

Administration of recombinant follicle stimulating hormone in a woman with allergic reaction to menotropin: a case report

S. Harrison*, T. Wolf* and M. I. Abuzeid*[†]

*Michigan State University, College of Human Medicine; and [†]Department of Obstetrics and Gynecology, Hurley Medical Center, Flint, MI, USA

Key words: INFERTILITY, MENOTROPIN, RECOMBINANT FOLLICLE STIMULATING HORMONE, ALLERGY, PERGONAL[®]

ABSTRACT

This report describes a patient who experienced a generalized allergic reaction to Pergonal during controlled ovarian hyperstimulation in preparation for an intracytoplasmic sperm injection procedure for treatment of severe male factor infertility. The report describes a successful desensitization protocol which allowed the patient to complete her treatment cycle despite the allergic reaction to Pergonal. Subsequently recombinant follicle stimulating hormone was used successfully in inducing follicular growth in the absence of any allergic reactions. Therefore, this report confirms other studies which have suggested that an allergic reaction to human menopausal gonadotropins is due to impurities in such urine-derived products.

INTRODUCTION

Infertility continues to be a problem for many women, with current estimates of nearly 15% unable to conceive during their reproductive years¹. *In vitro* fertilization (IVF) is a widely used treatment option. However, when male factor is present, estimates of total fertilization rates with

routine IVF range from 11 to 22%². The concomitant use of intracytoplasmic sperm injection (ICSI) has demonstrated efficacy in avoiding complete fertilization failure as seen in patients with male factor infertility^{2–4}. Urine-derived menotropins have been widely used in assisted reproductive techniques for the induction of follicular development in various IVF–ICSI protocols.

In recent years, a few case reports have identified adverse reactions to human menopausal gonadotropins (hMG): in particular, local and generalized skin reactions^{5,6} and delayed-type hypersensitivity⁷. Recombinant follicle stimulating hormone (rFSH) products, by contrast, have fewer reported side-effects. This is probably due to an increase in purity from preparation and the lack of luteinizing hormone which further increases purity, decreases contaminants and strengthens the batch consistency⁸. Additionally, for patients with local reactions to intramuscular injections of hMG, rFSH products offer the added benefit of subcutaneous administration.

Correspondence: Dr M. I. Abuzeid, Department of Obstetrics and Gynecology, Hurley Medical Center, Two Hurley Plaza, Suite 101, Flint, MI 48503, USA

We report a case of a highly motivated patient with infertility due to advanced reproductive age and male factor, who underwent numerous IVF–ICSI protocols to achieve pregnancy. This patient experienced a high rate of fertilization failure and a generalized allergic reaction to Pergonal®. She was eventually started on rFSH, Gonal-F®, which she tolerated very well; the treatment ultimately resulted in fertilization and an ectopic pregnancy. To our knowledge, we describe here the first successful desensitization protocol to Pergonal.

CASE REPORT

A 39-year-old Caucasian woman who presented with a diagnosis of infertility due to reproductive age factor and her husband's male factor of oligoasthenoteratozoospermia, experienced an allergic reaction to the hMG Pergonal. The patient had no other drug allergies nor was she taking any medications other than those prescribed.

In September 1994, the patient underwent the ICSI procedure. The mid-luteal gonadotropin releasing hormone agonist (GnRH-a) leuprolide acetate (Tap Pharmaceuticals, Inc., Deerfield, IL) protocol and a combination of Metrodin® and Pergonal (Serono Laboratories, Inc., Norwell, MA) were administered. Although the dose of Pergonal was increased to 8 ampules per day, a poor ovarian response resulted. During the procedure, four eggs were retrieved; one was fertilized with delayed cleavage, and one embryo was transferred 3 days after oocyte retrieval. No conception occurred.

In November 1994, the GnRH-a nafarelin acetate (Oread Pharmaceutical Manufacturing, Inc., Palo Alto, CA) flare-up protocol was initiated. The patient received high-dose Premarin® conjugated estrogen tablets (Wyeth-Ayerst, Philadelphia, PA) for 2 months (1.25 mg three times a day), followed by Provera® medroxyprogesterone acetate tablets (Pharmacia & Upjohn, Kalamazoo, MI) 10 mg for 10 days. High-dose estrogen was used in an attempt to improve the ovarian response (unpublished data). In February 1995, treatment was reinitiated with a high-dose Pergonal protocol, 6 ampules per day, which was increased to 10 ampules per day after 5 days. On the 8th day of treatment, there were two follicles on the right ovary measuring 12.5 mm

and 10 mm, and one follicle on the left ovary measuring 9.5 mm. The estrogen level was 200 pg/ml. At this point in treatment, the patient experienced hives, upper lip swelling and periorbital edema. She was treated with prednisone (methylprednisolone; Duramed, Cincinnati, OH), Atarax® (hydroxyzine hydrochloride; Pfizer Inc. Consumer Health Care Group, New York, NY), hydrocortisone cream (hydrocortisone valerate; Westwood Squibb, Buffalo, NY) and Benadryl® (diphenhydramine hydrochloride; Warner, Lambert, Consumer, Morris Plains, NJ) intramuscularly. The patient was evaluated by an allergy specialist, and a positive skin test to Pergonal was confirmed. She underwent a desensitization protocol and, after an allergy specialist was consulted, and at the patient's request, her treatment cycle continued. She received her Pergonal daily in the allergy specialist's office, where her full doses were administered sequentially. The protocol of desensitization as described by the allergy specialist involved gradually increasing the dose of desensitization extract, which was prepared by ten-fold serial dilution of Pergonal. No anaphylactic or extended reactions were noted. The patient continued with Pergonal treatment of 10 ampules per day until March 1995, when 10 000 IU of human chorionic gonadotropin (hCG) (Profasi®; Serono Laboratories, Inc., Norwell, MA) was administered intramuscularly. On the day of hCG administration, the serum estradiol level was 580 pg/ml and three mature follicles were seen on a vaginal ultrasound scan. Thirty-six hours later, transvaginal ultrasound-guided oocyte retrieval was performed, resulting in retrieval of two immature oocytes and cancellation of the ICSI procedure.

In December 1996, due to the allergic reactions experienced with Pergonal, the patient was offered treatment with the rFSH Gonal-F. This was carried out as a part of research approved by Serono Laboratories and our Institutional Review Board. The patient started leuprolide acetate (Tap Pharmaceuticals) 0.5 mg subcutaneously daily with the onset of her period on 15 January 1997. Gonal-F 225 IU was started subcutaneously on 17 January 1997. The dosage of Gonal-F was increased gradually to 600 IU per day over the last 2 days of stimulation. Throughout this treatment, the patient had no allergic reaction. On the 14th day, the serum estradiol level was 282 pg/ml, and an ultrasound

scan revealed three mature follicles on the right ovary measuring 17 mm, 18.5 mm and 23 mm. Intramuscular hCG 10 000 IU was administered and, 36 h later, transvaginal ultrasound scan-guided oocyte retrieval was performed. All injected oocytes were fertilized, and three embryos resulted. Two embryos were of excellent quality and one of good quality. Tubal embryo transfer into the right tube was performed under general anesthesia. Two weeks later, a pregnancy test was positive. However, the patient had an unruptured ectopic pregnancy in the right tube for which she underwent laparotomy and right linear salpingostomy by her referring gynecologist. Her postoperative recovery was uneventful.

DISCUSSION

There are few reports in the literature describing allergic reactions to gonadotropin preparations. Various case reports have shown that exogenous administration of human proteins can induce immunoglobulin (IgG)-mediated reactions^{9,10}. One animal study revealed the possibility of developing an allergic systemic IgE-mediated reaction to human menotropins¹¹. Li and Hindle described a local reaction to Pergonal followed by a local reaction to Metrodin (hFSH) in a subsequent cycle¹². They observed that, when highly purified FSH was used in a subsequent treatment cycle, no reaction occurred. Therefore, they postulated that the local reaction is secondary to the high content of non-hormonal proteins present in human gonadotropin. Redfearn and co-workers described two additional cases of delayed-type hypersensitivity to human gonadotropins⁷. The local reaction was associated with malaise, headaches and fever⁷.

In this report, we have described a case of an allergic systemic IgE-mediated reaction to human gonadotropins. The patient underwent the ICSI procedure for treatment of male infertility. Additionally, there was an element of reproductive age factor. During the first treatment cycle, the patient had a poor ovarian response despite the use of high-dose Pergonal; one embryo of poor quality resulted and she failed to conceive. During her second treatment cycle, 2 months later, she experienced both local and generalized IgE-mediated allergic reactions which were treated initially with corticosteroids followed by a desensitization protocol that was successful in helping her to complete her treatment cycle without further reaction. However, once again, the patient had a poor ovarian response. The lack of mature oocytes resulted in cancellation of the ICSI procedure. Two years later, at the age of 43 years, the patient underwent a third treatment cycle using rFSH. She experienced no allergy to this regimen. Despite a poor ovarian response, three mature oocytes were retrieved and three embryos were transferred into the Fallopian tube; however, an ectopic pregnancy occurred.

To our knowledge, this report describes for the first time a successful desensitization protocol. This protocol allowed our patient to complete her treatment cycle despite an allergic reaction to Pergonal, although the final outcome was not successful. Furthermore, our report confirms the findings of Albano and colleagues that patients who develop allergic reactions to hMG products such as Pergonal may respond favorably to the use of rFSH⁶. This also confirms other reports which have speculated that an allergic reaction to human gonadotropins is due to impurities in urine-derived products of hMG^{6,11,13}.

REFERENCES

1. Speroff L, Glass RH, Kasse NG. *Clinical Gynecologic Endocrinology and Infertility*. Baltimore: Williams and Wilkins, 1994:810–15
2. Ruiz A, Guanesh P, Remohi J, et al. The role of *in vitro* fertilization and intracytoplasmic sperm injection in couples with unexplained infertility after failed intrauterine insemination. *Fertil Steril* 1997;68:171–3
3. Aboulghar MA, Mansour RT, Serour GI, et al. Intracytoplasmic sperm injection and conventional *in vitro* fertilization for sibling oocytes in cases of unexplained infertility and borderline semen. *J Assist Reprod Genet* 1996;13:38–42
4. Nagy ZP, Liu J, Joris H, et al. The result of intracytoplasmic sperm injection is not related to any of the three basic sperm parameters. *Hum Reprod* 1995;10:1123–9
5. Okink J, Zuiderwijkm PBM, Schoen ED, et al. A prospective, double-blind, split subject study on local skin reactions after administration of human

- menopausal gonadotropin preparation to healthy female volunteers. *Hum Reprod* 1995;10:1045-7
6. Albano C, Smitz J, Camus M, et al. Pregnancy and birth in an *in vitro* fertilization cycle after controlled ovarian hyperstimulation in a woman with a history of allergic reaction to human menopausal gonadotropin. *Hum Reprod* 1996;11:1632-4
 7. Redfearn A, Hughes EG, O'Connor M, et al. Delayed-type hypersensitivity to human gonadotropin: case report. *Fertil Steril* 1995;64:855-6
 8. Jennings JC, Moreland K, Peterson CC. *In vitro* fertilization. A view of drug therapy and clinical management. *Drugs* 1996;52:313-43
 9. Healy DI, Fraser IS, Lee VWK, et al. Characteristics of an antiluteinizing hormone isoantibody produced during gonadotropin induction of ovulation. *J Clin Endocrinol Metab* 1978;47:823-8
 10. Braunstein GD, Bloch SK, Rasor JL, et al. Characterization of antihuman chorionic gonadotropin serum antibody appearing after ovulation induction. *J Clin Endocrinol Metab* 1983;57:1164-72
 11. Biffoni M, Gattagliam A, Boreli F, et al. Allergic potential of gonadotrophic preparations in experimental animals; relevance of purity. *Hum Reprod* 1994;9:1845-8
 12. Li TC, Hindle JE. Case report: adverse local reaction to intramuscular injections of urinary-derived gonadotropins. *Hum Reprod* 1993;8:1835-6
 13. Verhoeff A, Schnoutziguer AP, Doesburg WH, et al. A randomized study of the effects of intramuscular injections with urinary gonadotropins (Humegon or Pergonal) on pain, local redness and fever in infertile women opting for *in vitro* fertilization. *Hum Reprod* 1997;12:1427-9