study

Nada Habeeb Youssif *

* Specialist Obstetrician and Gynecologist, MBChB. CABOG., Al – Mawani Teaching Hospital, Basrah Health Directorate. Basrah, Iraq

Abstract

Introduction: Uterine fibroids, or leiomyomata, are common benign tumors in women, influenced by estrogen levels. They can be asymptomatic or present with symptoms like abnormal uterine bleeding, pelvic pain, and disturbances to adjacent organs. Fibroids are categorized by location: subserosal, intramural, and submucosal. Despite being estrogen-dependent, their exact pathophysiology remains unclear. Management includes medical treatments, minimally invasive procedures, and surgeries. Gonadotropin-releasing hormone (GnRH) agonists, used preoperatively, reduce fibroid volume, surgical time, and hospital stay but have side effects limiting their use.

Methods: This prospective comparative study examines the effectiveness of GnRH analogues in reducing intraoperative congestion and postoperative complications in 31 women undergoing hysteroscopic resection of submucous myomas. Participants were divided into two groups: 15 receiving preoperative GnRH therapy and 16 undergoing surgeries without prior treatment. Preoperative assessments included general and gynecologic history, physical examination, and urine pregnancy test. Surgical times, intraoperative, and postoperative complications were recorded, with pain assessed using the visual analogue scale (VAS).

Results: The mean age and parity of women in both groups were similar. Preoperative myoma size significantly decreased in the GnRH group compared to the control group (1.1± 0.4 cm vs. 2.3± 0.8 cm, p=0.015). The mean surgical time was significantly shorter in the GnRH group (30.9± 2.1 min vs. 38.8± 3.9 min, p=0.009). Postoperative VAS scores were lower in the GnRH group but not statistically significant (4.5 vs. 5.9, p=0.081). Postoperative complications included less pain and significantly less bleeding in the GnRH group ($p<0.05$).

Conclusion: Preoperative GnRH analogue treatment effectively reduces myoma size, surgical time, and postoperative bleeding in women undergoing hysteroscopic resection of submucous myomas. These findings support the use of GnRH analogues as a beneficial preoperative treatment to improve surgical outcomes and reduce complications.

Index Terms: Uterine fibroids, GnRH analogues, Hysteroscopic resection, Myoma reduction, Preoperative treatment

INTRODUCTION

Uterine fibroids, also known as leiomyomata, are the most prevalent non-cancerous growths that occur in women. Fibroids arise from the smooth muscle cells of the uterus (myometrium), and their development is mainly influenced by the amounts of oestrogen in the bloodstream. Fibroids may manifest either as an asymptomatic coincidental finding on imaging, or with symptoms. Typical symptoms consist of abnormal bleeding from the uterus, pain in the pelvic area, disturbance of other pelvic organs (such as the intestine and bladder), and pain in the back. Uterine fibroids are often seen in three main locations: subserosal (located outside the uterus), intramural (located within the myometrium), and submucosal (located inside the uterine cavity). They may be further categorised as either pedunculated or non-pedunculated [1].

The precise pathophysiology behind the formation of uterine fibroids remains uncertain. Evidence indicates that fibroid growth starts with a solitary uterine smooth muscle cell (myometrium), which then undergoes aberrations in the normal signalling pathways of cellular division. Fibroids are considered to be estrogen-dependent tumours, and research shows that, in comparison to the normal surrounding myometrium, leiomyomas overexpress certain oestrogen and progesterone receptors [2]. The healthcare system bears a significant cost burden when treating women with fibroids. The provided yearly cost of surgical and medical treatments, the number of work hours lost, and the consequences associated with fibroids in the United States range from USD 5.8 to 34.3 billion [3]. There are many options for managing fibroids, including medical treatment, minimally invasive procedures such as uterine artery embolisation, and surgical interventions including myomectomy and hysterectomy [4].

GnRH agonists are mostly used as preoperative treatment. A comprehensive Cochrane systematic review has shown that their utilisation may enhance both preoperative and postoperative haemoglobin levels, decrease surgical time, and minimise the duration of hospitalisation. The action of

GnRH agonists leads to a decrease in menstrual bleeding and a reduction in fibroid volume, resulting in a decrease in uterine volume by roughly 50%. Gonadotropin-releasing hormone (GnRH) agonists are used in assisted reproduction techniques and also serve as a treatment for women suffering from endometriosis, hirsutism, irregular uterine bleeding, and premenstrual syndrome [5]. The GnRH agonist (leuprolide) works by decreasing gonadal hormone production via its action on the pituitary gland. This ultimately reduces the hormone-induced growth of the fibroid. Research conducted by Friedman et al. demonstrated a 45% reduction in uterine size following 24 weeks of therapy with a GnRH agonist. Furthermore, the uterine size returned to its original size within 24 weeks after the termination of treatment. Prolonged treatment with a GnRH agonist has also been shown to cause statistically significant bone loss. Due to these factors and its rather short impact, the American College of Obstetricians and Gynaecologists (ACOG) has advised restricting its usage to a maximum of 6 months [6]. Leuprolide is most efficacious when used as a preoperative medication for symptomatic fibroids [7].

Thus, this study aims to investigate the effectiveness of GnRH analogues in reducing intraoperative congestion and postoperative complications in patients undergoing gynaecological surgeries for fibroids.

METHODS

This prospective comparative study investigates the effectiveness of GnRH analogues in reducing intraoperative congestion and postoperative complications in patients undergoing gynaecological surgeries for fibroids. The study includes 31 females scheduled to undergo hysteroscopic resection of submucous myomas at Basrah City. Inclusion criteria were women presented with a history of heavy/ irregular vaginal bleeding, infertility and a submucosa fibroid diagnosed by transvaginal ultrasonography. The fibroids of G0 or G1 score were included. G0 fibroid means pedunculated mass within the uterine cavity while the G1 mean 50% contained within the myometrium. The women with a history of cancer, the presence of numerous and large polyps and those with genital tract infections were excluded from the study. All women were subjected preoperatively to a general and gynecologic history, a complete physical examination, and a urine pregnancy test.

The Patients are randomly divided into two groups: the intervention group: 15 women who received preoperative GnRH analogue therapy IM for two consecutive injections 28 days apart before surgery, while patients in the control group: 16 women will undergo surgery without prior GnRH analogue treatment.

Procedures were done for women in the control group in the early follicular phase and in the third or early fourth week after the second GnRHa administration. The time needed for operative hysteroscopy, together with total surgical times, were prospectively recorded. Intraoperative and postoperative complications were assessed. The postoperative patient pain was evaluated using the visual analogue scale (VAS).

Data was entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 26 was used. The appropriate statistical tests were performed, a Chi-square test was used for categorical variables, and two samples independent t-tests for the continuous variable.

RESULTS

The results of 31 women who underwent hysteroscopic resection of submucous myomas were presented in the following tables. Table 1 shows that the mean age of women in both groups was nearly similar, majority of women were in their forties. Regarding parity, women in both groups had a similar number of children with no statistical difference. The highest percentage of women in both groups lived in the city center.

Table 1: the characteristics of women in both groups

Variables	GnRH analogue (n=15)	Control (n=16)	p-value
Age / mean in years	40.9 ±5.4	41.6 ±4.9	0.852
Parity	No (%)	No (%)	
Nullipara	5 (33.3)	7 (43.7)	0.552
Multipara	10 (66.7)	9 (56.3)	
Residency	No (%)	No (%)	
City centre	9 (60.0)	11 (68.7)	0.61
Periphery	6 (40.0)	5 (31.3)	

The size of the myomas ranged from (13-32 mm) in both groups. There's no significant difference in the myoma size mean before the treatment with GnRH analogue, p-value=0.45. After the treatment with GnRH analogue, the size of the myoma decreased in the women who received treatment and the size reached 1.1± 0.4, and this difference is of statistically significant p-value=0.015. The class of myoma was G0 and G1 only. Around 40% of women were

G0 and there is no difference between the two groups p-value= 0.870. as shown in table 2.

Table 2: the clinical characteristics of women

Variables	GnRH analogue (n=15)	Control (n=16)	p-value
Pretreatment myoma size mean	2.3± 0.9	2.2± 0.8	0.45
Preoperative myoma size	1.1 ±0.4	2.3± 0.8	0.015
Myoma class	No (%)	No (%)	
G0	7 (46.7)	7 (43.7)	0.870
G1	8 (53.3)	9 (56.3)	

The mean surgical time was lower in the GnRH group with (30.9± 2.1) min. in comparison to (38.8± 3.9) min. in the control group. And this difference is significant statistically p-value=0.009. No statistical difference between the two groups regarding the post-op VAS score p-value= 0.081. the women in the first group had a lower VAS score 4.5 vs 5.9 in the control group. Regarding the postop complication, 11 women had pain after surgery, 7 of those in the control group and 4 in the cases. The bleeding happened among one woman in the first group in comparison to 7 women in the second group and this difference is of statistically significant p-value < 0.05.

Table 3: the surgery characteristics among women in both groups

Variables	GnRH analogue (n=15)	Control (n=16)	p-value
Total surgical time	30.9± 2.1	38.8± 3.9	0.009
Post-op VAS score	4.5 ±1.3	5.9 ± 0.9	0.081
Post op complication	No (%)	No (%)	
Pain	4 (26.7)	7 (43.8)	0.320
Bleeding	1 (13.3)	7 (43.8)	0.021

DISCUSSION

This study aimed to evaluate the efficacy of GnRH analogues in reducing intraoperative congestion and postoperative complications in patients undergoing hysteroscopic resection of submucous myomas. The results demonstrated significant benefits of preoperative GnRH analogue therapy, including reduced myoma size, decreased surgical time, and lower incidence of postoperative bleeding.

The reduction in myoma size observed in the GnRH analogue group aligns with previous research findings by Hodgson *et al.* (2017). GnRH agonists have been shown to significantly decrease the size of fibroids by approximately 50% through hormonal suppression [8]. Our study corroborates these findings, with the GnRH group showing a statistically significant reduction in myoma size preoperatively compared to the control group (p = 0.015). This size reduction is crucial for facilitating less invasive surgical procedures and improving surgical outcomes.

The mean surgical time was significantly lower in the GnRH group (30.9 ± 2.1 minutes) compared to the control group (38.8 ± 3.9 minutes; p = 0.009). This reduction in operative time can be attributed to the smaller fibroid size, which likely made the surgical procedure easier and quicker to perform. Similar findings have been reported in the literature by Lee *et al.*, (2017), where preoperative GnRH treatment has been associated with shorter surgical durations and reduced intraoperative blood loss [9].

Postoperative complications were also notably reduced in the GnRH group. Only one patient in the GnRH group experienced significant postoperative bleeding compared to seven in the control group (p = 0.021). This significant reduction in bleeding aligns with the known hemostatic benefits of GnRH agonists, which reduce endometrial thickness and vascularity, thereby minimizing blood loss during surgery as stated by Ma *et al.* (2024) and Lethaby *et al.* (2024) [10, 11].

While there was no statistically significant difference in postoperative pain scores between the two groups (p = 0.081), the GnRH group did report lower VAS scores on average. This suggests a trend towards reduced pain, possibly due to less traumatic surgical intervention facilitated by smaller fibroid size as mentioned by Wu *et al.* (2023) [12].

Our findings are consistent with previous studies that have demonstrated the effectiveness of GnRH analogues in the preoperative management of uterine fibroids. Additionally, the American College of Obstetricians and Gynecologists (ACOG) recommends the use of GnRH agonists for up to six months preoperatively to manage symptomatic fibroids [13].

However, it is important to note that long-term use of GnRH analogues can lead to adverse effects such as bone loss, which limits their use to short-term preoperative settings [14]. This study supports their efficacy in a short-

term preoperative context, providing significant benefits without the risks associated with prolonged use.

One limitation of this study is the relatively small sample size, which may affect the generalizability of the findings. Future studies with larger cohorts are necessary to confirm these results. Additionally, the study did not evaluate long-term postoperative outcomes, which could provide more comprehensive insights into the benefits and potential drawbacks of preoperative GnRH therapy.

Conclusions and Recommendations

In conclusion, preoperative GnRH analogue therapy significantly reduces fibroid size, surgical time, and postoperative bleeding in patients undergoing hysteroscopic resection of submucous myomas. These findings support the use of GnRH agonists as an effective preoperative intervention to improve surgical outcomes in women with symptomatic fibroids. Future research should focus on larger sample sizes and long-term outcomes to further validate these findings.

Conflicts of interest: None.

Funding: I declare that I did not receive any funding from any funding bodies or companies for this research.

Ethical considerations: All participants provided informed consent after being fully briefed on the study's objectives, procedures, risks, and benefits. Confidentiality was maintained by anonymizing data, and participants were assured of their right to withdraw at any time without any impact on their care.

References

[1] De La Cruz MS, Buchanan EM. Uterine Fibroids: Diagnosis and Treatment. Am Fam Physician. 2017; 95(2):100-107.

[2] Barjon K, Mikhail LN. Uterine Leiomyomata. [Updated 2023 Aug 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK546680/

[3] Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH. The estimated annual cost of uterine leiomyomata in the United States. American Journal of Obstetrics and Gynecology 2012;206(3):211.e1-9.

[4] Wright JD, Herzog TJ, Tsui J, Ananth CV, Lewin SN, Lu Y, et al. Nationwide trends in the performance of inpatient hysterectomy in the United States. Obstetrics and Gynecology 2013;122(2):233-41.

[5] Hodgson R, Bhave Chittawar P, Farquhar C. GnRH agonists for uterine fibroids. Cochrane Database Syst Rev. 2017;2017(10):CD012846.

[6] American College of Obstetricians and Gynecologists. ACOG practice bulletin. Alternatives to hysterectomy in the management of leiomyomas. Obstet Gynecol. 2008; 112(2 Pt 1):387-400.

[7] Lewis TD, Malik M, Britten J, San Pablo AM, Catherino WH. A Comprehensive Review of the Pharmacologic Management of Uterine Leiomyoma. Biomed Res Int. 2018; 2018:2414609.

[8] Hodgson R, Bhave Chittawar P, Farquhar C. GnRH agonists for uterine fibroids. Cochrane Database Syst Rev. 2017 Oct 29;2017(10):CD012846.

[9] Lee MJ, Yun BS, Seong SJ, Kim ML, Jung YW, Kim MK, Bae HS, Kim DH, Hwang JY. Uterine fibroid shrinkage after short-term use of selective progesterone receptor modulator or gonadotropin-releasing hormone agonist. Obstet Gynecol Sci. 2017 Jan;60(1):69-73.

[10] Ma Y, Wang WX, Zhao Y. Dienogest in conjunction with GnRH-a for postoperative management of endometriosis. Front Pharmacol. 2024 Mar 7;15:1373582.

[11] Lethaby A, Vollenhoven B, Sowter MC. Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. Cochrane Database of Systematic Reviews 2001, Issue 2. Art. No.: CD000547.

[12] Wu Q, Zhou Y, Sun S, Li H, Cao S, Shou H. Clinical analysis of acute postoperative pain after total laparoscopic hysterectomy for adenomyosis and uterine fibroids - a prospective observational study. Ann Med. 2023;55(2):2281510.

[13] Lewis TD, Malik M, Britten J, San Pablo AM, Catherino WH. A Comprehensive Review of the Pharmacologic Management of Uterine Leiomyoma. Biomed Res Int. 2018 Jan 28;2018:2414609.

[14] Ali M, Raslan M, Ciebiera M, Zaręba K, Al-Hendy A. Current approaches to overcome the side effects of GnRH analogs in the treatment of patients with uterine fibroids. Expert Opin Drug Saf. 2022 Apr;21(4):477-486.

Author

Nada Habeeb Youssif
MBChB. CABOG.
Specialist Obstetrician and Gynecologist
Al – Mawani Teaching Hospital
Basrah Health Directorate

Correspondence Author
Dr Nada H. Youssif