A protocol using a low dose of gonadotrophin-releasing hormone agonist might be the best protocol for patients with high follicle stimulating hormone concentrations on day 3

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We studied 98 in-vitro fertilization (IVF) patients with a high basal follicle stimulating hormone (FSH; >6.5 IU/l) concentration on day 3 who were treated with a low dose gonadotrophin-releasing hormone agonist (GnRHa) protocol and who had received in the previous 6 months a long protocol with GnRHa in a depot formula. The evaluation was made using the previous IVF cycle of the same patient as a control. The mean ± SD age of the patients was 34.1 ± 4.2 years. The use of a low dose agonist protocol ended with significantly less ampoules (37.5 versus 46.1), a shorter duration of stimulation (10.7 versus 12.3 days), a higher oestradiol concentration on day 8 (1068 versus 495 pg/ml), a higher number of mature oocytes (5.9 versus 4.4) and a higher number of good quality embryos (3.3 versus 2.3). The cancellation rate was lower (11 versus 24%). A GnRHa low dose protocol may be the protocol of choice for patients with high FSH concentrations on day 3. Larger randomized studies are needed to confirm these data.

Key words: GnRHa/low dose/poor responders

Introduction

Patients with high follicle stimulating hormone (FSH) concentrations on day 3 have a higher chance of having a 'poor response' to ovarian stimulation (Fenichel et al., 1989; Scott et al., 1989; Toner et al., 1991; Olivennes et al., 1993). Various treatments have been proposed in the literature for ovarian stimulation in poor responders. Among these treatments, it has been claimed that gonadotrophin-releasing hormone agonists (GnRHa) benefit poor responders (Bealisch-Allart et al., 1988; Serafini et al., 1988; Ben-Rafael et al., 1990, 1991; Hershlag et al., 1990). However, ovarian stimulation with GnRHa has been associated with the need for a higher dose of human menopausal gonadotrophin (HMG), which could be related to ovarian hyporesponsiveness (Ben-Rafael et al., 1991).

Protocols avoiding the use of GnRHa have produced disappointing results in poor responders (Bealisch-Allart et al., 1988; Karande et al., 1990) and are associated with the risk of premature luteinization. Recently, it has been proposed that using ovarian stimulation in conjunction with low doses of GnRHa would provide the advantages of GnRHa without compromising the ovarian response (Davis and Rosenwaks, 1993). These protocols have been recommended especially for patients with high FSH concentrations on day 3 (>6.5 IU/l) with the results of a so-called 'long protocol' using GnRHa in a depot formula.

Materials and methods

Population

From 1994, an agonist low dose ovarian stimulation protocol was routinely used at A. Béclère Hospital (Clamart, France) for patients with high basal FSH concentrations on day 3 (>6.5 IU/l; range 6.5-9.5). Of these patients, 98 had had in the preceding 6 months a previous in-vitro fertilization (IVF) attempt with a so-called long protocol. Patients with indications for the intracytoplasmic sperm injection procedure were excluded from the study because the fertilization rate cannot be analysed and the evaluation of oocyte maturity is made after hyaluronidase treatment on the day of oocyte retrieval.

Experimental design and protocols

The stimulation protocol in the previous cycle consisted of administering a long-acting preparation of 3.75 mg triptorelin (3.75 mg Decapeptyl; Ipsen-biotech, Paris, France) on one of the first 4 days of the menstrual cycle. After down-regulation, the patient underwent ovarian stimulation with four ampoules/day of HMG.

The patients were monitored daily for oestradiol concentration and using ultrasounds for follicular growth. Criteria for human chorionic gonadotrophin (HCG) administration were at least three follicles ≥18 mm in diameter with an adequate oestradiol concentration.

The low dose agonist cycle consisted of administering 0.5 mg s.c. of leuprolide acetate (LUCRIN, Abbott, Rungis, France), starting in the mid-luteal phase. Down-regulation was controlled on day 13 of GnRHa therapy in the absence of menstruation, or on day 3 of menses if menstruation occurred. Ovarian stimulation was started when down-regulation was confirmed. The dose of leuprolide acetate was halved to 0.25 mg/day on day 13 of treatment in the absence of menstruation or on day 1 of menses if menstruation occurred. This dose was administered until the day of triggering of ovulation (Figure 1). The monitoring of ovarian stimulation was identical to that in the long protocol.

In the two treatment protocols, the triggering of ovulation was obtained with 10 000 IU HCG (O rganon, St Denis, France), and the luteal phase was supported with 600 mg natural progesterone administered vaginally.

We studied the IVF indications, age, the duration of infertility, the number of HMG ampoules, the duration of ovarian stimulation, the oestradiol concentration on day 8 and on the day of HCG administration.
Without bleeding

With bleeding

Figure 1. Low dose gonadotrophin-releasing hormone agonist stimulation protocol. HMG = human menopausal gonadotrophin; HCG = human chorionic gonadotrophin.

Table I. Results of ovarian stimulation with the low dose gonadotrophin-releasing hormone agonist protocol (LDA) and the long protocol

<table>
<thead>
<tr>
<th></th>
<th>Long protocol</th>
<th>LDA protocol</th>
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<tbody>
<tr>
<td>No. of patients</td>
<td>98</td>
<td>98</td>
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<tr>
<td>No. of ampoules</td>
<td>46.1 ± 13.5</td>
<td>37.5 ± 11.3*</td>
</tr>
<tr>
<td>Stimulation duration (days)</td>
<td>12.3 ± 1.5</td>
<td>10.7 ± 1.3*</td>
</tr>
<tr>
<td>Oestradiol concentration on day 8 (pg/ml)</td>
<td>495 ± 312</td>
<td>1068 ± 562*</td>
</tr>
<tr>
<td>Oestradiol concentration on the day of HCG (pg/ml)</td>
<td>2118 ± 752</td>
<td>2276 ± 818</td>
</tr>
<tr>
<td>No. of follicles ≥16 mm in diameter</td>
<td>4.5 ± 2.3</td>
<td>5.1 ± 2.2</td>
</tr>
<tr>
<td>Total no. of oocytes</td>
<td>7.9 ± 3.8</td>
<td>8.3 ± 4.3</td>
</tr>
<tr>
<td>No. of mature oocytes</td>
<td>4.4 ± 3.0</td>
<td>5.9 ± 3.6*</td>
</tr>
<tr>
<td>No. of embryos (transferred + frozen)</td>
<td>2.3 ± 1.9</td>
<td>3.3 ± 2.5*</td>
</tr>
<tr>
<td>No. of embryos transferred</td>
<td>1.8 ± 1.4</td>
<td>2.3 ± 1.3*</td>
</tr>
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HCG = human chorionic gonadotrophin.
*Significant difference (P < 0.05).

The results of the ovarian stimulation protocols are presented in Table I. The use of a low dose agonist protocol ended with significantly fewer ampoules of HMG (37.5 versus 46.1), a shorter duration of stimulation (10.7 versus 12.3 days), higher oestradiol concentrations on day 8 (1068 versus 495 pg/ml), a higher number of mature oocytes (5.9 versus 4.4) and a higher number of good quality embryos (transferred + frozen) and embryos transferred (3.3 versus 2.3 and 2.3 versus 1.8 respectively), all at P < 0.05. No statistical difference was observed for the oestradiol concentrations on the day of HCG, the number of follicles ≥16 mm in diameter or the total number of oocytes collected. The cancellation rate was 24% in the long protocol and 11% in the low dose agonist protocol. The clinical pregnancy rate per transfer was 16.3% in the low dose agonist protocol.

Discussion

Patients with high FSH concentrations on day 3 tend to respond poorly to ovarian stimulation using a long protocol (Feldberg et al., 1994). In poor responders, the use of GnRHα can prevent a premature luteinizing hormone (LH) surge but can be accompanied by a lack of ovarian response, despite a high dose of HMG (Ben-Rafael et al., 1990). This may be related...
to pituitary suppression (Ben-Rafael et al., 1991) or to a direct ovarian effect of GnRHa.

Kledzik et al. (1978) have shown a direct ovarian effect of GnRHa with a reduction of LH and FSH receptors in the rat. The first report of GnRH receptors in human granulosa cells was made by Latouche et al. (1989). The effects of GnRHa on granulosa cells have been studied by various authors (Casper et al., 1982; Tureck et al., 1982; Parinaud et al., 1988; Olsson et al., 1990; Frederick et al., 1991; Seifer et al., 1992). However, the results of these different studies did not agree, and inhibitory or stimulatory effects of GnRHa have been reported in their own dose- and type-dependent pattern.

Different benefits of the use of GnRHa in poor responders (aside from its prevention of the LH surge) have been proposed, including the reinforcement of follicle recruitment by the initial flare-up (Sathanandan et al., 1989), the enhancement of follicle growth (Meldrum et al., 1989), higher pregnancy rates (Drosch et al., 1989) and higher numbers of retrieved oocytes and transferred embryos (Liu et al., 1992). However, while the use of GnRHa may be beneficial, the best dose and protocol for their use in poor responders remain to be established.

In this study, the use of a low dose of GnRHa gave a better response to ovarian stimulation in patients with high FSH concentrations on day 3 at risk for a poor response when compared with the use of a so-called long protocol with GnRHa in a depot formula. The low dose of GnRHa was sufficient to prevent LH surges. This is in accordance with the properties of GnRHa, the doses of which when required to maintain pituitary suppression decrease with the length of treatment (Sandow and Donnez, 1990).

The better ovarian response observed with the low dose agonist protocol was obtained with a shorter treatment duration and with fewer HMG ampoules. The patients had a higher number of mature oocytes, good quality embryos and embryos transferred. The oestradiol concentrations were twice as high on day 8, but were not different on the day of HCG administration. This can be explained by a slower response and the fact that in the 'long protocol' the HCG was administered later, as a result of waiting for a high oestradiol concentration. The relatively high oestradiol concentrations on the day of HCG administration in the long protocol are also due to the fact that 24% of the cancelled patients are not included. This is confirmed by the longer duration of stimulation in the long protocol (12.3 versus 10.7 days). The pregnancy rate obtained (16.3%) was in the range expected for patients with a poor prognosis. This pregnancy rate could not be compared with the long protocol because of the experimental design of this study. In their randomized study, Feldberg et al. (1994), using the same type of low dose agonist protocol but with triptorelin (short-acting form) instead of leuprolide acetate, found a pregnancy rate of 28.1% in the low dose agonist compared with 6.2% in the long protocol.

The design of this study allows direct comparisons of multiple stimulation parameters in individual patients. It must be emphasized that this study was not prospective and randomized. It is possible that the previous stimulation had an impact on the second treatment cycle or that the response would have improved even if the same protocol was used again. However, the delay between the two treatments (3.2 ± 1.5 months) and the repeated poor responses of poor responders (Ben-Rafael and Feldberg, 1993) make this hypothesis unlikely.

The use of a low dose agonist protocol might be the protocol of choice to improve the responsiveness to ovarian stimulation in patients with high FSH concentrations on day 3 who are known to be at risk for a poor response. However, large randomized studies are needed to confirm these data.

References
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A low dose GnRHa protocol


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