

Allergic reaction to a highly purified urinary follicle stimulating hormone preparation in controlled ovarian hyperstimulation for *in vitro* fertilization

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ABSTRACT

We report a case of general hypersensitivity-like allergic reactions to intramuscular injections of highly purified urinary follicle stimulating hormone (uFSH-HP) successfully managed by using intramuscular recombinant FSH (rFSH).

The patient underwent a first cycle of *in vitro* fertilization (IVF) and controlled ovarian hyperstimulation (COH) was achieved with a combination of gonadotropin releasing hormone against (GnRH-a) and uFSH-HP. Because, after oocyte recovery, no fertilization occurred, the couple subsequently entered an intracytoplasmic sperm injection (ICSI) program. During the COH, the woman developed general hypersensitivity-like allergic reactions with itching, redness and swelling. Although there was regular follicular growth, the allergic symptoms worsened and, on day 8 of COH, the stimulation cycle was suspended. A few months later, the patient entered a new ICSI cycle. COH was achieved by using a combination of GnRH-a and rFSH. The cycle was completed and the patient did not report any allergic reaction.

To avoid allergic reaction to the protein components of the urine-derived FSH preparations, the use of rFSH is suggested in those patients who present local and/or general hypersensitivity-like allergic reactions.

INTRODUCTION

Gemzell and colleagues¹ were the first to induce ovulation by using human pituitary gonadotropins. Human menopausal gonadotropins (hMG) have been successfully used for ovarian stimulation for nearly 40 years, since their administration was reported to achieve pregnancy in a case of hypothalamic amenorrhea². With the introduction of assisted reproductive techniques, the indication for their use has been considerably broadened. Although hMG preparations contain both follicle stimulating hormone (FSH) and luteinizing hormone (LH), it is now clear that the stimulation of follicular development is dependent on only FSH.

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A modest FSH increase (< 30%) is required for initiating follicular growth. It is unlikely that LH is involved in recruiting primordial follicles into the population of developing follicles (no LH receptor has been found in primordial and small antral follicles)³. Furthermore, excessive LH is associated with reduced fertilization and reduced natural conception rates and may be the cause, along with increased follicular androgens, of the high risk of miscarriage. In addition, minimal LH is required to achieve full effectiveness in the follicle and the action of LH on theca cells is amplified by paracrine signals, in particular inhibin and insulin-like growth factor-1, from granulosa cells maturing in response to FSH alone. Therefore, preparations containing only FSH may be considered a good alternative to hMG in controlled ovarian hyperstimulation (COH).

Over the past 15 years a preparation of highly purified urinary FSH has been available for clinical use. The purification techniques have resulted in a product with a high purity (> 95% of the protein content is FSH) and a very low LH residual content (< 0.1 IU per 1000 IU FSH)⁴. The scarce amount of non-hormonal proteins has been supposed to allow subcutaneous administration and to prevent local allergic reactions.

In the present case we report a successful and uneventful COH, with recombinant FSH (rFSH), in a woman who previously showed general hypersensitivity-like allergic reactions to highly purified FSH.

CASE REPORT

A 36-year-old woman with a history (7 years) of primary infertility was referred to our Infertility Clinic in January 1998 after being treated elsewhere with three cycles of intrauterine insemination. The patient was oligomenorrheic (menstrual cycle length > 35 days), overweight (body mass index > 25) and moderately hirsute (Ferriman–Gallwey score 8), and she was shown to have a polycystic ovary on ultrasonographic and Doppler evaluation⁵. Tubal patency was confirmed by color Doppler hysterosalpingography⁶. Her partner was fertile according to World Health Organization standards. The couple underwent an *in vitro* fertilization cycle.

Ovarian stimulation was achieved with a combination of the gonadotropin releasing

hormone agonist (GnRH-a) leuporelin acetate (Enantone Depot[®]; Takeda, Rome, Italy) and highly purified FSH (Metrodin HP[®]; Serono, Rome, Italy). Leuporelin was administered from day 1 of the menstrual cycle (3.75 mg intramuscularly) and Metrodin HP (150 IU/day) commencing after pituitary desensitization (plasma estradiol concentrations < 35 pg/ml; ovaries with no follicles of > 5 mm in diameter and endometrial thickness < 5 mm). When more than three follicles of > 17 mm in diameter were present, Metrodin HP was withdrawn and 10 000 IU human chorionic gonadotropin (hCG; Profasi[®]; Serono) was administered intramuscularly. Ultrasonographic oocyte recovery was performed transvaginally 35 h after hCG injection. Twelve oocytes were retrieved and subsequently inseminated according to standard methods⁷. No fertilization occurred.

Two months later the couple entered an intracytoplasmic sperm injection (ICSI) program. The COH was similar to the previous procedure. Three days after the beginning of gonadotropin treatment, the woman developed a cutaneous allergic reaction with itching, redness and swelling. The symptoms were present and persistent in many areas of the woman's body, especially the arms (Figure 1), and their intensity increased after every Metrodin HP injection. Although there was regular follicular growth, as assessed by ultrasonography, the symptoms worsened and, on day 8 of the stimulation cycle, FSH was withdrawn and the cycle suspended. The normal ovarian response suggested that no specific anti-FSH antibodies had been developed and that the cutaneous symptoms could be related to an immune reaction to exogenous non-gonadotropin proteins.

In October 1998 the woman came to our center for a second ICSI attempt. Ovarian stimulation was achieved by an intramuscular injection on day 20 of the cycle of the GnRH-a leuporelin (Enantone Depot) and recombinant FSH (Gonal-F 75[®]; Serono). Gonal-F 75 (225 IU/day) was administered after pituitary desensitization (plasma estradiol concentrations of < 35 pg/ml; ovaries with no follicles of > 5 mm in diameter and endometrial thickness of < 5 mm). When more than three follicles of > 17 mm in diameter were present, Gonal-F 75 was withdrawn and 10 000 IU hCG (Profasi) was administered intramuscularly. Ultrasonographic oocyte recovery was



Figure 1 Allergic reaction on the right arm 5 days after the beginning of purified urine-derived follicle stimulating hormone treatment for controlled ovarian hyperstimulation. Papulac with redness and swelling are evident

carried out transvaginally 35 h after the hCG injection. Fourteen oocytes were retrieved and ICSI was performed. Ten embryos were obtained. Three of the best embryos were replaced at the 6–12-cell stage. Transcervical transfer was carried out using a Frydman® catheter (SCS International, Genoa, Italy). The remaining cleaved embryos with 20% fragmentation were allocated to a cryopreservation protocol. Vaginal progesterone gel 8% (Crinone 8®; Wyeth Lederle, Rome, Italy) was prescribed daily as luteal support, until the -hCG assay was performed. No pregnancy was achieved. No adverse allergic reaction was observed during COH with rFSH.

DISCUSSION

In assisted reproduction, human gonadotropin preparations, over a mean period of 2 weeks, can lead to controlled hyperstimulation. The standard treatment utilizes daily administration. Although they have been demonstrated to be effective and relatively safe, they have been shown to be the cause of headache, weakness, local allergic reactions and pain^{8,9}. Furthermore, Biffoni and co-workers¹⁰ reported that general

hypersensitivity-like reactions occurred in 1.4% of all stimulated cycles. Some of these adverse reactions represent possible immunoglobulin (Ig) E-mediated and IgG-mediated reactions to proteins administered exogenously. The availability of a highly purified human urinary FSH preparation was expected to decrease the risk of allergic reactions because of the almost negligible content of co-administered contaminating proteins (FSH represents > 95% of the total proteins with approximately 10 000 IU of FSH/mg of protein) compared to the previously used urinary gonadotropin preparations.

In this paper we report, to our knowledge, the first case of a general hypersensitivity-like reaction to Metrodin HP. Although IgE-dependent allergic reactions to fertility hormones have been reported^{11,12}, in the present case the allergic reaction did not appear to be associated with a diminished ovarian response, suggesting that anti-FSH antibodies were not developed and that, if any immune response was stimulated, the most likely antigens would be the minute amounts of co-administered proteins.

The woman was not willing to undergo a third stimulation with highly purified FSH, because of the general hypersensitivity-like reaction. Recombinant FSH was administered and no adverse reaction was reported by the patient.

Recombinant FSH is produced by a Chinese hamster ovary cell line transfected by the genes encoding the subunit genes¹³. The polypeptide backbone of rFSH is identical to that of natural FSH and, in comparison to commercially available urinary FSH preparations, highly pure (99.9%) rFSH appears to lack intrinsic LH activity and to exhibit a very high specific bioactivity (> 10 000 IU/mg protein)¹³.

In conclusion, to avoid an allergic reaction to the protein components of the urine-derived FSH preparations in assisted reproduction techniques, we suggest the use of rFSH in those patients who experience a local and/or general hypersensitivity-like reaction.

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