The efficacy of gonadotropin-releasing hormone agonist administration for in vitro fertilisation

CJ Haines, EPL Loong

Gonadotropin-releasing hormone agonists are commonly used to achieve pituitary and ovarian downregulation in preparation for in vitro fertilisation. The purpose of this study was to examine the efficacy of gonadotropin-releasing hormone agonists in achieving downregulation prior to the commencement of ovarian stimulation. After a three-week pretreatment with a gonadotropin-releasing hormone agonist, a satisfactory response as determined by ultrasound was achieved in 164 of 200 cycles (82%). Treatment was continued for up to five additional weeks in 35 of the remaining 36 cases. Ovarian suppression was achieved in nine of 11 cases after an additional week of treatment, in nine of 14 cases after two additional weeks, and in two of the remaining 10. The results of this study suggest that downregulation will be achieved in over 80% of cases after a three-week pretreatment with a gonadotropin-releasing hormone agonist, and a short prolongation of treatment may be worthwhile in those cases where downregulation is not achieved in the first instance.

HKMJ 1995;1:93-95

Key words: Fertilisation in vitro; Gn-RH; Downregulation

Introduction

The practice of inducing pituitary and ovarian suppression with a gonadotropin-releasing hormone agonist (Gn-RHa) prior to the commencement of gonadotropin stimulation for in vitro fertilisation (IVF) is well established. The use of these drugs prevents premature ovulation, and is accompanied by improved IVF success rates. The agonists may be administered intramuscularly,[1,2] by subcutaneous injection,[3,4] or by nasal insufflation.[5,6] The duration of pretreatment is usually from two to three weeks, commencing on day 21 of the preceding cycle. Whilst this long protocol is inconvenient for the patient, it has been suggested that it may be superior to other stimulation protocols by producing a more uniform cohort of follicles and avoiding the potentially harmful effects of high luteinising hormone (LH) levels in the early follicular phase of the treatment cycle.[7]

Department of Obstetrics and Gynaecology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong
CJ Haines, MB, BS, FRACOG
EPL Loong, MB, ChB, FRCOG
Correspondence to: Dr CJ Haines

Before commencing ovarian stimulation for IVF, it is necessary to determine whether the Gn-RHa has been effective in downregulating the pituitary-ovarian axis. This may be assessed using either biochemical or ultrasound criteria,[5,8] or occasionally, a combination of the two.[9] However, there have been few reports describing the efficacy of this Gn-RHa preparation for ovarian hyperstimulation. Pretreatment with a Gn-RHa is associated with the formation of follicular cysts in 5% to 10% of cases,[10,11] and there is contradictory evidence regarding the presence of these cysts and the outcome of treatment.[11,12] It is not clear whether the continued administration of the Gn-RHa will result in the spontaneous resolution of such cysts. The aim of this study was to examine the effect of a three-week period of administration of a Gn-RHa prior to the commencement of gonadotropin administration on a long protocol, and to determine the effect of prolongation of the Gn-RHa pretreatment in those cases where the initial response was unsatisfactory.

Subjects and methods

The study group comprised 168 women having 216 cycles of ovarian hyperstimulation in preparation for

IVF or associated procedures. All were ovulatory before treatment began, with cycle lengths varying from 27 to 34 days. A long downregulation protocol was used in all cases. Buserelin nasal spray (Suprefact, Hoechst AG, Frankfurt am Main, Germany) 300 μg three times daily, was administered from day 21 of the preceding cycle and continued for a period of three weeks. Ultrasound examination of the ovaries was performed in 200 of 216 cycles using an Aloka 630 unit with a 5 MHz transvaginal probe. In the remaining 16 cases, ultrasound was not available, so these cases were excluded from the study. Downregulation was considered to have been successful when no cystic structures larger than 10 mm in diameter could be found on either ovary. When performing the ultrasound examination, care was taken not to confuse these simple cysts with either endometriotic cysts, fimbrial cysts, or hydrosalpinges. This was done by ensuring that the cysts lacked echogenicity, were spherical rather than oblong in shape, and were within the substance of the ovary. Ultrasound of the ovaries was used in preference to the biochemical assessment of downregulation as it was thought to be just as accurate and there was no delay in obtaining a result.

Ovarian hyperstimulation was commenced using human menopausal gonadotropins (Humegon, NV Organon, Oss, Holland) 150 IU daily, until the largest follicle was at least 16 mm in diameter. Human chorionic gonadotropin (hCG, Pregnyl, NV Organon, Oss, Holland) 10 000 IU was administered and transvaginal ultrasound-guided oocyte retrieval was performed approximately 35 hours later. Following embryo transfer, luteal phase support was randomised to either hCG 1500 IU every third day for four doses or progesterone in oil (Progesterone BP, Weimer Pharma GmBH, Rastatt, Germany) 50 mg daily for two days and then 25 mg daily for eight days. This randomisation was part of a separate trial, and it was not thought that it would interfere with the results of this particular study.

For those whose initial ultrasound examination failed to demonstrate adequate downregulation, the Gn-RHa was continued for a minimum of one week up to a maximum of five weeks in an attempt to achieve ultrasound evidence of downregulation. These time intervals were selected as in some cases only one further week of Gn-RHa administration was necessary to achieve downregulation. For those not showing evidence of downregulation by five weeks, it was not considered cost-effective to continue. During this time, ultrasound was performed on a weekly basis. Due to the size of this study, pregnancy was not used as an outcome indicator, although pregnancy rates are presented. Statistical analysis was performed using the binomial test on SPSS for Windows Version 5.0, with $p < 0.05$ accepted as significant.

Results

Ovarian suppression according to ultrasound criteria was present in 164 of 200 cases (82%) after three weeks of Gn-RHa pretreatment. The size of the cysts ranged from 15 to 32 mm in diameter. Menstruation occurred in all subjects after three weeks of Gn-RHa administration, but there was no consistent relationship between the time of onset of menstruation and the subsequent resolution of the cysts. Of the 36 cycles where downregulation was not achieved, the Gn-RHa was continued in all but one case. The results of this treatment are summarised in Table 1.

After one additional week of treatment, ovarian suppression was demonstrated in nine of 11 cases, and in nine of 14 when the treatment continued for two weeks. This compared with none of three achieving downregulation after three weeks, two of six after four weeks, and none of one after five weeks. There was no correlation between the size of the cysts and the time taken for them to resolve, and there were no spontaneous LH surges during the Gn-RHa administration.

Table 1. The outcome of an extended duration of pretreatment with Gn-RHa to induce pituitary suppression

No. of additional weeks of Gn-RHa	No. of cases	No. achieving downregulation	No. of pregnancies
1	11	9	1
2	14	9	2
3	3	0	0
4	6	2	0
5	1	0	0

There was no significant difference between the number achieving downregulation after one and two weeks of additional treatment ($p = 0.332$), but after three weeks, downregulation was achieved in fewer cases ($p = 0.031$). One pregnancy resulted when downregulation had been achieved with one week of additional treatment and two pregnancies occurred after two weeks' further treatment (12% per cycle). Two pregnancies resulted in a live birth and the third ended in a spontaneous first trimester abortion. There were no pregnancies in those cycles where treatment was continued for three weeks or more.

There were 22 pregnancies in the 164 cycles where the initial three-week period of downregulation had been successful (13.4% per cycle, 17.7% per embryo transfer). Of these, there were three biochemical pregnancies and three first trimester spontaneous abortions. The remainder resulted in live births.

Discussion

Previous studies have suggested that after a two- to three-week pretreatment with a Gn-RHa, suppression will be incomplete in up to 25% of cases.[4,5,8,13] These figures agree closely with our own experience, where inadequate ovarian suppression according to ultrasound criteria was present in 18% of cases. Should ovarian suppression not be demonstrated after a three-week course of treatment, the commencement of ovarian hyperstimulation may lead to further enlargement of existing ovarian cysts.[5] At that time, consideration can be given to abandoning treatment, aspirating the ovarian cysts, or continuing with treatment in the presence of the cysts. Although it is likely that prolonged administration of the Gn-RHa will eventually result in the required ovarian suppression, the inconvenience to the patient and the cost-effectiveness of such prolonged treatment should be considered. However, the results of this study suggest that while a three-week course of treatment with a Gn-RHa will achieve downregulation in the majority of cases, it may be worthwhile persisting for a further two weeks before deciding to withdraw treatment or aspirate the cysts, as in a few cases, downregulation may still be achieved. This will reduce the number of cases in which aspiration is necessary, and may also decrease the number of cycle cancellations.

As for future treatment—although our experience is limited—we found that the development of cysts on the long protocol tended to be recurrent, and an alternative regimen which avoids Gn-RHa pretreatment may be more suitable in these cases.

References

1. Lipitz S, Ben-Rafael Z, Dor J, et al. Suppression with gonadotropin-releasing hormone analogues prior to stimulation with gonadotropins: comparison of three protocols. Gynecol Obstet Invest 1989;28:31-4.
2. Feldberg D, Goldman GA, Dicker D, Ashkenazi J, Yeshaya A, Goldman JA. The value of GnRH agonists in the treatment of failed cycles in an IVF-ET program: a comparative study. Eur J Obstet Gynecol Reprod Biol 1990;34:103-9.
3. Serafini P, Stone B, Kerin J, Batzofin J, Quinn P, Marrs RP. An alternate approach to controlled ovarian hyperstimulation in "poor responders": pretreatment with a gonadotropin-releasing hormone analogue. Fertil Steril 1988;49:90-5.
4. Meldrum DR, Wisot A, Hamilton F, Gutlay AL, Huynh D, Kempton W. Timing of initiation and dose schedule of leuprolide influence the time course of ovarian suppression. Fertil Steril 1988;50:400-2.
5. Bentick B, Shaw RW, Iffland CA, Burford G, Bernard A. A randomized comparative study of purified follicle stimulating hormone and human menopausal gonadotropin after pituitary desensitization with Buserelin for superovulation and in vitro fertilization. Fertil Steril 1988;50:79-84.
6. MacLachlan V, Besanko M, O'Shea F, et al. A controlled study of luteinizing hormone-releasing hormone agonist (Buserelin) for the induction of folliculogenesis before in vitro fertilization. N Engl J Med 1989;320:1233-7.
7. Palermo R, Amodeo G, Navot D, Rosenwaks Z, Cittadini E. Concomitant gonadotropin-releasing hormone agonist and menotropin treatment for the synchronized induction of multiple follicles. Fertil Steril 1988;49:290-5.
8. Rutherford AJ, Subak-Sharpe RJ, Dawson KJ, Margara RA, Franks S, Winston RM. Improvement of in vitro fertilization after treatment with buserelin, an agonist of luteinizing hormone releasing hormone. BMJ 1988;296:1765-8.
9. Frydman R, Belaisch-Allart J, Parneix I, Forman R, Hazout A, Testart J. Comparison between flare up and down regulation effects of luteinizing hormone-releasing hormone agonists in an in vitro fertilization program. Fertil Steril 1988;50:471-5.
10. Jenkins JM, Anthony FW, Wood P, et al. The development of functional ovarian cysts during pituitary downregulation. Hum Reprod 1993;8:1623-7.
11. Parinaud J, Cohen K, Oustry P, et al. Influence of ovarian cysts on the results of in vitro fertilization. Fertil Steril 1992;58:1174-7.
12. Jenkins JM, Davies DW, Anthony F, et al. The detrimental influence of functional ovarian cysts during in-vitro fertilization cycles. Hum Reprod 1992;7:776-80.
13. De Ziegler D, Cedars MI, Randle D, Lu JK, Judd HL, Meldrum DR. Suppression of the ovary using a gonadotropin releasing-hormone agonist prior to stimulation for oocyte retrieval. Fertil Steril 1987;48:807-10.