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Original Article

Dose-finding study of Leuplin depot for prevention of premature luteinizing hormone surge during controlled ovarian stimulation: a pilot study in intrauterine insemination treatment

Heng-Ju Chen [a, b], Yu-Hung Lin [a, b], Mei-Zen Huang [c], Kok-Min Seow [a], Lee-Wen Huang [a, b], Bih-Chwen Hsieh [a, b], Chii-Ruey Tzeng [d], Jiann-Loung Hwang [a, b, d, *]

[a] Department of Obstetrics and Gynecology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan
[b] College of Medicine, Fu Jen Catholic University, Sinchuang City, Taipei County, Taiwan
[c] Graduate Institute of Nursing, National Taipei University of Nursing and Health Sciences, Taipei, Taiwan
[d] Department of Obstetrics and Gynecology, Taipei Medical University, Taipei, Taiwan

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ABSTRACT

Objective: The standard dose of depot gonadotropin releasing hormone agonist (GnRHa) may be too much to prevent premature luteinizing hormone (LH) surge in controlled ovarian stimulation (COS). The purpose of this study was to find out the minimal effective dose of Leuplin depot to prevent premature LH surge in patients undergoing intrauterine insemination (IUI).

Materials and Methods: From January 2006 to December 2007, unexplained infertile patients who were going to undergo IUI were recruited into the study. They were assigned sequentially to one of the following treatment groups. The first 50 patients received the 1/3-dose of Leuplin depot in the midluteal phase of the cycle preceding COS. If no premature LH surge occurred in the 50 patients, the study was continued with 1/4-dose of Leuplin depot in the subsequent 50 patients. Similarly, if no premature LH surge occurred with 1/4 dose, the study was continued with 1/5-dose of Leuplin depot in the following 50 patients. Ovarian stimulation was started with human menopausal gonadotropin (hMG) at 112.5 IU/d after downregulation, then IUI was performed 36 hours after human chorionic gonadotropin (hCG) injection.

Results: Premature LH surge was effectively prevented with 1/3-dose and 1/4-dose of Leuplin depot. Premature LH surge occurred in three of the 50 patients (6%) in the 1/5-dose group. The patients in the 1/4-dose group received a significantly lower amount of hMG and fewer days of COS, compared with the 1/3-dose group.

Conclusion: The 1/4 dose of Leuplin depot is the minimal effective dose to prevent premature LH surge. Further trial is worthwhile to compare the reducing dose Leuplin depot and daily low-dose leuprolide in *in vitro* fertilization (IVF) programs.

Introduction

The benefits of using gonadotropin releasing hormone agonists (GnRHa) in women who received controlled ovarian stimulation (COS) in assisted reproductive treatment are well documented, such as prevention of premature luteinizing hormone (LH) surge and a lower cancellation rate [1]. Among the various types of GnRHa protocols, the long protocol is the most popularly used nowadays. There are two modes of GnRHa administration in the long protocol; the daily low-dose or the single-dose depot injection. Depot GnRHa formulations have been welcomed by both patients and physicians, because of the convenience of single administration. The major concern of depot GnRHa is excessive suppression of pituitary function, which in turn may influence pregnancy outcomes, duration of COS, and amount of gonadotropin

* Corresponding author. Department of Obstetrics and Gynecology, Shin Kong Wu Ho-Su Memorial Hospital, Number 95 Wen Chang Road, Shih Lin District, Taipei 111, Taiwan.
E-mail address: m004983@gmail.com (J.-L. Hwang).

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used [2]. Some authors have demonstrated that reducing the dose of depot GnRHa is still enough to prevent premature LH surge in *in vitro* fertilization (IVF) treatment. Half-dose depot leuprolide acetate [2–4] or 1/2-dose depot triptorelin [5,6] has been reported to result in similar clinical outcomes, including prevention of premature LH surge, compared with a daily low-dose GnRHa long protocol.

In a recent Cochrane review, no significant differences were detected between the single-dose depot protocol and daily low-dose GnRHa long protocol in the clinical outcomes of IVF, including live birth/ongoing pregnancy rates, clinical pregnancy rate, as well as number of oocytes retrieved, miscarriage rate, multiple pregnancy rate, and rate of severe ovarian hyperstimulation syndrome [7]. This Cochrane review included randomized, controlled trials comparing depot (using either full-dose or 1/2-dose) and a daily low-dose GnRHa long protocol in IVF treatment. However, excessive pituitary suppression by depot GnRHa (using either full-dose or 1/2-dose) resulted in more gonadotropin consumption and a longer duration of ovarian stimulation [7], which may increase the overall cost of IVF treatment.

The 1/3-dose depot triptorelin has been shown to effectively prevent premature LH surge in IVF cycles [8]. However, the duration of COS and amount of gonadotropin consumption showed a trend of lower, but nonsignificant decrease [8]. Whether or not further decreasing the dose of depot GnRHa is still effective for the prevention of premature LH surge is not known. Furthermore, the minimal dose of depot GnRHa to prevent premature LH surge has not yet been determined. Utilizing the minimal dose of depot GnRHa can potentially reduce the amount and duration of gonadotropin stimulation.

The purpose of this study was to find out the minimal effective dose of Leuplin depot (leuprolide acetate 3.75 mg; Takeda, Osaka, Japan) required to prevent premature LH surge in patients undergoing COS. For fear of premature LH surge that compromised the IVF outcomes, we performed a pilot study in patients undergoing intrauterine insemination (IUI) before application to the IVF program. The logic behind this was that insemination time could be advanced if premature LH surge occurred in an IUI cycle. If a particular dose of depot GnRHa failed to prevent premature LH surge in IUI, it would not be worth testing it further in IVF cycles.

Materials and methods

This prospective observational study was approved by the Institutional Review Board of Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan. All patients entered this study only after informed written consent was obtained. Patients with unexplained infertility who were going to receive COS/IUI were recruited for the study. The inclusion criteria were female aged < 38 years old, with regular menstrual cycles ranging from 21 days to 35 days, body mass index ranging from 18 kg/m^2 to 29 kg/m^2, normal ovarian function as detected by basal serum follicle-stimulating hormone and estradiol (E2), normal hysterosalpingography, normal semen parameter, and no history of ovarian or tubal surgery. Assuming that 20% of patients will have premature LH surge with gonadotropin only and 2% of patients will have premature LH surge with gonadotropin and GnRHa [9], 50 cases were needed in the study group to have a power of 0.8 ($\alpha = 0.05$, $\beta = 0.2$). Only patients who complied with all selection criteria were assigned sequentially to one of the treatment groups, starting from the 1/3-dose of Leuplin depot. If no premature LH surge occurred with the 1/3 dose in the first 50 patients, the study was continued with decreasing doses for the subsequent 50 patients (1/4 dose in the second group and 1/5 dose in the third group).

Pituitary desensitization was achieved with a specific dose of Leuplin depot in a single subcutaneous injection in the midluteal phase (Day 21) of the menstrual cycle preceding treatment. Serum E_2, LH, and progesterone levels were measured 16 days after Leuplin depot injection. The criteria of pituitary desensitization was defined as serum E2 level < 50 pg/mL and LH level < 5 mIU/mL. If pituitary desensitization was not achieved, blood sampling was repeated every 3 days until pituitary desensitization. Ovarian stimulation with human menopausal gonadotropin (hMG, Merional; IBSA, Lamone, Switzerland) 112.5 IU/d was prescribed for 6 days and then the dose was adjusted according to ovarian response. Human chorionic gonadotropin (hCG, Ovidrel; Merk-Serono, Modugno, Italy) 250 μg was given when two follicles reached 18 mm in diameter. IUI was performed 36 hours later. Serum concentrations of LH, E2, and progesterone were measured daily from Day 4 of hMG stimulation until the day of hCG administration. If premature LH surge was detected, IUI was arranged on two occasions on the next 2 consequent days after hCG administration. Premature LH surge is defined as LH level > 10 mIU/mL with progesterone elevation > 1 ng/mL before leading follicles reached 18 mm [10]. The primary outcome measure was the percentage of premature LH surge. The secondary outcome measures were the ampoules of hMG used and the pregnancy rates.

Results

From January 2006 to December 2007, 150 patients were included in this study. No premature LH surge occurred in the first 50 patients who received the 1/3-dose of Leuplin depot. The next 50 patients were assigned to the 1/4-dose group. This lower dose also was able to prevent premature LH surge and to maintain constantly low serum LH concentrations during the follicular phase (Figure 1). In accordance with the study protocol, the subsequent 50 patients received the 1/5-dose of Leuplin depot. The serum LH level was still maintained at a low level during the follicular phase (Figure 1). However, premature LH surge occurred in three patients (6%, Figure 2). Because of the high incidence of premature LH surge, the study was stopped here without further lowering the Leuplin dose. The outcomes of the 1/3-dose, 1/4-dose, and 1/5-dose groups are shown in Table 1. Compared with the 1/3-dose group, patients in the 1/4-dose group and 1/5-dose group required a significantly lower amount of hMG and fewer days of hMG stimulation. There were no significant differences in hMG amount required and days of hMG stimulation between the 1/4-dose group and the 1/5-dose group. Mean serum E2, LH, and progesterone levels on the day of hCG injection were similar between the three groups. The pregnancy rates and miscarriage rates were also comparable.

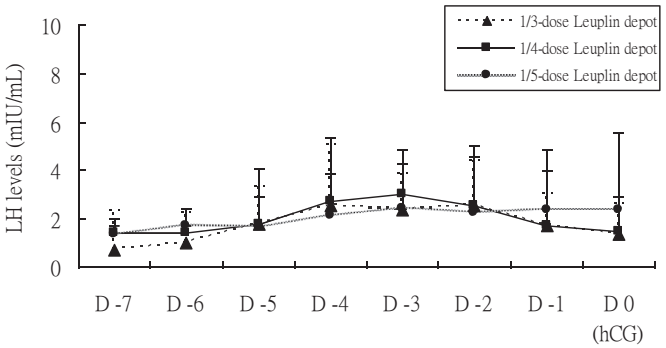

Figure 1. Serum luteinizing hormone (LH) values (mean ± standard deviation) in 1/3-, 1/4-, and 1/5-dose Leuplin depot groups relative to the day of human chorionic gonadotropin (hCG) injection (D0). D = day.