

Short-term use of Goserelin depot in the treatment of dysfunctional uterine bleeding

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Summary: Study-Plan: an open study aimed at evaluating the results of a short term therapy (3 months) with Goserelin depot as a medical treatment of premenopausal dysfunctional uterine bleeding.

Patients: 60 premenopausal women (aged 36-50) with dysfunctional uterine bleeding, presenting simple endometrial hyperplasia.

Results: after the treatment, spontaneous menstrual bleeding recurred in 57/60 patients, while 3/60 (5%) patients remained amenorrheal during the whole period of follow-up, showing a post-menopausal hormonal pattern.

In the first post-therapy menstrual cycle all the 57 patients had a bleeding score <100; patients relapsing during the second, third and fourth cycle were respectively 2/54 (3.7%), 5/48 (10.7%) and 17/38 (44.7%).

The fourth post-therapy cycle was delayed 6-9 months after the last injection of Goserelin. Both the mean blood loss and the mean duration of bleeding were significantly reduced in all post-therapy cycles.

Eleven patients were anaemic before therapy (Hb <12 g%); Goserelin treatment resulted in a normalization of the hematological parameters.

At the end of treatment a small area of hyperplasia persisted in only 4/60 patients (6.7%). Localised or diffused hyperplasia were found respectively in 5/54 (9.3%) and in 1/54 patients (1.9%) at three months, and in 5/48 (10.4%) and 4/48 (8.3%) at a six-month follow-up.

Side effects were infrequent.

Conclusions: the long symptom-free period and the low incidence of side effects indicates Goserelin depot as a valuable medical treatment for dysfunctional uterine bleeding.

Key words: Dysfunctional uterine bleeding; Goserelin.

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INTRODUCTION

Abnormal uterine bleeding is one of the most frequent reasons for referral of premenopausal women to a gynecologist⁽¹⁾.

At present, hysterectomy is still offered as an elective therapy⁽²⁾ even in the absence of any demonstrable organic or neoplastic condition.

This is a consequence of the non-availability of a curative medical approach combining a good success rate, a low rate of recurrence or relapse and a good tolerability.

Cyclical therapy with estrogens and progesterone or with progesterone alone is effective during the treatment, but the abnormal bleeding tends to recur almost immediately upon discontinuation of the medications⁽³⁾.

Danazol therapy, on the other hand, carries the risk of severe side effects which most women would not accept⁽⁴⁾.

Goserelin, a GnRH analogue available in depot formulation, can offer a new approach to the medical therapy of dysfunctional uterine bleeding, since the treatment with this compound causes a marked endometrial atrophy and a complete cessation of menses.

However, few data have been published on the use of this or other GnRH analogues for the treatment of dysfunctional uterine bleeding⁽⁵⁾.

Although some authors have reported the use of GnRH analogues for the treatment of menometrorrhagia, either followed by a conservative surgical approach consisting of endometrial ablation^(5, 6, 7), or, in a long term schedule, combining the GnRH analogue with a hormonal replacement therapy⁽⁸⁾, only preliminary results with small numbers of patients have been reported on the short term use of these compounds as a sole therapy for abnormal uterine bleeding^(9, 10, 11).

No definitive conclusion on the validity of a short term treatment with GnRH analogues in this pathology can be drawn on the basis of the data available so far^(5, 11).

Although the abnormal bleeding may recur with the return of menses after stopping the treatment, the rate of recurrence or the delay in recurrence after the discontinuation of the therapy may prove

the short term treatment with GnRH analogues to be a valid therapeutic option for women with dysfunctional uterine bleeding.

In this paper we present the results of an open study aimed at evaluating the efficacy of a short term treatment with Goserelin depot as sole therapy for premenopausal dysfunctional uterine bleeding.

MATERIALS AND METHODS

Sixty premenopausal women (aged 36-50) with dysfunctional uterine bleeding (menometrorrhagia) were enrolled in this study.

Inclusion criteria were:

- Bleeding score > 100 (blood loss > 80 ml) during two consecutive cycle;
- age > 35 years;
- endometrial hyperplasia with no atypical cellular findings and no organic endo-uterine disease.

Quantitative evaluation of the amount of uterine bleeding was obtained by counting the number of vaginal pads used and the degree of saturation of each pad, and the appropriate score was determined. Highman and Shaw⁽¹²⁾ demonstrated that this method is as accurate as the direct quantitative measurement of alkaline hematin as described by Hallberg & Nilson⁽¹³⁾.

A score > 100 (indicating a blood loss > 80 ml) indicates an existing menometrorrhagia.

The diagnosis of hyperplasia was reached by histopathological examination of endometrial biopsies following hysteroscopy.

Patients were enrolled in the study regardless of previous treatment (no treatment, danazol or progesterone), provided that any previous treatment had been concluded for at least 6 months.

Patients with other concomitant pathological conditions, such as liver disease, cardiovascular or cerebrovascular disease, jaundice or porphyria or a high risk for osteoporosis were excluded from the study.

Complete haematological tests were performed to exclude any patient with blood dyscrasia or coagulation defects.

An informed consent was obtained from each patient.

Potentially fertile patients were asked to avoid pregnancy starting one month before treatment and up to four months after the

treatment had been discontinued. A pregnancy test was performed immediately before starting the therapy.

Goserelin depot (Zoladex, Zeneca plc, UK), was administered subcutaneously on the first day of the menstrual cycle or in the late luteal phase; the administration was repeated every 28 days for three times.

All patients were asked to record the onset of menstrual bleeding or any adverse drug reaction occurring during the therapy.

Blood loss was evaluated during goserelin administration, at the end of therapy and during the first 4 menstrual cycles following discontinuation of treatment, regardless of the time elapsed between discontinuation of the medication and the beginning of the cycles.

At the end of treatment and 3 and 6 months after the last goserelin injection, patients underwent a complete haematological and clinical examination, including hysteroscopy and histopathological examination of endometrial biopsies.

Statistical significance was evaluated by using the Student "t" test.

RESULTS

All patients became amenorrhoeal after the administration of the second depot of goserelin.

Spontaneous menstrual bleeding recurred between 59 and 162 days after the administration of the last depot in 57/60 patients.

All 57 patients were assessed for blood loss at their first post-treatment cycle; 54/57 were assessed for two, 48/57 for three and 38/57 for four cycles.

Three out of sixty patients (5%) remained amenorrhoeal for the whole dura-

tion of follow-up; their hormonal pattern was postmenopausal.

As shown in Table 1, during the first post-therapy menstrual cycle, all patients reported a bleeding score < 100; while during the second, third and fourth cycle, respectively 2/54 (3.7%), 5/48 (10.4%) and 17/38 (44.7%) patients reported a score > 100.

Compared to the two pre-therapy cycles, both the mean blood loss (Fig. 1) and the duration of bleeding (Fig. 2) were significantly reduced during the post-therapy cycles ($p < 0.005$).

Eleven out of sixty (18.3%) patients were anaemic (Hb < 12 g %) before starting the therapy. As shown in Fig. 3, the mean haemoglobin concentration at the end of the treatment rose at the lower limits of normal range, with a significant difference compared to pre-treatment levels ($p < 0.00001$).

Table 2 shows the hysteroscopy findings before and after the treatment. Endometrial biopsies were obtained from all 60 patients both before and at the end of the three months treatment; patients evaluated at the 3 and 6 months follow-up were 54/60 and 48/60 respectively.

All patients had a pre-therapy diagnosis of simple endometrial hyperplasia, 49/60 (81.6%) presenting a diffuse hyperplasia.

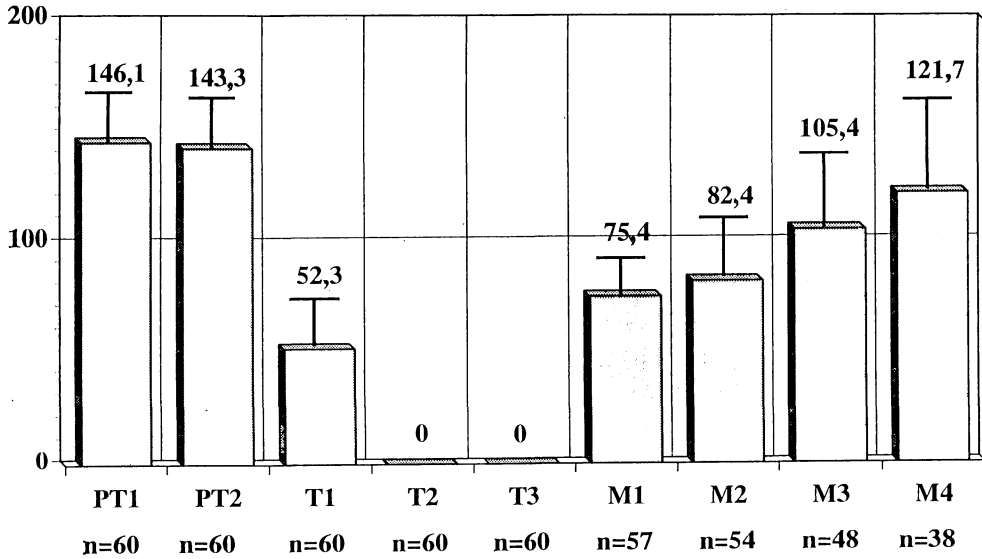
At the end of treatment, only 4/60 patients (6.7%) were found with a small, localised area of residual hyperplasia.

Table 1. - Incidence of dysfunctional uterine bleeding before and after the treatment.

	PT2	M1	M2	M3	M4
Score > 100	60 (100%)	-	2 (3.7%)	5 (10.7%)	17 (44.7%)
Score < 100	-	57 (100%)	52 (96.3%)	43 (89.6%)	21 (55.3%)
Total	60	57	54	48	38

Number of patients reporting a bleeding score > or < 100 is indicated. A score > 100 is indicative of meno-metrorrhagia. The incidence % is reported in brackets. Menstrual cycles are indicated as in Fig. 1.

Score



Menstrual Cycle

Fig. 1. — Quantitative evaluation of the amount of uterine bleeding. Scores were calculated according to Highman and Shaw (12), as described in the Patients and Methods section. A score > 100 is indicative of meno-metrorrhagia. Values reported are the mean ± SD. The number of patients evaluated at each point (n) is also reported. PT1 and PT2 = pre-treatment menstrual cycles 1 and 2; T1, T2, T3 = treatment cycles; M1, M2, M3, M4 = post-treatment menstrual cycles 1, 2, 3, 4.

Table 2. — Histological examination of endometrial biopsies.

	PT	T3	3 Months follow-up	6 Months follow-up
Symple hyperplasia:				
Widespread	49 (81.7%)	—	1 (1.9%)	4 (8.3%)
Localized	11 (17.3%)	4 (6.7%)	5 (9.3%)	5 (10.4%)
Normotrophy	—	—	46 (85.1%)	39 (81.3%)
Hypo-atrophy	—	56 (93.3%)	2 (3.7%)	—
Total	60	60	54	48

Number (and %) of patients is indicated.

PT = pre-treatment;

T3 = end of treatment (28 days after the injection of the third depot of Goserelin).

Days

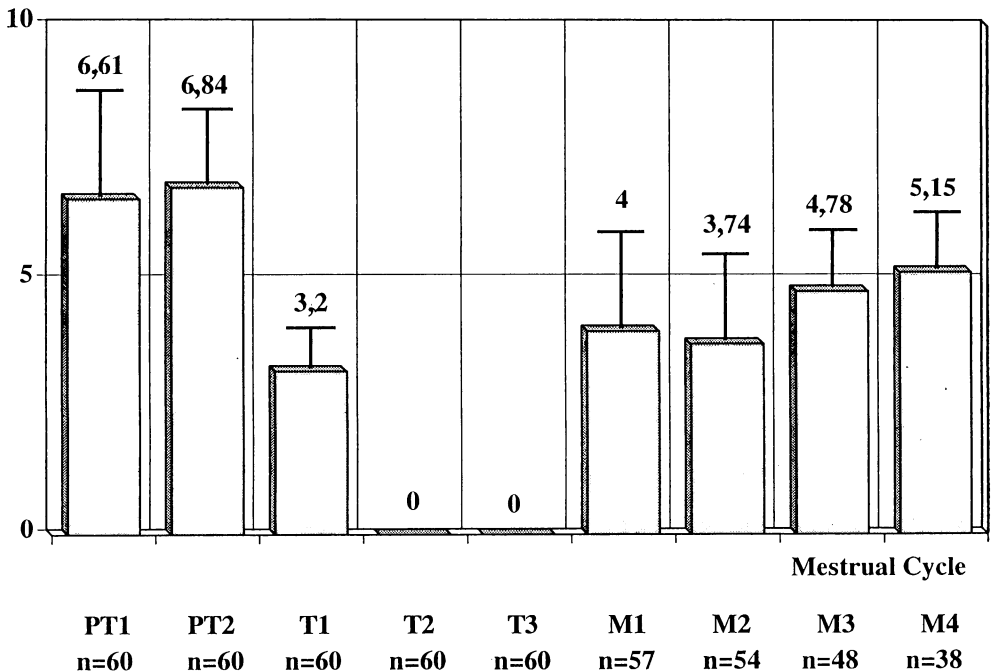


Fig. 2. — Quantitative evaluation of the number of days of bleeding. Values reported are mean \pm SD. The number of patients evaluated at each point (n) is reported. Menstrual cycles are indicated as in fig. 1.

At three months follow-up 5/54 patients (9.3%) presented a localised hyperplasia and 1/54 (1.9%) a diffuse hyperplasia; while at 6 months we found 5/48 cases (10.4%) of localised hyperplasia and 4/48 cases (8.3%) of diffuse hyperplasia. The remaining 39/48 patients (81.3%) had a normotrophic endometrium.

The drug therapy was well tolerated, and no clinically relevant adverse reaction was recorded (Fig. 4).

DISCUSSION

Despite being one of the most common gynaecological pathologies, no ideal medical therapy is yet available for the treatment of dysfunctional uterine bleeding.

GnRH analogues, known to cause a marked endometrial atrophy and a complete cessation of menstruations, are a potential therapeutic option for the treatment of this pathology.

However, only limited data on the use of these compounds in women with dysfunctional uterine bleeding have been published so far, mainly as an adjunct to a surgical therapy or in a long term treatment combining GnRH analogues with a hormonal replacement therapy⁽⁵⁾.

We have reported the results of an open study aimed at evaluating the efficacy of a short term treatment with Goserelin depot as the sole therapy for premenopausal women with dysfunctional uterine bleeding.

HB (g %)

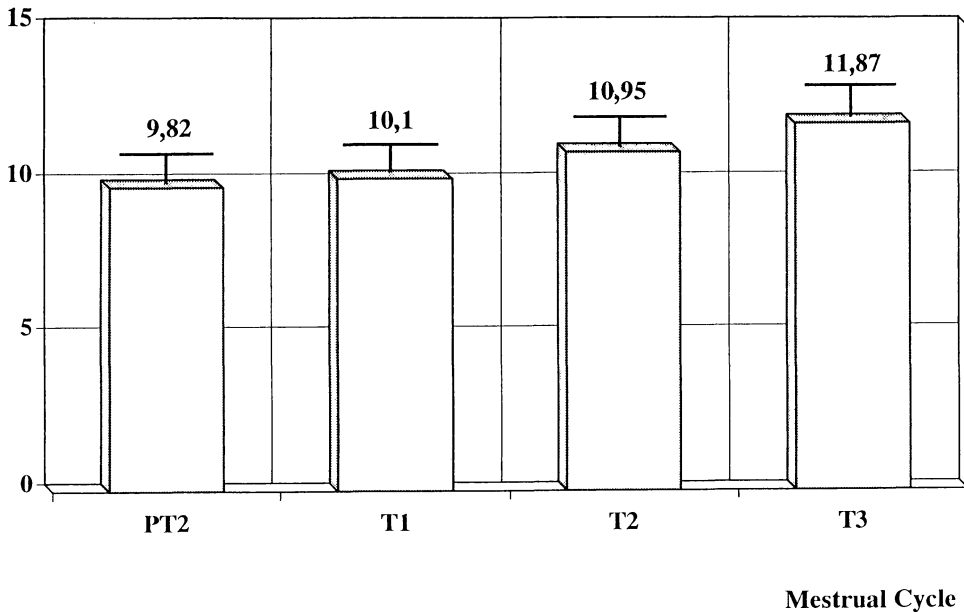


Fig. 3. — Hemoglobin serum levels in anemic patients (n = 11). Values reported are mean \pm SD. Menstrual cycles are indicated as in fig. 1.

Since the onset of menstrual bleeding in the present study varied in time between 59 and 162 days after the administration of the last depot, the follow-up on this group of patients was performed according to the spontaneously occurring menstrual cycles and not according to the time elapsed since the last administration of Goserelin.

Otherwise, women in a different functional status could have been considered as being temporarily homogeneous.

Moreover, this follow-up can permit the comparison of the results of the present study with those previously reported in studies where non-amenorrhea-inducing treatments had been administered (Progestins, Gestrinon, Danazol).

In the present study, although all the patients reported a complete normaliza-

tion of their bleeding pattern at the first post-therapy menstrual cycle, further follow-up revealed a rate of relapse increasing with time, with 3.7, 10.4 and 44.7% of patients relapsing at the second, third and fourth post-therapy cycle, respectively.

The rate of relapse at the fourth post-treatment menstrual cycle does not seem to be significantly different from the data we obtained previously at the same cycle after using different medical approaches⁽¹⁴⁾.

Moreover, considering the growing trend evidenced in the rate of relapse, it might be inferred that the number of patients relapsing will probably increase further with a longer follow-up.

However, it must be noted that in the case of the Goserelin treatment the

SIDE EFFECTS

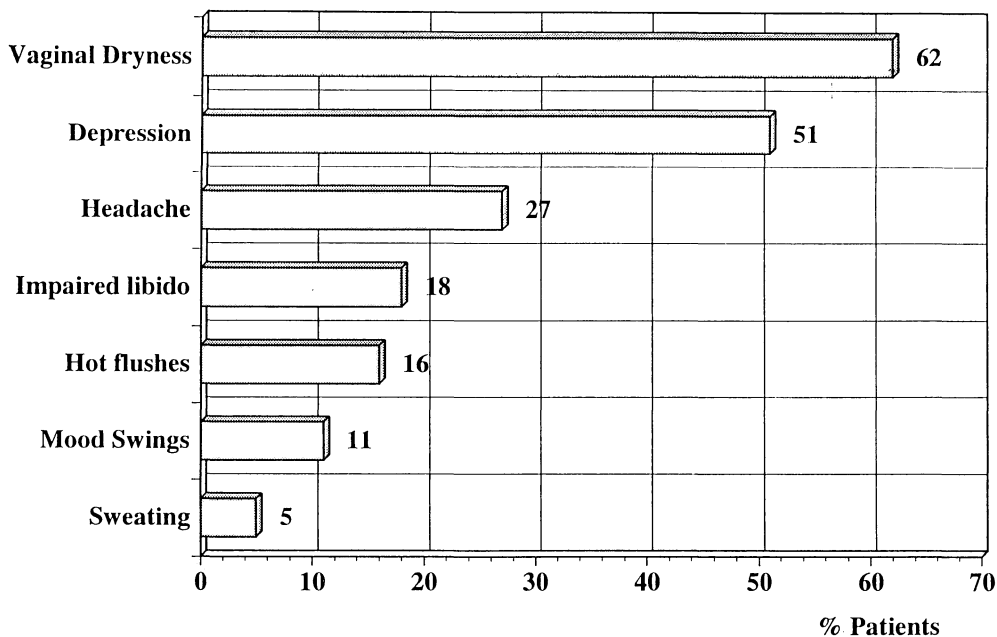


Fig. 4. — Side effects during treatment. Bars indicate the % of patients reporting the side-effects.

fourth post-therapy menstrual cycle is delayed 6 to 9 months after the administration of the last depot, and 9 to 12 months after starting the therapy.

Histological examination of endometrial biopsies revealed a similar trend, with no patient presenting widespread endometrial hyperplasia at the end of the treatment, compared to 1.9% at 3 months and 8.3% at 6 months follow-up.

Areas of localized hyperplasia were present in 6.7% of the patients at the end of the treatment, in 9.3% at three months and 10.4% at 6 months follow-up.

In summary, although the rate of recurrence does not seem to be significantly different compared to other medical treatments when comparing women in the same functional status (i.e. at the same post-therapy menstrual cycle), the time

from the end of the therapy at which recurrence occurs appears to be significantly delayed when Goserelin is administered.

In our opinion, the longer symptom-free period and the low incidence of side effects indicates Goserelin as the medical therapy of choice for the management of abnormal uterine bleeding.

Although only a small number of patients will achieve a permanent cure, the administration of Goserelin can induce amelioration of symptoms and of the haematological parameters in all the patients for at least 9-12 months after starting the therapy.

At relapse, patients may be treated as follow:

a) for patients relapsing within the third post-therapy menstrual cycle, we

suggest a conservative surgical approach (endometrial ablation), possibly following an appropriate pharmacological pre-treatment (7);

b) for patients relapsing after the third post-therapy cycle (especially if over 45 or in the case of refusal of surgery) we suggest a medical treatment till the physiological menopause is reached, either by repeating the three-month treatment with Goserelin when the symptoms recur (bone mineral content should be monitored), or by a long term treatment with Goserelin + Hormonal replacement therapy (8).

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