

# Severe Ovarian Hyperstimulation Syndrome from Treatment with Urinary Follicle-Stimulating Hormone: Two Cases

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## Severe ovarian hyperstimulation syndrome from treatment with urinary follicle-stimulating hormone: two cases

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Urinary follicle-stimulating hormone (uFSH) is a relatively "pure" FSH containing 75 IU of FSH with only a small contaminant of 1 IU of luteinizing hormone (LH). A recent study was unable to show any distinct advantage of uFSH versus human menopausal gonadotropins (hMG) as far as the number of ovulations, length of treatments, and amount of medication administered were concerned.<sup>1</sup> Nevertheless, there have been some suggestions that a preparation with a high FSH/LH ratio causes a smaller incidence of ovarian hyperstimulation syndrome (OHSS).<sup>2, 3</sup>

Because the incidence of severe OHSS is low (< 1.5%)<sup>4</sup> it would take a large double-blind study to determine which hormone (uFSH versus hMG) was safer. As one way to test the hypothesis of safety of uFSH in a more rapid fashion, the protocol that we employed required that human chorionic gonadotropin (hCG) be given when a mature follicle size, as determined by pelvic sonography, was accomplished even when the estradiol (E<sub>2</sub>) level had exceeded normal safety levels. However, if the E<sub>2</sub> level had been too low when the follicle was the correct size, 18 to 24 mm, then more uFSH would have been given.

We report two women with normal endogenous estrogen who developed severe OHSS in their

first treatment cycles with uFSH. However, these same patients had no side effects from multiple treatment cycles with hMG.

### MATERIALS AND METHODS

Eighteen patients were selected for treatment with uFSH. No patient was allowed to be estrogen-deficient. The patients were started on one ampule uFSH for 3 or 4 days, then increased to two ampules daily. The medication was continued until at least one follicle achieved a size of 17 mm in diameter with sonographic monitoring. Although E<sub>2</sub> levels were monitored for analysis, hCG was not to be withheld no matter how high the level of serum E<sub>2</sub>. Ten thousand units of hCG was administered approximately 36 hours after the last uFSH injection when follicular maturation was achieved.

### RESULTS

Two cases of severe OHSS developed in 18 patients in 38 treatment cycles. Grade 2 to grade 4 (mild to moderate hyperstimulation), as defined by Schenker and Weinstein,<sup>4</sup> occurred in seven cycles in five other patients.

### CASE REPORTS

#### CASE 1

A 26-year-old woman with a 5-year primary infertility history was treated with uFSH. She

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was anovulatory, as evidenced by amenorrhea and a monophasic basal body temperature chart. She did have adequate endogenous estrogen production, as evidenced by consistent withdrawal menstrual bleeding in response to medroxyprogesterone acetate, and vaginal cytology showing a good estrogen effect (60% superficial cells, 20% large intermediate cells, 18% small intermediate cells, and 2% parabasal cells). Her baseline LH level was slightly increased, at 30.8 mIU/ml (normal, 2 to 25 mIU/ml), and her serum FSH level was normal, at 9.0 mIU/ml (normal, 2 to 10 mIU/ml). The dehydroepiandrosterone sulfate level was normal at 1754 ng/ml (normal, 820 to 3380 ng/ml), as was the serum free testosterone (T) of 6.7 pg/ml (normal, 1.5 to 9.5 pg/ml) and a total T of 66 ng/ml (normal, 70 ng/ml or less). She had no abnormal clinical findings other than mild hirsutism.

The patient was started on 75 IU uFSH (one ampule) for 4 days, beginning on day 5 of her cycle. The dosage was increased to 150 IU uFSH, beginning on day 9. Ovarian sonography was performed on cycle days 13, 18, 20, and 22. Serum E<sub>2</sub> levels were performed on cycle days 10 and 20. The objective was to push the uFSH until at least one follicle attained an average diameter of 18 mm. On day 20, though, the E<sub>2</sub> measured 3120 pg/ml; the largest follicle only measured 14 mm. Thus, uFSH was given for 2 more days until day 22, when two follicles were now between 18 and 24 mm; then 10,000 U of hCG was given.

Symptoms of OHSS began 9 days after the hCG injection. Physical examination showed the blood pressure to be only 70 palpable with a pulse of 120. Her skin was clammy, with marked diaphoresis. She had moderate abdominal tenderness in the left lower quadrant, with rebound tenderness. No bowel sounds were audible. Her hemoglobin was 17 gm/dl, her hematocrit was 54.2%, and her white blood cell count was 32,000/mm<sup>3</sup>. Pelvic sonography demonstrated bilaterally enlarged ovaries with multiple cysts. The left ovary measured 7.2 × 5.5 × 5.0 cm, and the right ovary was 5.2 × 5.2 × 4.8 cm. A large amount of free fluid was seen in both pericolic gutters. Over the 10-day course in the hospital, her ovaries enlarged to over 12 cm each with more peritoneal fluid. The patient recovered following conservative intravenous fluid therapy and was discharged. After her discharge, the patient developed moderate scalp alopecia, but this returned to normal after several months.

After 3 months, the patient began treatment again, but this time with hMG. She conceived after eight treatment cycles. She averaged 22 ampules of hMG (75 IU/ampule) for each cycle but needed 60 in the cycle during which she conceived. She had no symptoms or signs of OHSS in any of the treatment cycles. The E<sub>2</sub> level never exceeded 500 pg/ml per follicle 17 mm or greater, and in the cycle during which she conceived she had three follicles between 18 and 24 mm and the E<sub>2</sub> level was 720 pg/ml.

#### CASE 2

The patient was a 30-year-old woman with 3 years of primary infertility who had failed to ovulate after treatment with 150 mg clomiphene citrate for 5 days. Although oligomenorrheic, she always had withdrawal bleeding in response to medroxyprogesterone acetate.

Her baseline endocrine studies showed a serum FSH level of 7.3 mIU/ml, an LH level of 27.4 mIU/ml, a prolactin level of 12.4 ng/ml, and a dehydroepiandrosterone sulfate level of 1740 ng/ml. Her serum T was slightly increased, at 104 ng/dl (normal, 30 to 95 ng/dl).

She was started on one ampule of uFSH for 3 days, beginning on day 5, then increased to two ampules daily to day 12, when ultrasound revealed only one follicle the correct size of 22 mm with multiple small follicles under 10 mm seen on both ovaries. The right ovary measured 4.5 × 3.5 × 3.5 cm and the left ovary measured 5.0 × 3.0 × 3.5 cm. The serum E<sub>2</sub> on day 12 was 2129 pg/ml. hCG (10,000 IU) was given on day 13. She had received a total of 13 ampules of uFSH prior to that point.

Two weeks later the patient was admitted to the hospital with severe OHSS as manifested by severe nausea, vomiting, and abdominal pain. Her hemoglobin on admission was 17.1 gm/dl and the white blood cell count was 29,000 with 93% polymorphonuclear cells. A β-hCG test was positive, at 242 mIU/ml, drawn 17 days after the hCG injection.

The patient was treated conservatively with intravenous fluids and was discharged 12 days later. She aborted 6 weeks from conception. Her only sequelae from the OHSS were moderate scalp alopecia and a malar erythematous rash, and both resolved after several months.

Three months later the patient was treated with hMG. She conceived on her second cycle af-

ter 18 ampules of hMG. She had three follicles on ultrasound over 17 mm, and her E<sub>2</sub> level was 652 ng/ml. She subsequently delivered a full-term male infant.

### DISCUSSION

These two cases demonstrate that at least some individuals may develop severe OHSS following treatment with uFSH without development of a large number of multiple mature follicles prior to hCG injection. Furthermore, these same "sensitive" cases did not develop OHSS despite multiple treatment cycles with hMG.

Normally, when we employ hMG, we try to achieve an E<sub>2</sub> level of 200 pg/ml per each follicle between 17 and 24 mm and try not to exceed an E<sub>2</sub> level > 500 pg/ml per each mature follicle. Thus, had we followed the same principles for uFSH as we do with hMG, hCG would not have been given in either of the two cycles where OHSS developed. Cases 1 and 2 averaged well over the safety level of 500 pg/ml per follicle.

These two cases of uFSH occurred in 18 patients treated with uFSH in 38 treatment cycles (5.3%). This is much higher than the incidence we see in hMG-treated patients (< 1%). However, if the same requirements for hMG of not exceeding 500 pg/ml E<sub>2</sub> per follicle are similarly followed for uFSH, it is possible that the safety of the two drugs could still be found to be comparable.

Nevertheless, these cases highlight certain potential advantages of hMG over uFSH, in that with hMG in ten cycles in these two cases, not once did hMG have to be cancelled because the E<sub>2</sub> averaged over 500 pg/ml per follicle; whereas with uFSH, this could not be accomplished.

Thus, these two cases shed some doubt on the hypothesis that uFSH may be safer than hMG

from the standpoint of holding less risk of inducing OHSS. Furthermore, the cases illustrate that in some instances the patient will have to cancel cycles after full treatment with uFSH while not having to do so with hMG. Because the drug's expense is comparable to hMG, this would have to be considered when choosing treatment.

hCG administration is critical for the development or prevention of OHSS except in sporadic cases.<sup>4</sup> Because pure FSH has been shown to reverse anovulation in polycystic ovarian disease without the use of hCG,<sup>5</sup> possibly, used in this way, uFSH may prove to hold less risk of inducing OHSS. Obviously, however, the efficacy of uFSH without hCG must be compared with that of hMG with hCG, and a decision must be made on the basis of the risk/benefit ratio.

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