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Research Letter

Using a half dose of leuplin depot in a long-term protocol for *in vitro* fertilization

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A retrospective review of medical charts was used to compare the use of a half dose of leuplin depot (3.75 mg/vial; Takeda, Osaka, Japan) in a long agonist protocol for *in vitro* fertilization (IVF) (long protocol) with the conventional pill-leupron-HMG/FSH short agonist protocol (short protocol).

From January 2008 through December 2010, our unit completed 108 IVF case cycles (Table 1). The major variation between cases is the protocol for ovulation stimulation. The same personnel used the fixed protocol to perform oocyte retrieval, fertilization, *in vitro* culture, and embryo transfer. In the long, half-dose depot protocol (long protocol), a half dose of leuplin depot was given during menstruation. Then, we started 150–225 IU HMG (Menopur, Ferring GmbH, Kiel, Germany)/FSH (Puregon, Merck Serono, Modugno, Italy) on a Thursday 3–4 weeks later. Ovulation was induced with a 10,000 IU ßHCG (5000 IU Pregnnyl; Organon, Oss, Holland) i.m. injection when the two leading follicles were 16 mm above. Oocyte retrieval was performed 34–39 hours later. We performed fixed-length (6 cm) embryo transfer 3 days after oocyte retrieval. For luteal support after oocyte retrieval, we administered 4 mg/day estrade (2 mg estradiol valerate; Synmosa, Taipei, Taiwan) and crinone 8% vaginal gel (Merck Senoro). Additionally, 1500 IU HCG was administered at D3, D6, and D9. A urine pregnancy test was administered 14 days later. If the pregnancy test was positive, a vaginosonogram was performed 2 weeks later. We defined clinical pregnancy as the observation of a gestational sac inside the uterine cavity on the vaginosonogram.

In our cases series, the cases that were administered the long protocol achieved a relatively higher pregnancy rate, although it was not statistically significant (39.28% for patients administered the long protocol vs. 28.75% for patients administered the short protocol; 31.48% total pregnancy rate; $p = 0.071$). The induction time was longer in patients administered the long depot protocol (11.14 ± 1.075 days for the long protocol vs. 9.55 ± 1.25 days for the short protocol; $p = 0.002$). More gonadotropin doses were required in the long depot protocol (1799 IU for the long depot protocol vs. 1231 IU days for the short protocol; $p = 0.008$). No significant differences were observed in terms of the ovarian hyperstimulation rate, fertilization rate, implantation rate, or abortion rate.

A previous comparative study reported that IVF using an agonist achieved better clinical pregnancy and delivery rates than IVF using an antagonist [1]. We stopped using an antagonist protocol due to poor results 2 years ago, even though the antagonist protocol required fewer injections. The IVF treatment protocol is a stressful procedure for the patient because of many factors, including the limited success rate, the use of multiple injections, and high cost [2].

Administering leuplin depot using the long protocol began in 1991 [3]. In the conventional long protocol that utilizes a short-acting agonist, the patient needed to receive daily injections or a nasal spray for 2 weeks before ovulation could be induced [4,5]. In the long leuplin depot protocol, we preferred depot injections because it simplified the treatment protocol and improved patient compliance [6,7]. Considering the success rate, we found that using the long protocol resulted in a relatively higher pregnancy rate (39.28% for the long depot protocol vs. 28.75% for the short protocol; 31.48% total pregnancy rate; $p = 0.071$), although this result is not statistically significant. No significant differences were found in terms of the fertilization rate, implantation rate, or abortion rate. Our findings seem compatible with the previously reported meta-analysis of the Cochrane database, which demonstrated the superiority of the long protocol over the short and ultrashort protocols for GnRH agonist use in IVF and GIFT [4,8]. However, due to the limitations of the review analysis and the poor study structure of the reviewed cases, we plan to pool more cases and conduct a stricter study protocol in order to consolidate our findings in the future.

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Table 1
Descriptive retrospective analysis of 108 IVF cases, including the half-dose leuplin depot cycle and the short protocol cycle.

	Leuplin depot	Short	Total	*p*
Cases	28	80	108	
Mean age (range) (y)	33.24 (26−41)	34.6 (23−43)	33.78 (23−43)	
Etiology				< 0.05
Tubal	16%	29%		
Other, female	44%	24%		
Male factor	16%	4%		
Multiple	20%	28%		
Unknown	4%	15%		
HMG/FSH	1799 (1000−2600)	1231 (750−3325)		0.008
Time required to induction (d)	11.14 ± 1.075	9.55 ± 1.25		0.002
E2 (IU/L)	1394.3	2071	1952	0.087
P4 (pg/ml)	0.876	1.24	1.22	0.463
No. of oocytes retrieved	6.44	5.51	5.76	0.37
Fertilization rate	71.20%	74%	73%	0.565
Ovarian hyperstimulation syndrome rate	3.5% (1/28)	5% (4/80)	4.6% (5/108)	0.828
No. of transferred embryos	3.03 (0−4)	2.58 (0−4)	2.78 (0−4)	0.137
Pregnancy rate	39.28%	28.75%	31.48%	0.071
Implantation rate	21.9%	15.4%	16.8%	0.254
Abortion rate	18.18%	17.39%	17.64%	0.912
Live birth rate	32.14%	23.8%	25.9%	> 0.05

Compared with the short protocol, long depot preparations are associated with a longer period of stimulation (11.14 days for the long protocol vs. 9.55 days for the short protocol; $p = 0.002$) and higher doses of gonadotropin (1799 IU for long protocol vs. 1231 IU for the short protocol), indicating that it would cost NT$ 7000−9000 (US$ 240−310) more to perform the long depot protocol with an agonist.

Regarding the possible adverse effects, we did not find a significant difference in terms of the hyperstimulation rate (3.5% for the long protocol vs. 5% for the short protocol) or the abortion rate (18.18% for the long protocol vs. 17.64% for the short protocol). We used a half dose of the agonist depot, and none of the patients needed additional treatments for hormone deprivation. It is possible that this is the fourth study to report the use of a half dose or low dose of an agonist depot for IVF [6,9,10]. The adequate dose of the agonist depot still requires further elucidation.

Safety is an unavoidable issue that must be considered. To date, no evidence has been found of increased risk of pregnancy wastage or teratogenicity in human pregnancies exposed to long-acting agonists [11]. Considering the benefits of easy handling and the high success rate, we conclude that using a half dose of the agonist depot in the long protocol is a viable procedure. However, the possible downsides of this procedure should be explained to the patient during consultation.

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