Ovarian Stimulation for in Vitro Fertilization Using Pure Follicle-Stimulating Hormone with and Without Gonadotropin-Releasing Hormone Agonist in High-Responder Patients

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There is a distinct pattern of response to gonadotropin stimulation in some patients marked by high peak estradiol (E₂) levels, multifollicular ovarian response, and elevated basal luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratios. We reviewed the stimulation profiles of five such high-responder patients who failed to conceive during in vitro fertilization with ovarian stimulation using pure FSH. All patients had baseline LH/FSH >1.5 and peak E₂ >800 pg/ml. One cycle was canceled prior to hCG administration because of marked ovarian response (E₂ >2500 pg/ml, multiple small follicles). In a subsequent cycle, all patients were pretreated with the gonadotropin releasing-hormone agonist (GnRHa) leuprolide acetate for 10-14 days prior to initiation of FSH for ovarian stimulation. Leuprolide was continued until the day of hCG administration. During cycles using GnRHa, there was a statistically significant decrease (P < 0.05) in serum FSH on day 3 (<5 vs 8.3 mIU/ml), serum E₂ on day 3 (14.6 vs 34.6 pg/ml), and peak serum E₂ (1197.6 vs 1923.0 pg/ml). Patients during cycles with GnRHa had a greater number of preovulatory (8.6 vs 3.0) and total (12.4 vs 6.0) oocytes retrieved (P < 0.05). The fertilization rate of preovulatory oocytes was also higher during cycles using GnRHa (83% vs 64%). Two pregnancies occurred in the cycles pretreated with GnRHa. These preliminary data indicate that in high-responder patients, a combination of GnRHa and pure FSH results in lower E₂ levels during the stimulation cycle and a greater number of total and mature oocytes retrieved and fertilized.

KEY WORDS: human in vitro fertilization; follicle-stimulating hormone; gonadotropin-releasing hormone agonist; ovarian stimulation.

INTRODUCTION

Various methods of ovarian stimulation are used in in vitro fertilization (IVF) in an effort to obtain multiple fertilized oocytes. Gonadotropin-releasing hormone (GnRH) (1), human menopausal gonadotropin (hMG) (2), pure follicle-stimulating hormone (FSH) (3), and clomiphene citrate (4) have been used alone or in multiple combinations by different programs.

Jones et al. (3), in 1985, first reported stimulation using only pure FSH. They concluded that follicular recruitment and estrogen synthesis could proceed without exogenous LH and that excessive LH exposure may lead to suboptimal stimulation in certain cases. Furthermore, it has been shown that pure FSH stimulation may benefit patients with multifollicular ovarian response, high peak estradiol (E₂) levels, and elevated baseline LH/FSH ratios (5).

Gonadotropin-releasing hormone agonists (GnRHs) have been demonstrated to induce reversible hypogonadotropic hypogonadism. Their usefulness in IVF is associated with a reduction in the variability of E₂ patterns in response to exogenous gonadotropin administration (6), prevention of pre-
mature LH surges, and possibly prevention of the recruitment of follicles before exogenous stimulation, allowing a larger cohort of synchronous follicles (7).

This study examines the effects of pure FSH with and without GnRHa on the IVF outcome of patients identified as high responders.

MATERIALS AND METHODS

The study population consisted of five patients who underwent ovarian stimulation for IVF with pure FSH. The mean age of the patients was 36.8 years, with a range of 34 to 39 years. The etiologies of infertility were tubal disease in four cases and anovulation in one case. All patients were classified as high-responders, having peak E_2 levels >800 pg/ml and baseline LH/FSH >1.5 on cycle day 3. The results of the pure FSH cycles were compared with subsequent cycles in which each patient received pure FSH and the GnRHa leuprolide acetate (Lupron, TAP Pharmaceuticals, Abbott Park, IL).

During leuprolide cycles, patients were treated with 1 mg subcutaneously daily for 10 to 14 days prior to initiation of FSH for ovarian stimulation. Leuprolide was continued until the day of human chorionic gonadotropin (hCG) administration. In all cycles, 2-4 ampoules of pure FSH (Metrodin, Serono Laboratories, Inc., Randolph, MA) was administered intramuscularly from cycle day 3 onward. Monitoring of the stimulated cycles was identical for all patients. Blood was drawn daily at 8 AM starting on cycle day 3 for determination of serum E_2, FSH, and LH by radioimmunoassay. Beginning on day 6, follicle development was monitored by transvaginal ultrasonography. hCG (10,000 IU) was administered im when sonography revealed at least two follicles measuring >15 mm in diameter, in association with previously described criteria for serum E_2 and clinical parameters (2).

Thirty-four to 36 hours after hCG administration, oocytes were retrieved by ultrasound-guided transvaginal aspiration. The maturational status of the oocytes was recorded, according to the criteria of Veeck et al. (8).

Sperm processing, fertilization procedures, and embryo transfers were performed, as previously described (9). Patients began progesterone (P) supplementation (25 mg im) on the day after aspiration. Beta-hCG levels were determined on luteal days 11 to 15. If the beta-hCG was negative, P injections were discontinued; if the test was positive, the patient was given Delalutin (E. R. Squibb and Sons, Inc., Princeton, NJ), 250 mg weekly, until the 14th week of pregnancy.

Differences in mean values between cycles with and cycles without GnRHa were compared by Student’s paired t test.

RESULTS

Table I shows the endocrine profile of the study patients during FSH stimulation with and without GnRHa. Results are expressed as the mean ± standard error of the mean (SE). Mean serum FSH on day 3 was significantly lower in leuprolide cycles (8.3 ± 0.4 to <5 ± 0 mIU/ml; P < 0.05). Serum LH decreased from 22.3 ± 4.7 to 12.9 ± 1.1 mIU/ml, although this did not reach statistical significance. Baseline E_2 decreased significantly, from 34.6 ± 6.6 to 14.6 ± 1.7 pg/ml (P < 0.05), after leuprolide therapy. Mean E_2 levels on the day on hCG administration (906.8 ± 173.5 vs 1733.8 ± 291.9 pg/ml) and peak E_2 levels (1197.6 ± 196.6 vs 1923.0 ± 264.1 pg/ml) were also significantly decreased (P < 0.05) in the leuprolide cycles.

A significantly greater number of ampoules of FSH was required for ovarian stimulation in leuprolide cycles compared to cycles with FSH alone (20.2 ± 1.4 vs 12.0 ± 0.6; P < 0.05). The mean day of hCG administration was 10.6 ± 0.4 in leuprolide cycles compared to 10.0 ± 0.6 in pretreatment cycles (not significant).

Table II lists the classification and outcome of oocytes retrieved in cycles with and without GnRHa therapy. The patient with anovulatory infertility during the cycle without leuprolide was

Table I. Characteristics of Cycles With and Without GnRH Agonist Therapy

<table>
<thead>
<tr>
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<th>FSH alone (N = 5)</th>
<th>FSH and GnRH agonist (N = 5)</th>
</tr>
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<tbody>
<tr>
<td>LH on day 3 (mIU/ml)</td>
<td>22.3 ± 4.7</td>
<td>12.9 ± 1.1</td>
</tr>
<tr>
<td>FSH on day 3 (mIU/ml)</td>
<td>8.3 ± 0.4</td>
<td>&lt;5 ± 0*</td>
</tr>
<tr>
<td>E_2 on day 3 (pg/ml)</td>
<td>34.6 ± 6.6</td>
<td>14.6 ± 1.7*</td>
</tr>
<tr>
<td>Ampoules of FSH</td>
<td>12.0 ± 0.6</td>
<td>20.2 ± 1.4*</td>
</tr>
<tr>
<td>LH on day of hCG (mIU/ml)</td>
<td>30.2 ± 5.6</td>
<td>14.5 ± 1.9*</td>
</tr>
<tr>
<td>E_2 on day of hCG (pg/ml)</td>
<td>1733.8 ± 291.9</td>
<td>906.8 ± 173.5*</td>
</tr>
<tr>
<td>Peak E_2 (pg/ml)</td>
<td>1923.0 ± 264.1</td>
<td>1197.6 ± 196.6*</td>
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* P < 0.05 compared to FSH alone.