Local reaction to s.c. injections of a recombinant gonadotrophin preparation possibly related to the osmolality of the reconstituted solution

Dear Sir,

We report the case of a 31 year old woman who presented for management of her documented polycystic ovarian syndrome (PCOS). Her body mass index at the time of treatment was 35.9 kg/m². Previously, she had conceived following ovulation induction with urinary gonadotrophins in 1992 and gave birth to a son. She now wished to have another child. Induction of ovulation with clomiphene citrate (Clomid; Hoechst Marion Roussel, Uxbridge, UK), ovarian diathermy and repeat treatment with further clomiphene citrate were unsuccessful.

She underwent ovulation induction with recombinant follicle stimulating hormone (rFSH, Follotropin A; Gonal-F, Serono Laboratories, Welwyn Garden City, UK). This was self-administered after the patient was instructed by the reproductive medicine specialist nurse on the manner in which the drug should be prepared and administered. Initially, the rFSH was given by s.c. injection according to the manufacturer’s instructions: one ampoule of powder (75 IU) for reconstitution diluted with one ampoule (1 ml) of diluent. When the injection was administered in this way the patient complained of severe pain at the injection site, which lasted the duration of the injection and a few s afterwards. However, she observed that when the dose was increased and two ampoules of powder (150 IU) were mixed with 1 ml of diluent, she had no pain. A similar observation was made when one ampoule (75 IU) of powder was diluted with half the ampoule (0.5 ml) of diluent, i.e. no pain was experienced.

Subsequently, two other patients have complained of similar pain at the injection site with rFSH when only one ampoule (75 IU) of the preparation was mixed in 1 ml of diluent. Again, this was alleviated when the volume of diluent was reduced.

Recombinant FSH is synthesized in vitro by cells into which genes encoding for FSH subunits have been inserted. This preparation is physiologically similar to native human FSH. These preparations lack contamination by proteins, which in the urinary extracts are uncontrolled, mostly unidentified and may account for 95–98% of the total protein. One of the clinical advantages of the new rFSH preparation is that they can be given s.c., are pain free and can be self-administered by the patients.

There are cases of severe local reactions to crude urinary extracts (Li et al., 1993). These reactions did not occur when the highly purified FSH preparation was administered. One of the mechanisms which has been proposed to account for this is that some urinary proteins are biologically active, acting as an antigenic stimulus which provoke an immune response (Dore et al., 1994) yet this would not be applicable with the recombinant preparations.

In this case, the pain observed with rFSH must be due to another mechanism. With more concentrated solutions, i.e. more than one ampoule reconstituted in 1 ml of diluent, the pain occurs less regularly. Conversely, more dilute solutions may provoke pain in some patients. We propose that the pain is related to the osmolality (concentration) of the solution injected. If experienced by the patient, we recommend that pain may be alleviated by reducing the osmolality of the solution with a reduction in the volume of diluent needed. This is in accordance with manufacturer’s instructions.

References

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