# Long term follow-up of endometriosis after two different therapies (Gestrinone and Buserelin)

A. NIETO - C. TACURI - M. SERRA - J. KELLER - J. CORTÉS-PRIETO

*Summary*: *Objective* -- To compare the efficacy, tolerance and recurrence rate of endometriosis after 5-year follow-up of treatment with Gestrinone and Buserelin, respectively.

*Study design*: A prospective study with randomized follow-up of 5 years duration (minimum) for each patient was done. We included 43 cases of endometriosis diagnosed by laparoscopy or laparotomy and treated them wih Gestrinone (Group G, n = 25 cases) or Buserelin intranasal spray (Group B, n = 18) for 6 months.

*Results*. General data: Age, height, weight of patients and AFS score of endometriosis were without significant differences in either group. Specific data: *A*) Global clinical efficacy was good or excellent in 74% (16/25) of group G and in 78% (14/18) of group B without significant differences. *B*) Global clinical tolerance was good in 50% of the patients in group G and in 0% in group B ($p < 0.001$). *C*) Global evaluation after 5-year follow-up showed "success" only for 36% of patients in group G and in 33% in group B (no significant differences), with "failure" in 40% and 33%, respectively (no significant differences).

*Conclusions*: 1) Gestrinone and Buserelin intranasal spray are valid treatments for the remission of endometriosis, with "success", "failure" and "clinical recurrence" rates similar after a follow-up of 5 years of initial treatment. 2) The most significant androgenic effect of Gestrinone was the presence of acne. Vascular effetcs were also considered as very undesirable effects according to the comments of patients. On the contrary, the effects of analogs are generally better tolerated.

*Key words*: Endometriosis; Analogs of LHRH; Buserelin; Gestrinone; Efficacy; Tolerance.

## INTRODUCTION

Pain and infertility are the most relevant clinical findings related to endometriosis. The etiology of this disease is still unknown. Its occurs in approximately 5% of the female population in fertile age ([1]).

The majority of pharmacologic treatments have been designed to eliminate, by different means, the ectopic endometrium. To achieve this, the agonists of LH-RH and antigonadotropic drugs are currently the most used.

Gestrinone has demonstrated good antiendometriosis efficacy ([2, 3, 4]). It is a synthetic molecule derived from 19 Norsteroid with antiprogesterone, antiestrogenic and androgenic activity. It possesses good biological availability which

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means that it can still be detected in blood plasma three days after its initial administration. One of its principal applications is the treatment of endometriosis ([5]).

For more than a decade, we have known that the partial agonist of LH-LH, Buserelin is an effective hormone used in the remission of endometriosis ([6, 7, 8]). Buserelin is a non-apeptide with changes in the tenth and sixth aminoacids in its molecule. It has a half-life that ranges from minutes to hours. It is distributed to the tissues and is broken-down by endo and exo-peptidases in the liver and kidney and is eliminated by the urine ([9]). Buserelin can be administered by intranasal spray or subcutaneously and causes hypoestrogenic state during its application.

There are numerous studies on different drugs concerning anti-endometriosis efficacy, but little is known about studies that deal with long-term follow-up. The purpose of this study was to compare efficacy, tolerance and recurrence rate of endometriosis after a 5-year follow-up using Gestrinone and Buserelin.

## MATERIALS AND METHODS

A randomised prospective study with follow-up of 5 years duration (minimum) for each patient in the University Hospital "Principe de Asturias" of Alcalá de Henares, Madrid was done. Forty-three cases of endometriosis diagnosed by laparoscopy or laparotomv were treated with Gestrinone (Group G, n = 25 cases) or Buserelin intranarsal spray (Group B, n = 18) for 6 months.

The AFS classification ([10]) was used. Treatment associated for Group G involved: liberation of adherences or fulgurations of implants in 17 cases (68%), cystectomy in two (8%) and adnexectomy in four (16%). In Group B we associated liberation-rfulguration in seven cases (39%), cystectomy or adnexectomy in nine (50%) and hysterectomy with unilateral adnexectomy in two (11%). No significant differences were observed in either group.

Gestrinone was administered 5 mg/week orally, divided in 2 doses. Buserelin was administered 300 µgrs/8 hours by intranasal spray. In both groups the beginning of treatment coincided with the first day of first menstruation after diagnosis.

This comparative study was evaluated on the basis of three aspects:

1) Global Clinical Efficacy, by analysis of response to pain, adjusted to a verbal scale: None, bad, moderate, good or excellent; and pregnancy in infertile patients.

2) Global Clinical Tolerance, by evaluation of undesirable effects based on four criteria: good tolerance (without secondary effects), regular-good (moderate secondary effects), regular-bad (considerable secondary effects) or bad (it was necessary to abort treatment).

3) Global evaluation after 5 years of follow-up of this disease by the presence of symptoms and periodic clinical or ultrasound examination which was formulated into three categories:

– Success. - When after the initial treatment it was not necessary to administer more drugs or perform surgery; or gestation in infertile patients.

– Failure. - When it was necessary to perform a surgical method after initial treatment or no pregnancy in infertile patients.

– Clinical recurrence. - When the patient had pain but it subsided with the use of basic analgesics.

The main statistical analysis was conducted with a Macintosh computer, model CX (Apple, Cupertino, California, USA), and principally used the statistical program "Statview II. Chi Square test, Student's t-test and Anova were employed following the standard criteria of applicability.

## RESULTS

### 1) General Data

Table 1 shows general characteristics. No significant differences were observed for parameters such as age, previous deliveries, height or abdominal pain and infertility rate between the two groups.

Mean AFS score (Table 2) was 23.1± 19.1 (2-58) for Group G versus 31.1± 21.2 (2-60) for Group B. The majority of patients were in stage III (36% for G group vs 39% for B group). No significant differences were found between the two groups.

Table 1. — *General characteristics of both groups studied.*

| Parameter | Group G (n = 25) X ± SD | Group B (n = 18) X ± SD | p |
|---|---|---|---|
| Age (years) | 33.9±6.6 | 31.5±5.4 | NS |
| Height (cm) | 159.8±6.4 | 159±6 | NS |
| Weight (kg) | 58.3±3.9 | 59.4±4.1 | NS |
| | n (%) | n (%) | p |
| Pain | 20/25 (80) | 15/18 (83) | NS |
| Infertility | 9/25 (36) | 4/18 (22) | NS |

Table 2. — *Extention of endometriosis. (AFS classification at the moment of diagnosis).*

| AFS stage | Group G (n = 25) n (%) | Group B (n = 18) n (%) | p |
|---|---|---|---|
| I | 7 (28) | 3 (17) | NS |
| II | 3 (12) | 2 (11) | NS |
| III | 9 (36) | 7 (39) | NS |
| IV | 6 (24) | 6 (33) | NS |

Mean of AFS score (Gestrinone): 23.1 ± 19.1 points (2-58)

NS

Mean of AFS score (Buserelin): 31.1 ± 21.2 points (2-60)

2) Specific Data

2a) *Clinical efficacy*

– Eighty percent of patients in Group G and 83% in Group B had pain as an expression of clinical data; infertility presented in 36% and 22%, respectively. Thus, for Group G, partial or total response to pain was observed in 95% (19/20) of patients with previous pain and pregnancy postreatment occurred in 33% (3/9) of patients with infertility; for Group B the results were 100% and 25%, respectively, without significant differences.

– Global clinical efficacy (pain and gestation) (Table 3) was good or excellent in 74% (16/25) of Group G and 78% (14/18) of Group B without significant differences. In the second group, hypoestrogenic status was maintained during treatment with Buserelin.

2b) *Tolerance during treatment* (Table 4)

In Group G we observed the following secondary effects:

– Metrorragia-spotting in 76% (19/25) of patients. Sixty percent had amenorrhoea, especially after the 2nd month of treatment.

– Eigty-four percent of patients showed androgenic effects. Acne was the most frequent complication (68%), being reversible after 4.1 months of post-treatment. Seborroea and hirsutism affected 36% of patients and both of these findings were also reversible after 3.3 and 4.7 months of post-treatment, respectively.

– Vascular effects such is heaviness sensation and edema in the lower limbs were observed in 56% of the patients which disappeared after 3.3 months of post-treatment.

– The mean increase of weight was 3 ± 3.1 kg for each patient (-3 - ±9).

– Other symptoms such as nausea (1 patient), constipation (1 patient), headaches (1 patient) and flushes (2 patients) were infrequent.

In Group B, 100% of patients had amenorrhoea, 33% had metrorragia and 67% showed flushes, especially after the first three months.

Table 3. — *Endometriosis. Global clinical efficacy (pain and gestation) according to different therapies (Gestrinone vs Buserelin).*

| | Group G (n = 25) n (%) | Group B (n = 18) n (%) | p |
|---|---|---|---|
| None | 5 (20) | 0 (0) | NS |
| Bad | 2 (8) | 3 (16.5) | NS |
| Moderate | 2 (8) | 1 (5.5) | NS |
| Good | 3 (12) | 5 (28) | NS |
| Excellent | 13 (52) | 9 (50) | NS |

Table 4. — *Undesirable effects during treatment with Getrinone and Buserelin.*

| Undesirable effect | Group G n (%) | Group B n (%) | p |
|---|---|---|---|
| Metrorragia - Spotting . . | 19 (76) | 6 (33) | < 0.05 |
| Amenorrhea . . . . . | 15 (60) | 18 (100) | < 0.01 |
| Androgenic effects . . . | 21 (84) | 0 (0) | < 0.001 |
| Vascular symptoms . . . | 14 (56) | 0 (0) | < 0.001 |
| Flushes . . . . . | 2 (8) | 12 (67) | < 0.05 |
| Vaginal dryness . . . . | 0 (0) | 9 (50) | < 0.01 |
| Others . . . . . | 3 (12) | 2 (11) | NS |

Global clinical tolerance (Table 5) was good in 50% of patients in Group G and in 0% in Group B ($p < 0.001$).

2c) *Current evaluation 5 years after initial treatment* (Table 6)

In Group G, 16% (4/25) of patients needed a hysterectomy with bilateral oophorectomy due to clinical recurrence, pathologic ultrasound findings or other associated pathologies such as a myoma. All these women were more than 35 years old and had given birth; six infertile patients were unable to conceive.

In Group B, 11% (2/18) needed a hysterectomy (with adenomyosis as the result of the ensuing pathology), one patient required nephrectomy due to recurrent vesicle endometriosis, and three infertile patients were unable to conceive.

Global evaluation after 5-years follow-up (Table 6) showed "success" only for 36% of patients in Group G and 33% in Group B (no significant differences), with "failure" in 40% and 33%, respectively (also without significant differences).

## DISCUSSION

Our results confirm that Gestrinone and Buserelin are efficacious in the remission of endometriosis and are in agreement with previous reports ([11, 12, 13, 14, 15]).

Percentages of response to pain fluctuate depending on different Authors, but all confirm a partial or total eradication of this symptom in the majority of cases. Kiesel, *et al.* ([16]) have reporterd a clinical efficay in 80-90% of patients. We found

Table 5. — *Global clinical tolerance during treatment with Gestrinone and Buserelin.*

| Scale of tolerance | Group G n (%) | Group B n (%) | p |
|---|---|---|---|
| *Good* (without undesirable effects) . . . . . | 0 (0) | 9/18 (50) | < 0.001 |
| *Regular-good* (moderately undesirable effects of one type) | 17/25 (68) | 5/18 (28) | < 0.05 |
| *Regular-bad* (considerably undesirable effects, more than one type, but not meriting cessation of treatment) . . . . . | 8/25 (32) | 4/18 (22) | NS |
| *Bad* (undesirable effects meriting cessation of treatment) . . . . . | 0/25 (0) | 0/18 (0) | NS |

Table 6. — *Endometriosis. Global evaluation after 5 years of initial treatment for both groups.*

| Results | Group B n (%) | Group G n (%) | p |
|---|---|---|---|
| *Success* (no symptoms and/or pregnancy in infertile patients) | 6/18 (33) | 9/25 (36) | NS |
| *Failure* (new surgery intervention and/or pregnancy in infertile patients) | 6/18 (33) | 10/25 (40) | NS |
| *Clinical recurrence* | 6/18 (33) | 6/15 (24) | NS |

a response to pain in 95% of patients with Gestrinone and 100% with Buserelin. This clinical response can be justified by two mechanisms: *a*) provoked by endometrial atrophy, *b*) ovarian rest with no influence on the endometrium, without forgetting placebo effect ([17]).

Thirty-three percent of gestations in infertile patients in Group G and 25% in Group B are not sufficient data to take into account due to the few cases in our study, but this rate is well within the range of previously reported studies and applicable to steroids (Danazol or Gestrinone) ([18, 19, 20]) as well as to analogs administered by intranasal spray ([9, 14]). All have proved to be valid drugs in the management of infertile patients with endometriosis ([21]).

Gestrinone possesses undesirable effects that occasionally may limit its use. Metrorragia which in the majority of patients is minimal and is reflected by spotting can be justified because of the antiestrogenic and antiprogesterone effects of the drug. Nevertheless, it can occasionally be caused by improper dosification. Our rate of spotting (76%) is higher thatan that reported by other Authors (14.5%) ([22]), and this may be due to different genetic susceptibility and a difference in dosage for each patient. This secondary is inferior in patients using Buserelin as shown in our results and in agreement with other Authors ([22]).

One of the most undesirable effects with Gestrinone is their androgenic action, above all acne, but this effect is reversible after four months of treatment. Authors such Thomas *et al.* ([13]), and Coutinho ([23]), reported rates of 50-60% of acne in their patients after six months of treatment with Gestrinone. Our results were somewhat higher (68%). We were very precise in compiling this data, and we have established a scale of evidence from positive to minimum. In Group B the tolerance was better and these patients showed principally flushes. No patient required a reduction in dosage due to the intensity of this symptom contrary to what has been suggested in other studies ([24]).

In 56% of our patients in Group G, vascular effects manifested by edema of the lower limbs and sensation of heaviness were present. These effects were of no significance since they did not contribute to trombophlebitis and had a tendency of disappearing after three months of post-treatment. Our proportions are higher than those published by other Authors, such as Coutinho ([3]), who indicates 35%, suggesting a conclusion that different genetic susceptibility proper to distinct populations exists.

Undesirable effects, even though reversible, are of major concern, since they constitute the greatest number of complaints on the part of our patients, especially the group treated with Gestrinone.

Nevertheless, they did not cause the cessation of treatment.

Once the treatment was completed the resurgence of symptoms was considerable in a number of patients. Waller *et al.* ([25]) report the recurrence rate to fall between 37-74% in the 5th year ([18]). Our results show clinical recurrence rates as follows: 24% in Group G and 33% in Group B. Forty percent of Group G and 33% of Group B patients required surgery and/or did not get pregnant, being previously infertile. The above considerations make one realise that there still remains a lot to be learnt about this pathology. Even though efficient anti-endometriosis drugs are being used, endometriosis continues to be a problem after treatment.

Finally, we conclude that: 1) Gestrinone and intranasal Buserelin are valid treatments in the remission of endometriosis, with "success", "failure" and "clinical recurrence" rates similar after a follow-up of 5 years of initial treatment; 2) the most significant androgenic effect of Gestrinone is the presence of acne. Vascular effects have also been seen as very undesirable according to the patients. On the contrary, treatment with analogs are generally better tolerated.

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Address reprint requests to:
Dr. ANÍBAL NIETO DIAZ
c/ Toledo n. 2, 1° A.
28804 Alcalá de Henares, Madrid (Spain)