

A Randomised Controlled Study of Goserelin as Adjunctive Therapy Prior to Surgery in the Management of Uterine Fibroids

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Abstract

Context: Luteinising hormone analogues are being increasingly advocated in the management of common oestrogen-dependent gynaecological conditions, notably uterine fibroids, endometriosis and menorrhagia.

Objective: The aim was to assess the effects of depot injections of goserelin (Zoladex[®]), a GnRH-agonist analogue, on the management of uterine fibroids.

Patients and Methods: Forty female pre-menopausal patients aged between 26 and 50 years, with uterine sizes 12 to 26 weeks were enrolled in a randomised controlled study. One group was prospectively randomized to surgery (deferred for 0 to 4 months) and another to goserelin treatment for 3 months, followed by surgery. Patients were included if they had a diagnosis of benign uterine fibroids and an abdomino-pelvic mass greater than 12 weeks gestational size.

Results: Uterine and fibroids volumes were reduced by a median value of 31.7% and 58.1% respectively for Zoladex patients compared with an increase of 3.3% and 0.6% in uterine and fibroid volumes in the surgery-only patients. The difference between the treatment groups for the absolute changes was statistically significant ($p < 0.0001$). Patients in the goserelin group had a somewhat higher haemoglobin level by the time of surgery compared to the time of entry ($p = 0.06$), had an easier operation and a shorter stay in hospital. Adverse events were more numerous in the goserelin treated patients.

Conclusion: Goserelin treatment, prior to surgery, demonstrated benefit in terms of uterine and fibroids volumes, symptoms reduction and improvement of haematological profile in Nigerian patients with uterine leiomyoma.

Key Words: Uterine Fibroids, Goserelin, Adjunctive Therapy, Surgery.

Introduction

Uterine fibroids are the most common benign solid neoplasia of the female genital tract, occurring in 20-25% of women over 30 years of age especially the nulliparous one^{1,2}. They are frequently found in gynaecological practice and may be associated with sub fertility and symptoms such as menorrhagia, pelvic discomfort, and dyspareunia. The incidence of these tumors is several times higher in black women than in white women.

Treatment of uterine fibroids traditionally has ranged from careful observations to surgical interventions, either myomectomy or hysterectomy. In 1983, however, Filicori and co-workers presented a case report, which showed that the administration of a gonadotrophin releasing hormone (GnRH) analogue reduced the size of uterine fibroids³. Further studies involving the use of pelvic ultrasonography have confirmed that fibroids reduce in size during treatment with gonodotrophin releasing analogues^{4,5,6}.

Luteinizing hormone analogues are being increasingly advocated in the management of common oestrogen-dependent gynaecological conditions, notably uterine fibroids^{7,8,9}, endometriosis^{10,11} and menorrhagia¹². They

have also been shown to have a place in the management of metastatic breast cancer^{13,14}.

Recent studies^{9,15} have shown the effectiveness of both buserelin and goserelin in reducing uterine fibroids to about 50% of their original size (assessed by ultrasonic measurement). In women with symptomatic fibroids, use of a GnRH-A has produced amenorrhea and successfully reduced uterine and tumour volumes. However, regrowth of the fibroids to their former size have been shown to occur within 3-6 months of stopping therapy^{16,17}. This work prompted Shaw to suggest that LHRH analogues should be used as an adjunct to the surgical management of fibroids^{16,18}.

When choosing the therapy, it is necessary to account for several factors: dimensions, position, number of myomas; patient's age; uncommon malignant degeneration; hormone-dependence and desire for child bearing. Classic management presents potential

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risks: operative blood loss requiring transfusion and causing post-operative anaemia, which can lead to increased morbidity post-operatively. There is therefore, the need to have the haemoglobin level at the normal range pre-operatively, a context in which the use of LHRH analogues has utility²¹. Following various conclusions, drawn on the efficacy and tolerability of the GnRH-agonists, many authors suggest an advantageous use of GnRH-agonist before surgery^{22,23}.

The aim of this study, therefore, was to assess the effect of goserelin (Zoladex), given by monthly subcutaneous injections for three months prior to surgery in Nigerian female patients.

Patients and Methods

This was a randomised controlled study of goserelin (Zoladex) as adjunctive therapy prior to surgery in the management of uterine fibroids in two Teaching Hospitals in Nigeria viz: The Lagos University Teaching Hospital, Lagos and the Ahmadu Bello University Teaching Hospital, Zaria, between June 1999 and December 2001.

Women aged between 25 and 49 years who presented in the gynaecological clinics with symptoms and signs of uterine fibroids, were screened after giving a written consent to participate in the study. Patients were eligible for entry into the trial, if they were pre-menopausal, aged between 25 and 50 years, had a diagnosis of uterine fibroids made on ultrasound scan, had symptoms related to the fibroids such as anaemia [Hb < 10g/dl - or a pelvic mass > 12 weeks gestation size] and were awaiting hysterectomy or, in exceptional cases, myomectomy for the fibroids. Patients who were pregnant or breastfeeding, or had concomitant illness, or had been on sex hormone therapy within two months prior to entry were excluded.

The study was conducted in accordance with the Declaration of Helsinki and ethical clearance was obtained from the local ethics committee of each of the investigating institutions. The patients were randomised following confirmation that they satisfied the selection criteria, agreed to accept either treatment modality and had given informed consent after the objectives of the study were explained to them.

All patients in the goserelin and control groups had, on recruitment into the study, a detailed history taken and had the uterine and fibroid volumes assessed by ultrasound scan. Based on these data, the type of operation and incision planned were recorded by the surgeon who later performed the operation.. Patients randomised to the "goserelin" group, received a 3.6 mg

"goserelin" depot administered subcutaneously every 28 days. Patients received a total of three depots. The depot dose of 'goserelin' was presented in pre-filled sterile delivery devices. Patients randomized to the control group did not receive goserelin but received similar monitoring and follow-up as the goserelin group, before their surgery.

In all, a total of five visits were undertaken. During the first visit (enrolment visit) other details recorded included a detailed menstrual history including the frequency and severity of vaginal bleeding, pelvic pain and pressure symptoms, details of previous abdominal surgery and any complications, which were relevant to the planned operation, were recorded. A blood sample was taken for estimation of haemoglobin, and haematocrit. Another blood sample was taken for estimation of serum urea, creatinine, total bilirubin, alkaline phosphatase, aspartate amino-transferase and total protein. The presence of symptoms such as vaginal discomfort and dryness, hot flushes, night sweats, headaches, depression, irritability, tension and any adverse reaction were also recorded.

During visits 2 and 3 (interim visits), details of the frequency and severity of vaginal bleeding, menstruation, pelvic pain and pressure symptoms were recorded. Any interventions required by patients during the previous 28 days were documented and any additional medication recorded. The presence of adverse events, reported spontaneously or elicited on physical examination, were also recorded. All patients who have completed earlier visits were on visit 4 admitted to hospital for surgery. For patients randomised to 'goserelin', surgery was performed not earlier than 3 weeks and not later than 5 weeks after receiving the third and last depot injection.

On the day preceding the surgery, all patients had all earlier assessments repeated medical history, physical examination, haematological and biochemical tests, abdominal ultrasound and the presence of symptoms suggestive of adverse events. On the day of the operation, the type of surgery performed and the type of incision used were reviewed. The same investigator who predicted the type of surgery and incision at Visit 1 performed the operation. The reason for any change in the type of operation performed or incision used from that planned at Visit 1 was documented.

Conservative myomectomy was performed instead of hysterectomy for all patients who complied with all the following criteria: wishing to have children in future, number of fibroid nodules less than three, no nodules in the uterine cervix; isthmus of the uterus, and no intra-ligamentary nodules, each nodule is less than 3cm in

diameter, no signs of infection of the reproductive system, no sign of malignant change in the uterus and age below 45 years. Any complications with the operation were recorded in addition to the following assessments: the duration of the operation from the time of the first incision to the time of the last stitch to close the abdomen, blood loss during the operation (assessed by measuring the weight of the swabs and the volume of blood collected into receptacles such as aspiration bottles), details of any blood transfusion requirements, the degree of difficulty of the operation, details of prophylactic antibiotic usage, the pre-medication required and the type of anaesthesia.

All patients that had surgery were monitored and assessed for pyrexia, excessive bleeding, haemoglobin levels, blood transfusion requirement and duration of hospitalisation. The fifth visit (follow-up) was usually between 4-6 weeks after surgery during which their full recovery/fitness were confirmed.

Results

A total of 40 female patients with uterine fibroids were recruited to participate in the clinical trial; 20 patients were randomised into each of the treatment groups.

Table 1 shows the baseline summary statistics of patient's age, parity, duration of menstrual flow and haemoglobin in the 2 treatment groups. The difference between the 2 treatment groups was not statistically significant.

The changes in the patients' uterine and fibroid volumes as well as duration of menstrual flow over time in the 4 visits prior to operation by treatment groups are shown in Figures 1, 2 & 3. The significance was investigated using the Friedman's Test, a non-parametric equivalent of the two-way ANOVA. There was a statistically significant difference in the uterine volume between patients in the control group and those on goserelin prior to operation ($p < 0.05$).

Similarly, the fibroid volume of the patients on goserelin was statistically and significantly reduced over the period of pre-operative visits, from the baseline median value of 184.55 to 93.54 at the fourth visit, but the reverse situation occurred in the control treatment, as their fibroid volume increased over time as they awaited surgery from the baseline median value of 174.52 to 224.26 at the fourth visit (immediately before the surgical operation). There was a statistically significant difference between the fibroid volume of patients on goserelin and those on control at each visit. ($p < 0.05$).

Table 1
Baseline Summary Statistics of Patients Enrolled in the Study

Parameters	Study Group	Summary Measure		
		Mean	S.D	Range
Age	Goserelin	33.85	5.33	26-43
	Control	38.47	5.92	28-50
Parity	Goserelin	1.05	1.67	0-6
	Control	1.95	1.88	0-5
Duration of Menstrual flow (days)	Goserelin	6.80	4.25	3.0 - 21.0
	Control	5.40	1.50	3.0 - 8.0
Haemoglobin	Goserelin	10.43	1.42	
	Control	10.74	1.12	
Haematocrit	Goserelin	31.27	4.14	
	Control	32.25	2.90	
		Median	Deviate	Range
Uterine Volume	Goserelin	293.9	18.7	91.4 - 5802.4
	Control	384.8	21.4	22.2 - 953.5
Fibroid Volume	Goserelin	187.5	21.1	7.2 - 1432.6
	Control	174.5	20.0	5.8 - 637.9

Figure 1
The Trends in Uterine Volume Over Time in Goserelin-Treated and Control Patients

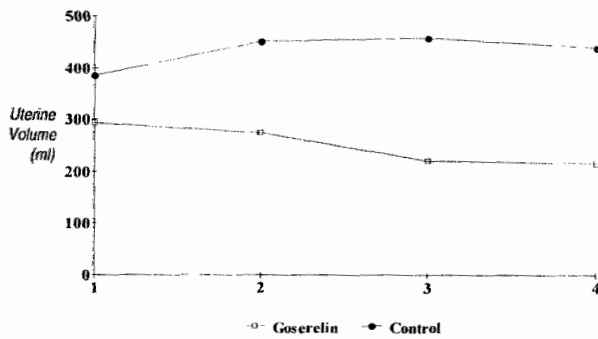


Figure 2
The Trends in Fibroid Volume Over Time in Goserelin-Treated and Control Patients

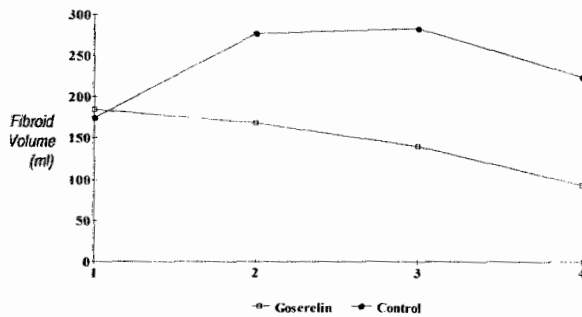
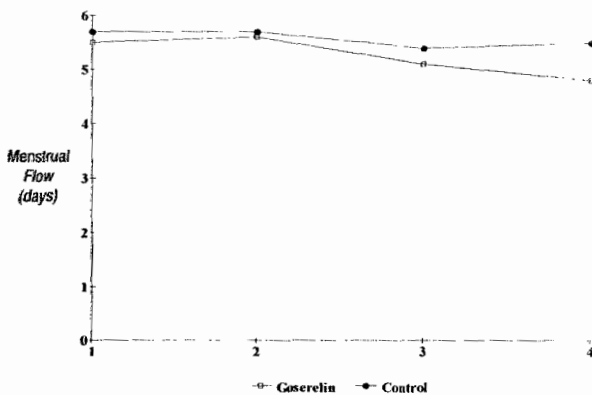


Figure 3
Temporal Trends in Duration of Menstrual Flow in Goserelin-Treated and Control Patients



The duration of menstrual flow (days) was also reduced for patients on goserelin over this period, a statistically significant difference, whereas the reverse was the case for those in the control group. There was a statistically significant difference between the duration of menstrual flow value of patients on goserelin and the controls at the end of the pre-operative waiting period.

The haemoglobin level of both groups of patients increased over the period of pre-operative visits. The baseline values were lower among the goserelin

treatment but by the fourth visit, these patients' haemoglobin values had increased and were higher than those of the patients in the control group. There was a statistically significant difference between the mean haemoglobin values of patients on goserelin and those in the control group ($p < 0.05$).

Discussion

This study had demonstrated that the pre-operative administration of goserelin (Zoladex®) before surgery for uterine myomas is beneficial to patients. Treatment with goserelin led to significant reduction of size of fibroids within 3 months and these were associated with improved clinical conditions of the patients. The treatment also induced oligomenorrhoea in the vast majority of women which is likely to be beneficial to those with menstrual problems, especially when they have to wait for sometime before the surgical operation could be carried out. A greater proportion of the operations in the goserelin group were performed through transverse incisions, which are preferable because they are less painful, heal better and are cosmetically more acceptable.

Pre-operative treatment with goserelin also enables another option to be undertaken here, in this case, myomectomy rather than hysterectomy. This conservative approach means a shorter hospital stay, better and faster patient recovery, and psychological acceptance to patients. The shorter hospital stay also results in less cost to the patient and less stress on the medical and nursing staff. In fact, it has been demonstrated that prior treatment with a GnRH agonist, such a goserelin may enable more hysterectomies to be performed vaginally with reduced morbidity and no abdominal scar²⁴.

There was also a difference (though not statistically significant) in the haemoglobin concentration between the two groups at visit 4 and post-operatively. This confirms what other workers had demonstrated earlier^{25,26}, and is due to the reduced severity of bleeding during menstrual cycles when goserelin is being administered.

The side effects experienced by women who received goserelin during the pre-operative period tended to be outweighed by the relief of symptoms and the subsequent benefits. Besides, in some patients, these could not be demonstrated as treatment related since they were either present before the treatment or were just as likely to occur in the controlled group. Increasingly, emphasis is being directed at having more conservative surgery in patients with uterine fibroids, besides the need to have a surgically fit patient and the avoidance of blood transfusion. These benefits can be achieved with the use of goserelin²⁷.

In conclusion, it has been demonstrated that this medico-surgical approach to the management of large fibroids is safe, effective and beneficial to the patients with this clinical condition.

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Acknowledgement

ASTRAZENECA provided clinical trial materials, paid for investigations and provided other logistic support.