

Goserelin versus Norethisterone in the Management of Menorrhagia with Uterine Fibroid

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Abstract

Menorrhagia is common in patients with uterine fibroids, if operation needs to be delayed for a particular reason, goserelin can be used safely to reduce bleeding and the size of the tumor. The objective is to compare between goserelin acetate and norethisterone on patients with menorrhagia and uterine fibroid. A randomized controlled study conducted in Elwiya maternity teaching hospital, Baghdad from the first of November 2007 to the end of April 2009. 90 patients from the consultant outpatient clinic with menorrhagia and fibroid, and their operations were delayed for medical reason were allocated in two groups, the first group, was given 3.2 mg goserelin acetate subcutaneously monthly for 3 months and the second group was given 5 mg norethisterone orally three times daily during the attack of bleeding and 5 mg once daily, cyclically if no bleeding for 3 months. The fibroid was measured in two dimensions, using convex real-time ultrasound before treatment and three months after treatment. Haemoglobin and the number of pads used were also reported before and after treatment, also the side effects in both groups and the need for operations. The size of fibroid in two dimensions measurement was reduced from $28.24 \text{ cm}^2 \pm 6.14$ to $12.3 \text{ cm}^2 \pm 3.45$ in the goserelin group ($P=0.0001$) versus $26.56 \text{ cm}^2 \pm 5.96$ to $25.22 \text{ cm}^2 \pm 5.01$ in the norethisterone group ($P= 0.2589$). The haemoglobin level was $9.28 \text{ gm}/100\text{ml} \pm 2.44$ pre-treatment in the goserelin group and $11.2 \text{ gm}/100\text{ml} \pm 1.88$ post-treatment ($P= 0.0001$) versus $10.08 \text{ gm}/100\text{ml} \pm 2.86$, and $10.24 \text{ gm}/100\text{ml} \pm 2.46$ respectively in the norethisterone group ($P= 0.7798$). The need for operation was decreased significantly in the goserelin group. Goserelin showed better patient response and reduction in the tumor size than norethisterone in treatment of patients with menorrhagia and uterine fibroids if operation is delayed for medical or other reasons.

Key words: Goserelin, Norethisterone, Menorrhagia, Uterine Fibroid

الخلاصة

إن دواء كوزرلين (Goserlin) يظهر نتائج أفضل من دواء (نوراثي ستيرون) Norethisterone في معالجة وتقليص حجم العقد الليفيّة في الرحم و خاصة عند المريّضات اللواتي يعانين من نزف شديد أثناء الدورة الشهرية أو هناك أسباب طبية تؤدي إلى تأجيل عملية رفع العقد الليفيّة جراحياً . ووجد أن إعطاء دواء (الكوزرلين) (Goserlin) لمدة 3 أشهر فعال في معالجة المريّضات اللواتي يعانين من نزف شديد أثناء الدورة الشهرية بسبب وجود عقد ليفيّة على الرحم إذ وجد انه يقلل من شدة النزف ويرفع من نسبة الهيموكلوبين بالدم مما يقلل الحاجة إلى إعطاء دم أو اللجوء إلى التداخل الجراحي مع وجود أعراض جانبية طفيفة .

Introduction

Uterine fibroids are the most common tumor in the female reproductive system. They are estimated to occur in 25% of women of reproductive age. ⁽¹⁾ In the USA, 30% of women will have had a hysterectomy by the age of 60 years and 60% will be performed to treat fibroids. ⁽²⁾ Hysterectomy or myomectomy remain the most common types of treatment and it is associated with high level of satisfaction. Myomectomy is carried out when fertility is to be preserved, it can relief symptoms associated with myoma. Goserelin acetate, a Gonadotrophin releasing hormone (GnRH) agonist is a synthetic form of gonaderelein. It acts on the luteinizing hormone releasing hormone (LHRH) receptors in the pituitary gland, in the same way as natural gonadorelin. The available data seems to

support the use of GnRH agonist treatment before surgery for uterine fibroids in selected circumstances. ⁽³⁾ Administration of GnRH agonist for only two or three months preoperatively in cases of uterine fibroid decreases the bleeding, mucus debris and diameter, limiting side effects and cost, ⁽³⁾ and increase the haematocrit value with no metabolic side effects or detectable bone demineralization . ⁽⁴⁾ Norethisterone is a synthetic progestin. It has several indications in gynaecology and primary care. At low dose $\leq 1\text{mg}$ it can be used in contraception and hormone replacement therapy. At higher dose $\geq 5\text{mg}$ it can be used in menorrhagia. ⁽⁵⁾ In our study we compare the effect of goserelin acetate versus norethisterone on patients with menorrhagia and uterine fibroid.

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Patients and Methods

This study is a randomized controlled study conducted in Elwiya maternity teaching hospital, Baghdad from the 1st of November 2007 to the 30th of April 2009. The patients enrolled in the study were 102 women, with menorrhagia and the presence of uterine fibroid(s). Patients with previous myomectomy and those with known or suspected to have breast carcinoma were excluded from the study. All patients were not suitable for near surgery because of medical problem, long waiting lists or refusal of surgery by the patient. Uterine bleeding was considered abnormal according to the patients subjective evaluation in comparison with previous menstrual status. The degree of the bleeding was assessed by the number of the pads used and hemoglobin estimation before and after treatment. 52 patients received monthly SC injection of Goserelin acetate 3.6 mg (Zoladex, AstraZeneca, UK) for three months, the second group was 50 patients received 5 mg of norethisterone tablets (Primolut N, Schering, Germany) orally three times daily during the attack of bleeding and 5 mg daily if there is no bleeding to complete 21 days per cycle for three cycles. Twelve patients failed to complete the study, two from the goserelin group and ten from the norethisterone group, so the final number was 50 in the goserelin group and 40 in the norethisterone group. The measurement of the fibroid was done by taking two dimensions of the largest fibroid, including the biggest diameter using ultrasound with a convex 3.5 MHz probe (Hunda, Japan) pretreatment and after three months. Pretreatment hemoglobin was checked, and then after three months. General investigations were carried out for both groups including complete blood picture, fasting blood sugar, blood urea, and liver function tests. Patient's acceptance and response were subjectively registered on a special questionnaire with any side effects occurred in that period. The results were statistically analyzed, using the Statistical Package for Social Sciences (SPSS) version 11. Descriptive statistical analyses (frequency distributions and percentages) were used, while inferential statistics limited to t test, for comparison of means, and chi-square test of proportions. $P < 0.05$ was considered significant.

Results

Table-1 showed the characteristics of both groups, both were comparable in age ($P =$

0.772) and parity ($P = 0.5397$). About 80% of both groups were housewives. The measurements of the fibroids were taken in 2 dimensions, in the goserelin group the mean was 28.24 cm², and in the norethisterone group it was 26.56 cm², with no statistical significant difference. There was no statistical significant difference in the mean hemoglobin concentration, 9.28 mg/100ml and 10.08mg/100ml in the goserelin and norethisterone respectively. The duration of menorrhagia was also comparable in both groups and the number of changed pads per day. The acceptance of both groups to the treatment showed no significant difference.

Table 1: The characteristics of both groups

	Group 1 (goserelin) No. 50	Group 2 (Norethisterone) No. 40	P value
Age(years)			
Mean	34.62	36.38	0.0772
SD	4.22	5.12	
Parity			
Mean	3.12	2.98	0.5397
SD	1.14	0.98	
Occupation			
Housewife	40 (80%)	33 (82.5%)	0.949
Government	6(12%)	4(10%)	
free	4(8%)	3(7.5%)	
Size of Fibroid (cm²)			
Mean	28.24	26.56	0.1947
SD	6.14	5.96	
Duration of menorrhagia (months)			
Mean	3.24	3.58	0.2337
SD	1.22	1.47	
Number of pads changed/day			
Less than 5	5	4	0.926
6-7	8	6	
8-9	23	21	
More than 10	14	19	

Table-2 showed the effect of both drugs, for the size of fibroid the two dimensions square reduced from 28.24 to 12.3 cm² in the goserelin group with more than 50% reduction, and for the norethisterone group there was no significant reduction. The mean hemoglobin concentration was elevated from 9.28 gm/100ml to 11.2 in the gosereline group with statistical significant difference ($P = 0.0001$), but in the norethisterone group there was no statistical significant difference. The number of changed pads showed statistical significant

difference reduction in number in the goserelin group, but not in the norethisterone group.

Table 2 : The effect of goserelin (group 1) and norethisterone (group 2)

	Groups	Treatment		P value
		Before	After	
Size of fibroid (cm ²)	Group I	28.24 6.14	12.3 3.45	0.0001
	Group II	26.56 5.96	25.22 5.01	
Mean SD				0.2589
Hb level (mg/dl)	Group I	9.28 2.44	11.2 1.88	0.0001
	Group II	10.08 2.86	10.24 2.46	
Mean SD				0.7798
Number of Pads changed per day	Group I	≤5	5	0.000
		6-7	8	
		8-9	23	
		≥10	14	
	Group II	≤5	4	0.102
		6-7	6	
		8-9	21	
		≥10	9	

Table-3 showed the side effects of both groups, there was no statistical significant difference between the two groups regarding all the side effects (P= 0.119), but there was more menopausal symptoms in the goserelin group, 15 versus 7 in the norethisterone group. Table-4 showed the operations that were done after finishing the treatment up to about one year. There were more operations in the norethisterone group. Twenty five (50%) of patients in the goserelin group had no operations versus four (10%) in the norethisterone group. Seven had hysterectomy in the goserelin group and 12 in the norethisterone group and myomectomy in nineteen and twenty four respectively. All operations showed statistical significant reduction in the goserelin group.

Table 3 : the side effects of Goserelin and the Norethisterone treated groups

Side effect	Goserelin group No. (%)	Norethisterone group No. (%)	P value
Menopausal symptoms	15 (30)	7 (17.5)	
Joint pain	13 (26)	5 (12.5)	
Skin allergy	7 (14)	4 (10)	
Increase weight	5 (10)	6 (15)	
acne	4 (8)	6 (15)	
No complaint	6 (12)	12 (30)	

total	50	40	
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Table 4 : the operations in both groups

Type of surgery	Group 1	Group 2	P value
Hysterectomy	7	12	0.000
Myomectomy	18	24	
No operation	25	4	

Discussion

The (GnRH) agonists are an effective medical approach for the management of both dysfunctional uterine bleeding (DUB) and uterine fibroids. However, their use is restricted to short courses due to its long effect on bone mass. (6) Norethisterone is a common treatment of menorrhagia in our clinical practice; it is cheap, always available and well tolerated by the patients. After the introduction of Goserelin in our clinical practice, we designed this study to compare both drugs in cases of menorrhagia with uterine fibroids. Regarding blood loss, the increase in haemoglobin is significant after Goserelin use, (7) (8) with about 1 and 1.5 gm/100ml increase in both studies respectively. In our study the increase was about 2 gm/100 ml in the Goserelin group, it was not significant in the norethisterone group. In assessing the blood loss we use the subjective method by patient observation in comparison with her previous menses and the objective methods by counting pads and hemoglobin estimation, all showed significant improvement in the Goserelin group. Ranke HR, found no significant difference in adding estradiol/norethisterone to goserelin in reduction of blood loss. (9) Pre operative goserelin has been shown to decrease blood transfusion during operation and increase the post operative hemoglobin. (10) Goserelin was found to decrease the size of uterine fibroids. (11-15) In our study we used two dimensions measurement of the fibroid by ultrasound, as it can be done by the usual ultrasound equipment available in gynecology clinics; the reduction in the area of the fibroid was from 28.24± 6.14 cm² to 12.3±3.45 which represent more than 50%. Bozzini, 2004 found in a randomized controlled trial that Goserelin use in monthly injection for 3 months reduce the size of fibroid by 43%. (16) Adding goserelin after uterine artery embolization was found not to increase in the reduction of the size of leiomyoma, (17) in the same study the reduction of size of fibroid in Goserelin group was 45%. In a study done by Lumsden, 1994, on 71 ladies scheduled for hysterectomy for fibroid, and were divided in 2 groups, one was given Goserelin and the other placebo before operation and they found that the size of the fibroid is smaller in the

Goserelin group, also the haemoglobin level and the duration of the operation.⁽¹⁸⁾ Goserelin was also found to increase pregnancy rates if given before hysteroscopic resection of fibroid in cases of sub fertility.⁽¹⁹⁾ Many studies found that blood loss during operation for fibroid after Goserelin use was less than without it.⁽¹⁷⁾⁽²⁰⁾ Recent study showed that the use of triple tourniquets is associated with less blood loss than the use of pre-operative Goserelin in open myomectomy.⁽²¹⁾ Goserelin was found also to shorten the operative time.⁽¹³⁾ In our study these parameters were not measured. No significant medical problems were found after the short time use of Goserelin.⁽⁴⁾ In our study there was no significant difference in the side effects of both groups ($P=0.119$), but more vaso-motor symptoms noted in the Goserelin group, 39% versus 17.3% in the n group. Regarding the need for operations, 25 of the Goserelin group (50%) had operations, 7 hysterectomy and 18 myomectomy, versus 36 out of 40 in the norethsterone group, 12 hysterectomy and 24 myomectomy, so the need for operation is decreased with Goserelin , mostly due to improvement of symptoms, and the desire of most of the women to preserve the uterus. Hysterectomy rates for leiomyoma decreased significantly from 2.13 per 1000 to 1.91 ($P < .0001$), due to increase in uterine artery embolization and uterine ablation.⁽²²⁾ GnRH agonists shrink the uterus and fibroids, and this effect make it possible to change some of abdominal hysterectomies to vaginal hysterectomy, in one study, 76% of GnRH agonist-treated patients had vaginal hysterectomy versus 16% of non treated patients.⁽²³⁾ The use of GnRH agonists can make possible a conversion from abdominal hysterectomy to either vaginal hysterectomy or laparoscopic-assisted vaginal hysterectomy or laparoscopic supracervical hysterectomy.⁽²³⁾ In conclusion, Goserelin for three months is a reasonable choice of treatment for patients having menorrhagia with uterine fibroid, as it increases the hemoglobin concentration, decrease the need for operation, decrease blood transfusion during operation, and with limited side effects.

References

1. Buttram, V. and Reiter, R. Uterine leiomyomata: etiology, symptomatology and management. *Fertil. Steril.* 1981; **36**, 433–445.)
2. AHRQ (2000) *Management of uterine fibroids. Evidence report. Technology assessment: Number 34.* Agency for Healthcare Research and Quality of Life. [http://www.ahrq.gov/.](http://www.ahrq.gov/)
3. Crosignani PG, Vercellini P, Meschia M, Oldani S, Bramante T GnRH agonists before surgery for uterine leiomyomas. *Report Med 1996 ; 41(6):415-21.*
4. Cagnacci A, Paoletti AM, Soldani R, Angiolucci M, Arangino S, Falqui A, Melis GB Role of goserelin-depot in the clinical management of uterine fibroids. *Obstet Gynecol 1994; 21(4):263-5.*
5. Irvine GA; Campbell-Brown MB; Lumsden MA; Heikkila A; Walker JJ; Cameron IT, Randomised comparative trial of the levonorgestrel intrauterine system and norethisterone for treatment of idiopathic menorrhagia. *Br J Obstet Gynaecol 1998;105(6):592-8.*
6. Thomas EJ, Add-back therapy for long-term use in dysfunctional uterine bleeding and uterine fibroids. *Br J Obstet Gynaecol. 1996; 103 Suppl 14:18-21*
7. Gerris J, Degueudre M, Peters AA, Romao F, Stjernquist M, al-Taher H The place of Zoladex in deferred surgery for uterine fibroids. [Zoladex Myoma Study Group.] *Horm Res 1996; 45(6):279-84.*
8. Stovall TG, Summit RL, Washburn SA, Ling FW Gonadotropin-releasing hormone agonist use before hysterectomy. *Am J Obstet Gynecol 1994 ; 170(6):1744-8; discussion 1748-51.*
9. Franke HR, Snaaijer FF, Houben PW, van der Mooren MJ Treatment of dysfunctional uterine bleeding in the perimenopause: The effects of adding combined estradiol / norethisterone acetate therapy to goserelin acetate treatment: *Gynecol Endocrinol 2006 ; 22(12):692-7*
10. Lim SS, Sockalingam JK, Tan PC: Goserelin versus leuprolide before hysterectomy for uterine fibroids. *Int J Gynaecol Obstet 2007 27.*
11. Moris,EP, RymerJ, RobinsonJ, FogelmanI Efficacy of tibolone as "add-back therapy" in conjunction with a gonadotropin-releasing hormone analogue in the treatment of uterine fibroids. *Fertil Steril 2007 15.*
12. Russo P, Ciolli P, Atlante M, Carico E, Mancini R, Russo R, Vecchione A [Clinical use of leuprolide acetate depot in a group of gynecologic patients in the preoperative period; *Minerva Ginecol 1998 ; 50(11):499-502.*
13. Tiufekchieva E, Nikolov A: Hysteroresection of submucous myomas after treatment with zoladex; *Akush Ginekol (Sofia) 2006; 45(1):19-24.*
14. Donnez J, Hervais Vivancos B, Kudela M, Audebert A, Jadoul P A randomized, placebo-controlled, dose-ranging trial comparing fulvestrant with goserelin in

- premenopausal patients with uterine fibroids awaiting hysterectomy. *Fertil Steril* 2003 ; 79(6):1380-9.
15. Baytur YB, Ozbilgin K, Cilaker S, Lacin S, Kurtul O, Oruc S, Koyuncu FM A comparative study of the effect of raloxifene and gosereline on uterine leiomyoma volume changes and estrogen receptor, progesterone receptor, bcl-2 and p53 expression immunohistochemically in premenopausal women. *Eur J Obstet Gynecol Reprod Biol* 2006 Sep 12
 16. BozziniN, MessinaML, BorsariR, HilarioSG, PinottiJA Comparative study of different dosages of goserelin in size reduction of myomatous uteri. *J Am Assoc Gynecol Laparosc* 2004 ;11(4): 462-3.
 17. VilosGA, VilosAG, , Abu-RafeaB, PronG, KozakR, GarvinG, Administration of goserelin acetate after uterine artery embolization does not change the reduction rate and volume of uterine myomas. *Fertil Steril* 2006 ; 85(5):1478-83.
 18. Lumsden MA, West CP, Thomas E, Coutts J, Hillier H, Thomas N, Baird DT Treatment with the gonadotrophin releasing hormone-agonist goserelin before hysterectomy for uterine fibroids. *Br J Obstet Gynaecol* 1994 ; 101(5):438-42.
 19. Narayan R, Rajat, Goswamy K Treatment of submucous fibroids, and outcome of assisted conception. *J Am Assoc Gynecol Laparosc* 1994 ;1(4 Pt 1):307-11.
 20. Crosignani PG, Vercellini P, Meschia M, Oldani S, Bramante T GnRH agonists before surgery for uterine leiomyomas. *J Reprod Med* 1996 ; 41(6):415-21
 21. Al-Shabibi N, Chapman L, Madari S, Papadimitriou A, Papalampros P, Magos A Prospective randomised trial comparing gonadotrophin-releasing hormone analogues with triple tourniquets at open myomectomy. *BJOG* 2009 Feb 4.
 22. Jacobson GF, Shaber RE, Armstrong MA, Hung YY. Links Changes in rates of hysterectomy and uterine conserving procedures for treatment of uterine leiomyoma. *Am J Obstet Gynecol*. 2007; 196(6):601.e1-5; discussion 601.e5-6.
 23. Carter JE. Alternatives to total abdominal hysterectomy. *JSLs*. 1997; 1:259-262.