

Desensitization to urine-derived gonadotropins in a woman with secondary infertility

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Background: Urine-derived gonadotropins have been used to treat infertility but may cause allergic reactions. IgE-mediated hypersensitivity reactions can be treated with desensitization, especially when new therapies such as recombinant human gonadotropins are unavailable.

Objective: This case is described to highlight a successful intervention with desensitization in a woman with a complicated history of secondary infertility. She had been treated with ovulation-induction regimens, such as IVF-M (in vitro fertilization-human menopausal gonadotropin [hMG]) and IVF-C (human chorionic gonadotropin [hCG]), for intrauterine insemination. During treatment, however, she experienced reactions to IVF-M and IVF-C. Because she strongly wanted a baby and no alternative preparation was available, desensitization was attempted.

Methods: Intradermal tests with IVF-M and IVF-C using both negative and positive controls were performed on the patient and four normal control subjects. Immediate wheal-and-flare reactions occurred only in the patient. ELISA and ELISA inhibition tests showed positive responses to IVF-M and IVF-C, but not to highly purified hMG, hCG, or D-mannitol, a preservative in IVF-M and IVF-C. Desensitization to IVF-M and IVF-C was done with a protocol used for parenteral desensitization to penicillin.

Results: During the IVF-M desensitization, the intramuscular injections were well tolerated. For the next 2 days, daily administration of IVF-M was uneventful. Thirty-six hours later, desensitization to IVF-C was performed successfully. The patient had two intrauterine inseminations and became pregnant.

Conclusions: Nongonadotropin proteins in urine-derived gonadotropins cause IgE-mediated hypersensitivity reactions. Acute desensitization to urine-derived gonadotropins can be performed effectively, as shown in our current case.

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INTRODUCTION

Gonadotropin preparations are commonly used in the treatment of infertility in patients with or without ovulatory disturbances. Patients allergic to urine-derived gonadotropins have been successfully treated with recombinant human follicle-stimulating hormone (FSH).^{1,2} This alternative therapy is the preferred

management for drug hypersensitivity. When this new alternative product is not available, however, acute desensitization may be attempted. A MEDLINE search revealed no previously published reports of desensitization to urine-derived gonadotropins. We describe a case of successful acute desensitization to urine-derived gonadotropins in a patient with secondary infertility.

CASE REPORT

In January 1999, a 31-year-old woman with a complicated history of secondary infertility came to the infertility clinic at Chonnam University Hospital for intrauterine insemination. She had a history of ovulatory dysfunction as well as poor cervical mucus. Since October 1996, she

had been treated extensively with seven cycles of ovulation-induction regimens, including clomiphene citrate, in vitro fertilization-human menopausal gonadotropin [hMG] (IVF-M), and human chorionic gonadotropin [hCG] (IVF-C), in a private clinic. On the first day of treatment during her seventh cycle, however, she experienced shortness of breath, wheezing, flushing, generalized weakness, and dizziness 20 minutes after an intramuscular injection of 150 IU of IVF-M. She was treated parenterally with epinephrine, hydrocortisone, and pheniramine maleate, after which her symptoms resolved rapidly. Five days later, a similar hypersensitivity reaction occurred 25 minutes after administration of 5,000 IU of IVF-C. The ovulation-induction agents were discontinued, and the cycle was aborted.

In March 1998, she had visited the allergy clinic for an evaluation of allergic reactions to gonadotropin preparations for intrauterine insemination, including IVF-M and IVF-C. Intradermal tests with IVF-M and IVF-C from the same lot that caused the reaction produced immediate severe wheal-and-flare reactions, indicative of IgE-mediated sensitivity. The IVF-C skin test was performed 24 hours after the IVF-M test. In particular, a rash with hives involving her entire body developed 2 hours after the skin testing to IVF-C, reinforcing the presence of a hypersensitivity reaction. Four normal control subjects were similarly tested and were not reactive to undiluted solutions of IVF-M or IVF-C. Because the patient was afraid of the allergic reaction induced by the skin test, she refused further skin testing with highly purified hMG and hCG preparations (Organon Korea Ltd, Seoul, Korea), which had been purified by affinity

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chromatography, and D-mannitol (Choongwae Pharma Corporation, Hwasung, Korea), which was present as preservative in both IVF-M and IVF-C preparations.

Instead, the presence of specific IgE antibodies to IVF-M, IVF-C, highly purified hMG and hCG preparations, and D-mannitol was determined by ELISA. Microtiter plates (Nunc, Roskilde, Denmark) were first coated with 50 μ L/well of IVF-M (1.5 IU/well), IVF-C (2.5 IU/well), purified hMG (2 μ g/well), purified hCG (2.5 IU/well), and D-mannitol (2 μ g/well). The wells were then incubated with 50 μ L of either the patient's serum or control sera (1:10 diluted) from three healthy normal women who had negative skin test reactions to IVF-M, IVF-C, highly purified hCG and hMG, and D-mannitol. After washing, 50 μ L of the 1:2,000 (vol/vol) peroxidase-conjugated goat anti-human IgE antibody (ϵ -chain-specific IgG fraction of anti-serum; Sigma Chemical Co, St. Louis, MO) was added to the wells and incubated. The absorbance was read at 490 nm. The cutoff value of the positive IgE binding was determined from the mean plus 2 standard deviations of the absorbance value (optical density or OD) from the three normal control subjects. The cutoff values for IVF-M, IVF-C, highly purified hMG, highly purified hCG, and D-mannitol were determined as 0.22, 0.20, 0.17, and 0.18 absorbance value (OD), respectively. The patient showed positive specific IgE binding to IVF-M (0.42 OD) and IVF-C (0.35 OD) but negative ELISA responses to highly purified hMG (0.15 OD), highly purified hCG (0.17 OD), and D-mannitol (0.16 OD).

Competitive ELISA inhibition tests with highly purified hMG, highly purified hCG, and D-mannitol were performed to evaluate the specificity of the IgE binding to the IVF-M and IVF-C. An undiluted sample (50 μ L) of the patient's serum was preincubated with three concentrations of highly purified hMG (0.02 to 20 μ g/mL), hCG (0.02 to 20 IU/mL), IVF-M (0.02 to 20 IU/mL), IVF-C (0.02 to 20 IU/mL), and D-mannitol (0.02 to 20

μ g/mL). Each sample of the purified hMG, purified hCG, and D-mannitol was incubated with the IVF-M/IVF-C-coated microtiter plate. The same steps were followed as in the ELISA. After study of the control samples in which equal volumes of phosphate-buffered saline (pH 7.5) were used for preincubation instead of inhibitors, the inhibition of the specific IgE binding was expressed as $[100 - (\text{absorbance of samples preincubated with antigens/$

absorbance of samples preincubated with phosphate-buffered saline) $\times 100$ (%)]. The dose-response pattern of the inhibitory effects with addition of IVF-M and IVF-C antigen is illustrated in the IVF-M and IVF-C ELISA shown in Figure 1. No inhibition was noted with highly purified hMG and hCG preparations or with D-mannitol. Partial inhibitions of ELISA (33 to 41%) were achieved by both IVF-M and IVF-C at concentrations of 20

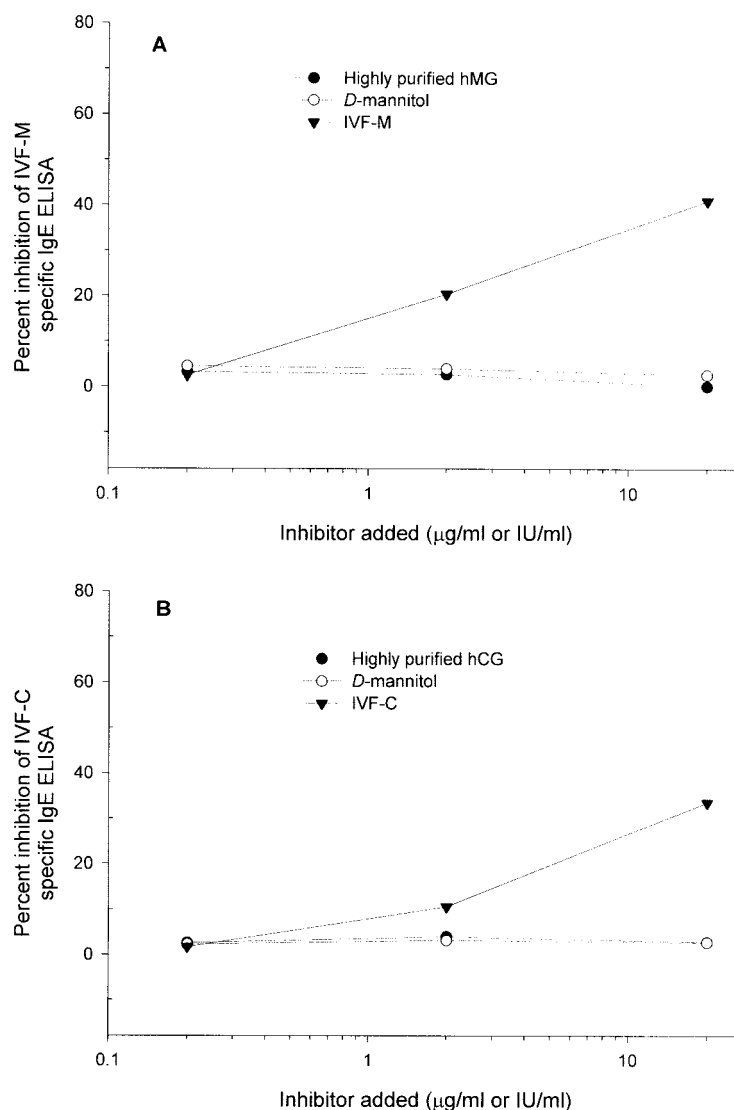


Figure 1. Percent inhibitions of specific IgE bindings to 1) IVF-M and 2) IVF-C with serial additions of highly purified hMG, highly purified hCG, and D-mannitol using serum from a patient who showed a positive skin response to IVF-M and IVF-C. Units for x-axis were expressed as μ g/mL for highly purified hMG and D-mannitol and as IU/mL for IVF-M, IVF-C, and highly purified hCG.

IU/mL and 20 IU/mL, respectively. These results indicate that nongonadotropin proteins in IVF-M or IVF-C were responsible for the hypersensitivity reaction.

Because the patient strongly wanted to have a baby and no alternative preparation was available, desensitization to IVF-M and IVF-C was attempted with use of a protocol described for parenteral desensitization to β -lactam antibiotic hypersensitivity.³ She understood the potential risks and benefits of the desensitization and gave informed consent.

On January 6, 1999, the patient was admitted to Chonnam University Hospital for IVF-M and IVF-C desensitization and intrauterine insemination. Analyses of her husband's semen had shown normal findings. In preparation for intrauterine insemination, she was treated with clomiphene citrate, 50 mg daily for 5 days, beginning on January 7. Results of an ultrasound study were consistent with downregulation 1 day before initiation of IVF-M treatment. The desensitization procedure for IVF-M was performed without premedication the next day, as shown in Table 1. The individual doses were administered intramuscularly at 30-minute intervals. During the desensitization period, the injections were well tolerated and caused no adverse reactions. No substantial change in peak expiratory flow rate (PEFR) was noted. For the next 2 successive

days, daily administrations of 150 IU of IVF-M were done uneventfully. Three days after administration of the last dose of IVF-M, the patient underwent the first intrauterine insemination. Another desensitization procedure for IVF-C proceeded 36 hours after administration of the last dose of IVF-M (Table 2). Individual doses were administered every 30 minutes. The desensitization procedure was successfully completed. No major changes in PEFR occurred. Two days later, the second intrauterine insemination was performed. An ultrasound study done at 5 weeks of gestation showed an apparently normal ongoing pregnancy. Her pregnancy resulted in a preterm vaginal delivery after premature rupture of membranes. She and her baby have enjoyed excellent health.

DISCUSSION

Ovulation-induction agents, such as the IVF-M and IVF-C used in our case, are derived from the urine of postmenopausal women. These preparations are relatively impure and contain nongonadotropin proteins, which represent a complex mixture of molecules.⁴ These proteins do not contribute to gonadotropin activities, although some of them are biologically active. Many of these proteins seem to be present to some degree in all conventional urine-derived human gonadotro-

pin preparations, regardless of the specific preparation or lot.

Urine-derived gonadotropins may cause many allergic reactions, which may be ascribed to nongonadotropin proteins.^{1,2,5-7} Phipps et al¹ reported a severe systemic IgE-mediated reaction to urofollitropin, providing evidence for the involvement of nongonadotropin proteins as a direct cause of some adverse reactions from urine-derived human FSH preparations. Li and Hindle⁵ described a woman who experienced local reactions to urine-derived gonadotropin but no reaction to a highly purified human FSH preparation. Redfearn et al⁶ reported a case of delayed-type hypersensitivity to urinary menotropins but no reaction to highly purified human FSH.

Our patient's allergic reactions to urine-derived gonadotropins such as IVF-M and IVF-C were confirmed by intradermal testing to be attributable to an IgE-mediated sensitivity. IVF-M and IVF-C are not irritants because normal control subjects showed no reactivity on skin testing. The allergic reaction may be supported by the fact that a generalized urticarial rash develops after intradermal testing with IVF-C. Further, *in vitro* tests can confirm that nongonadotropin proteins in IVF-M and IVF-C, but not highly purified hMG and hCG or D-mannitol, cause the hypersensitivity reactions. Whether IVF-M has the same nongonadotropin proteins as IVF-C, however, is

Table 1. Acute Desensitization Protocol for IVF-M Immediate Hypersensitivity and Monitoring of PEFR in Study Patient

Dose*	Concentration (IU/mL)	Amount (mL)	Dose (IU)	Cumulative dose (IU)	PEFR (L/min)
Baseline					430
1	0.1	1.25	0.125	0.125	420
2	0.1	2.5	0.25	0.375	410
3	1	0.5	0.5	0.875	400
4	1	1	1	1.875	370
5	1	2	2	3.875	360
6	10	0.4	4	7.875	380
7	10	0.8	8	15.875	360
8	10	1.6	16	31.875	370
9	10	3.2	32	63.875	400
10	100	0.64	64	127.875	410

* Doses were administered intramuscularly every 30 minutes.

Table 2. Acute Desensitization Protocol for IVF-C Immediate Hypersensitivity and Monitoring of PEFR in Study Patient

Dose†	Concentration (IU/mL)	Amount (mL)	Dose (IU)	Cumulative dose (IU)	PEFR (L/min)
Baseline					430
1	1	0.5	0.5	0.5	390
2	1	1	1	1.5	410
3	1	2	2	3.5	430
4	10	0.4	4	7.5	420
5	10	0.8	8	15.5	420
6	10	1.6	16	31.5	400
7	10	3.2	32	63.5	390
8	100	0.64	64	127.5	380
9	100	1.28	128	255.5	390
10	100	2.56	256	511.5	390
11	1,000	0.512	512	1,023.5	400
12	1,000	1.024	1,024	2,047.5	410
13	1,000	2.048	2,048	4,095.5	390

† Doses were administered intramuscularly every 30 minutes.

unclear. Considerable lot-to-lot variation has been noted in some proteins detected in all urine-derived gonadotropin products tested.⁴ Further studies are needed to investigate whether cross-allergenicity exists between nongonadotropin proteins in IVF-M and those in IVF-C. The extracted human urinary gonadotropin preparations may have electrophoretic protein profiles that differ in the amounts and species of proteins present. Most of these preparations contain tumor necrosis factor binding protein I, transferrin, and Ig-related proteins. Some of the products contain, in addition, urokinase, Tamm-Horsfall protein, and epidermal growth factor.⁴ If more sensitive techniques are used, many more proteins may be found in the preparations.

Patients with hypersensitivity reactions to urine-derived gonadotropins have been successfully treated with recombinant human FSH.^{1,2} In situations in which this new product is not available, however, as in our current case, acute desensitization may be useful for the treatment of infertility in patients with ovulatory disturbances. Our patient with IgE-mediated hypersensitivity reactions to urine-derived gonadotropins was

successfully treated with acute desensitization.

Unfortunately, our patient did not undergo skin tests with D-mannitol, a preservative present in both IVF-M and IVF-C preparations. Mannitol is known to cause hyperosmolar-induced release of mediators from mast cells and subsequent anaphylactoid reactions.⁸ In our patient, however, a non-IgE-mediated mechanism related to D-mannitol is unlikely to be responsible for the clinical anaphylaxis. This explanation is supported by our observation that a delayed-type rash developed after the skin test to IVF-C. The late-phase reaction occurring after allergen challenges has been known to be caused by IgE antibodies.⁹ In addition, D-mannitol did not inhibit IgE antibodies in the ELISA inhibition experiments. Further investigations, such as the D-mannitol skin test and an in vitro basophil histamine release test, are needed for confirmation.

To the best of our knowledge, this is the first report of successful desensitization for immediate hypersensitivity to urine-derived gonadotropins. We have documented that acute desensitization to urine-derived gonadotropins allows oocytes to be yielded, which were then inseminated in our patient with secondary infertility. Our experi-

ence suggests that desensitization to these gonadotropins may be done effectively, particularly when an alternative new product is not available.

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REFERENCES

1. Phipps WR, Holden D, Sheehan RK. Use of recombinant human follicle-stimulating hormone for in vitro fertilization-embryo transfer after severe systemic immunoglobulin E-mediated reaction to urofollitropin. *Fertil Steril* 1996;66:148-150.
2. Whitman-Elia GF, Banks K, O'Dea LS. Recombinant follicle-stimulating hormone in a patient hypersensitive to urinary-derived gonadotropins. *Gynecol Endocrinol* 1998;12:209-212.
3. DeSwarte RD, Patterson R. Drug allergy. In: Patterson R, Grammer LC, Greenberger PA, editors. *Allergic Disease*, 5th ed. Philadelphia: Lippincott-Raven, 1997:317-412.
4. Giudice E, Crisci C, Eshkol A, Papoian R. Composition of commercial gonadotrophin preparations extracted from human post-menopausal urine: characterization of non-gonadotrophin

- proteins. Hum Reprod 1994;9:2291–2299.
5. Li TC, Hindle JE. Adverse local reaction to intramuscular injections of urinary-derived gonadotrophins. Hum Reprod 1993;8:1835–1836.
 6. Redfearn A, Hughes EG, O'Connor M, Dolovich J. Delayed-type hypersensitivity to human gonadotropin: case report. Fertil Steril 1995;64:855–856.
 7. Biffoni M, Battaglia A, Borrelli F, et al. Allergenic potential of gonadotrophic preparations in experimental animals: relevance of purity. Hum Reprod 1994;9:1845–1848.
 8. Findlay SR, Kagey-Sobotka A, Lichtenstein LM. In vitro basophil histamine release induced by mannitol in a patient with a mannitol-induced anaphylactoid reaction. J Allergy Clin Immunol 1984;73:578–583.
 9. Dolovich J, Hargreave FE, Chalmers R, et al. Late cutaneous allergic responses in isolated IgE-dependent reactions. J Allergy Clin Immunol 1973;52:38–46.

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