

Effects of an extended-interval dosing regimen of triptorelin depot on the hormonal profile of patients with endometriosis: prospective observational study

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Objective. To evaluate the suppression of pituitary gonadotrophins and ovarian steroid hormone with the administration of triptorelin depot at 6-weekly intervals.

Design. Prospective observational study.

Setting. Obstetrics and gynaecology department of a public hospital, Hong Kong.

Patients. Consecutive patients with endometriosis, as diagnosed by laparoscopy or laparotomy from June 1998 through February 1999.

Intervention. Administration of four doses of triptorelin depot 3.75 mg either subcutaneously or intramuscularly every 6 weeks (21 patients), or conventional 4-weekly six-dose regimen (five patients).

Main outcome measures. Serum levels of 17- β -oestradiol, luteinizing hormone, and follicle-stimulating hormone; and pelvic pain symptoms.

Results. For the patients receiving the extended-interval dosing regimen of triptorelin, the levels of oestradiol and luteinizing hormone, and the pain score were significantly reduced throughout the treatment period and up to 10 weeks after the injection of the last dose. The level of follicle-stimulating hormone increased slowly but was still significantly lower than pretreatment levels. The hormonal profile was similar to that of patients receiving the conventional regimen.

Conclusion. The use of the extended-interval dosing regimen of triptorelin depot results in a consistent hypo-oestrogenised state, which is similar to that achieved by the conventional regimen and which would be considered satisfactory for the medical treatment of pelvic endometriosis. The new regimen thus reduces the cost of treatment without compromising the effect on hormonal suppression.

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Introduction

Gonadotrophin-releasing hormone (GnRH) analogues are commonly used in the treatment of pelvic endometriosis as the primary medical therapy or as adjuvant therapy to surgical treatment. These drugs can be given as a nasal spray, depot injection (either intramuscularly or subcutaneously), or a subcutaneous implant. Administration by depot every 4 weeks is a well-established regimen worldwide. Recent evidence,

however, suggests that triptorelin depot can be given in an extended-interval dosing regimen. Broekmans et al¹ have shown that after a single dose of triptorelin depot, the suppression of secretion of luteinizing hormone (LH) is maintained for 8 weeks afterwards. In addition, the level of follicle-stimulating hormone (FSH) normalises within 3 to 4 weeks and the 17- β -oestradiol (E₂) level starts to normalise in weeks 7 to 8.¹ By using a micro-encapsulated depot preparation of triptorelin, Filicori et al² have shown that the triptorelin level is still measurable, and that the secretion of gonadotrophins and gonadal steroids remains suppressed 8 weeks after the last injection. There have so far been no studies of the use of GnRH analogues in depot form with dosing intervals longer than 4 weeks. A small-scale observational study was thus performed to test if a 6-weekly triptorelin depot

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regimen can reduce hormone levels to those needed for the treatment of endometriosis.

Methods

Twenty-six consecutive patients with an operative diagnosis of pelvic endometriosis, for whom post-operative adjuvant therapy with a GnRH had been planned were recruited from June 1998 through February 1999. The first five patients were given triptorelin 3.75 mg (Decapeptyl CR; Ferring GmbH, Kiel, Germany) in the conventional depot regimen of six doses, each given 4 weeks apart. Their responses provided an indication of the extent of the reduction in hormone levels that was achievable by using the conventional regimen. The next 21 patients were given four doses of triptorelin depot 3.75 mg, either intramuscularly or subcutaneously, every 6 weeks. For both groups of patients, blood was taken to determine the serum hormonal profile of LH, FSH, and E₂ before each injection and at the end of the treatment period (week 24 of the study). Serum hormonal levels were also measured every 4 weeks until the resumption of menstruation. The first blood-taking and administration of triptorelin were performed in the early follicular phase (between days 2 and 6 of the menstrual cycle). The goal of the treatment was to reduce the E₂ level to postmenopausal levels (150 pmol/L).

Side effects and the pain symptoms experienced during the study period were also recorded. The pain symptoms were classified into the following groups: dysmenorrhoea, dyspareunia, and non-menstrual pelvic pain, and they were graded with a score ranging from 0 (absence of pain) to 10 (severe pain that required sick-leave and rest, or pain leading to avoidance of coitus). The total pain score was obtained by

summing the three scores (maximum score = 30). The Wilcoxon signed rank sum test was used to assess the extent of reduction in hormone levels after triptorelin administration. The Statistical Package for Social Science (Windows version 7.0; SPSS Inc., Chicago, United States) was used to analyse the data.

Results

Of the 21 patients who received 6-weekly injections of triptorelin depot, the mean (standard deviation [SD]) body mass index (in kg/m²) and age were 20.7 (2.2) and 29.8 (6.8) years, respectively. The majority of the patients had moderate-to-severe endometriosis (24% with moderate disease and 62% with severe disease). Only two patients had mild endometriosis. Most (19; 90%) patients had dysmenorrhoea, six (29%) complained of non-menstrual pelvic pain, and three (14%) had dyspareunia.

Hormonal profile

The serum LH level was reduced during the course of treatment with the extended-interval dosing regimen of triptorelin. The level decreased from a mean (SD) pretreatment LH level of 3.40 (0.31) IU/L to 0.33 IU/L in the 6th week of treatment. Thereafter, the LH level remained low, until week 28 (10 weeks after the injection of the last dose), when it increased to a mean (SD) of 0.53 (0.22) IU/L (Fig 1). The reduction in the LH level was statistically significant throughout the 24-week treatment period and also in week 28 ($P < 0.001$).

The serum FSH level decreased from a pre-treatment mean (SD) of 7.61 (0.61) IU/L to 2.35 (0.31) IU/L in week 6, after which it increased gradually until the end of the study (Fig 2). Nevertheless,

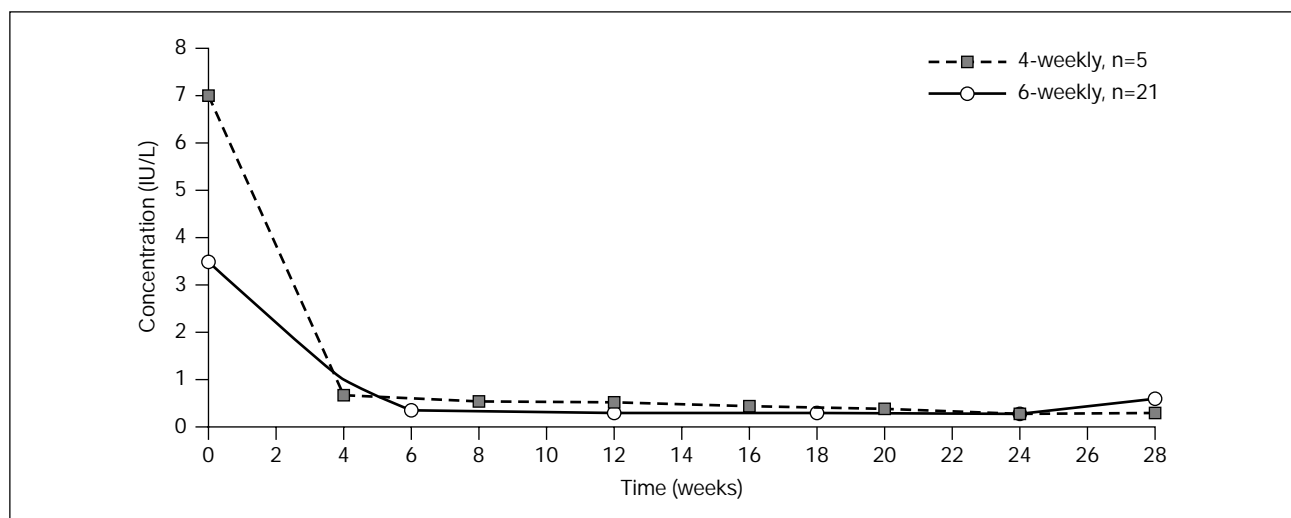


Fig 1. Mean levels of luteinizing hormone during and after treatment with 4- and 6-weekly regimens of triptorelin

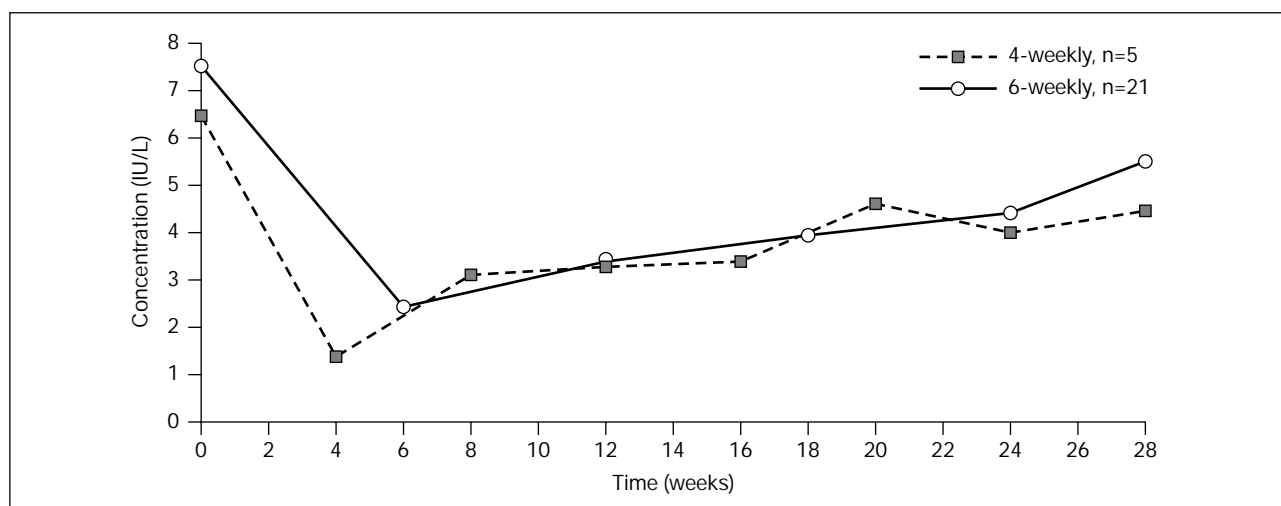


Fig 2. Mean levels of follicle-stimulating hormone during and after treatment with 4- and 6-weekly regimens of triptorelin

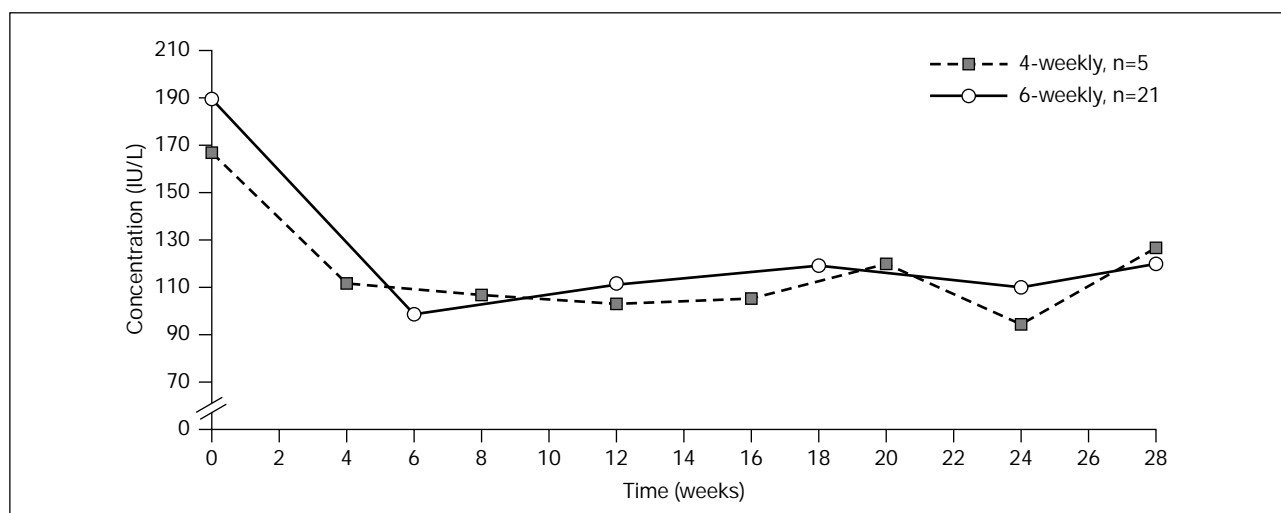


Fig 3. Mean levels of 17-β-oestradiol during and after treatment with 4- and 6-weekly regimens of triptorelin

the reduction that was achieved throughout the study period when compared with the pretreatment level was statistically significant ($P < 0.001$).

The serum E_2 level decreased from a pretreatment mean (SD) of 187.87 (14.78) pmol/L to 102.41 (6.16) pmol/L in week 6. The concentration thereafter fluctuated but remained below 120 pmol/L throughout the study period (Fig 3). The reduction was statistically significant throughout the study ($P < 0.001$), and the post-treatment E_2 levels were well below the postmenopausal level (150 pmol/L) up to 10 weeks after the injection of the last dose of triptorelin. The mean (standard error) reductions in hormone levels during the study are shown in the Table.

The hormonal profiles of the five patients who received the conventional regimen showed similar patterns of hormonal suppression to the 21 patients who received the extended-interval dosing regimen (Figs 1-3).

Clinical effects

The mean interval from the end of the treatment period (week 24) to the resumption of menstruation was 79 days (range, 56-120 days). For one patient, the interval was exceptionally long (120 days). In the group that received the conventional regimen, the mean interval from the 24th week of study to the resumption of menstruation was 91 days.

Side effects that were reported during the treatment were mild and included hot flushes, sweating, and headache. They were well tolerated by the patients, however, and no patient withdrew from the study because of the side effects. None of the patients experienced a local reaction at the injection site, whether the injection was given by the intramuscular or subcutaneous route. The mean total pelvic pain score before treatment was 9.9, and it decreased to 0 during the treatment period. When menstruation resumed after treatment, the mean pain score was 2.1.

Table. Hormonal suppression achieved during and after treatment with 6-weekly regimen of triptorelin

Week of study	Mean (SE) reduction in hormone level* (IU/L)		
	Luteinizing hormone	Follicle-stimulating hormone	17- β -oestradiol
6 [†]	3.07 (0.31)	5.27 (0.60)	84.46 (16.07)
12 [†]	3.13 (0.31)	4.23 (0.68)	75.90 (16.77)
18 [†]	3.19 (0.31)	3.64 (0.72)	69.73 (17.14)
24	3.20 (0.31)	3.23 (0.71)	77.21 (21.61)
28	2.87 (0.34)	2.12 (0.48)	68.78 (22.02)

* Compared with pretreatment level (n=21)

[†] Pre-injection level

Discussion

The rationale behind the treatment of pelvic endometriosis with GnRH analogues is to suppress gonadal function to achieve a prolonged hypo-oestrogenised state, which allows the regression or suppression of the endometriotic lesions. Of the different preparations of GnRH analogues available, monthly depot preparations have been shown to induce a more profound and stable hypo-oestrogenised state, and be better tolerated than intranasal sprays or daily injections.^{3,4} There is preliminary evidence that triptorelin depot injection can suppress the pituitary-gonadal axis for up to 8 weeks from the injection of the last dose.^{1,2} This duration is much longer than the usual interval between each injection in the conventional regimen. Patients' acceptability of and compliance to treatment should thus be increased by using the extended-interval dosing regimen, provided that comparable suppression of hormonal secretion is achieved.

To the best of our knowledge, this is the first study to use a 6-weekly dosing regimen of a GnRH analogue depot in the treatment of endometriosis. In this small-scale observational study, four doses of triptorelin depot were given, one every 6 weeks. An additional observational period of 6 weeks after the last injection meant that the total treatment period (24 weeks) was the same as that of the conventional regimen (six doses, 4 weeks apart, with a final observation period of 4 weeks). Any treatment period of longer than 6 months may induce irreversible osteoporosis.

The hormonal profile of LH, FSH, and E₂ showed significantly reduced concentrations during the treatment period and up to the 28th week of study. The E₂ levels remained well below 150 pmol/L, which indicated a consistent and satisfactory hypo-oestrogenised state. The resumption of menstruation took a mean of 79 days after the extended-interval dosing regimen, and it took 91 days after the conventional regimen. The mean duration from the injection of the last dose to the resumption of menstruation was quite similar for both regimens, however, being 121 days and 119

days for the new and conventional regimens, respectively. This interval is particularly long, when it is compared with the figures from other studies. In a study from Italy, the interval from the injection of the last dose to the return of menstruation ranged from 67 to 82 days.² A study from Thailand reported a mean interval of 83.8 days after the last dose.⁵ The reason for the longer delay in the return of menstruation in this study is unknown and could be multifactorial. A 35-year-old patient had the longest return of menses of 120 days after the treatment period. She had high pretreatment gonadotrophin levels, and reduced ovarian reserve possibly contributed to the delay in return of menstruation.

In conclusion, the use of an extended-interval (6-weekly) dosing regimen can reduce hormone levels to those needed for the treatment of endometriosis for up to 28 weeks (10 weeks after the last injection). Side effects during treatment are mild and tolerable, and pain associated with endometriosis decreases markedly during and after treatment. By using this new regimen, the cost of treatment can be reduced by one third and patients' acceptance is increased without compromising hormonal suppression. Further research into the clinical efficacy and recurrence rate of endometriosis after using this new regimen is urgently needed. The effect of this new regimen on fertility and bone loss when compared with the conventional regimen should also be addressed.

Acknowledgement

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