

## THE USE OF LONG-ACTING RECOMBINANT FOLLICLE-STIMULATION HORMONE FOR CONTROLLED OVARIAN STIMULATION

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Exogenous FSH preparations have relatively short half life which necessitate daily dosing when used to stimulate ovarian follicle development. In order to reduce the frequency of injections necessary during ovarian stimulation for IVF, number of technologic approaches have been used to develop longer-acting FSH molecules. For instance, it has been suggested that the  $t_{1/2}$  of FSH may be extended by glycosylation which would reduce glomerular filtration by increasing the molecular weight and charge of the molecule. Another approach was that described by Boime and co-workers, who attached the CTP of the hCG  $\beta$ -subunit to the FSH  $\beta$ -subunit using site-directed mutagenesis and gene transfer techniques. They constructed a chimeric gene containing the sequence encoding the CTP of the hCG  $\beta$ -subunit fused to the translated sequence of the human FSH  $\beta$ -subunit. The FSH  $\beta$ -CTP chimera was then transfected with the common glycoprotein  $\alpha$ -subunit and expressed in Chinese hamster ovary (CHO) cells.

Subsequent studies demonstrated a near 10-fold increase in biopotency for the chimeric molecule compared with wild-type FSH. Other longer-acting FSH molecules have been generated by adding sequences containing potential glycosylation sites at the N-terminus of the FSH  $\alpha$ -subunit. However, the former approach has led to the development of Corifollitropin alfa; a new gonadotrophin preparation currently in development for the stimulation of multi-follicular development in women undergoing ovarian stimulation for IVF or ICSI. Corifollitropin alfa interacts only with the FSH-receptor, but has a longer  $t_{1/2}$  and an extended time-interval ( $t_{max}$ ) to peak serum levels ( $C_{max}$ ).

In phase II trials, a single dose of corifollitropin alfa was able to induce and sustain multi-follicular growth during the first week of stimulation. Corifollitropin alfa has the same pharmacological activity as pure FSH preparations. However, a single dose of corifollitropin alfa is able to keep circulating FSH activity above the threshold necessary to support multi-follicular growth for an entire week. As such, one injection of corifollitropin alfa replaces the first seven daily injections of rFSH. Thereafter, stimulation may be continued with daily FSH injections until the criteria for final oocyte maturation have been reached. In the context of improving treatment simplicity and reducing the burden of IVF treatment, corifollitropin alfa has been developed in combination with GnRH antagonist co-treatment.

As described in a recent review (Fauser et al, Hum Rep Update 2009), corifollitropin alfa has been tested in over 400 women in phase I and II clinical trials, in doses ranging from 7.5 to 240  $\mu$ g. Two phase II studies of corifollitropin alfa have been conducted in patients undergoing ovarian stimulation for IVF or ICSI using single doses of 120–240  $\mu$ g and of 60–180  $\mu$ g (See Fauser et al 2009 for review).

Although the possible role of long acting FSH in the treatment of anovulatory infertility by ovulation induction has been investigated in pilot studies, initial data suggest that the response is highly variable and therefore not suitable when the therapeutic window is small, as is the case when mono-follicular development is the aim.

Injection of corifollitropin alfa in the early follicular phase of the menstrual cycle results in the ongoing stimulation of the recruited cohort of antral follicles, rendering it a suitable alternative to FSH for the stimulation of multi-follicular growth for IVF. Indeed, the pharmacokinetic profile of long acting FSH such as corifollitropin alfa mimics that associated with giving a high starting dose of FSH followed by a step-down regimen.

Around 5 years ago, we reported the first case of a pregnancy and live birth following corifollitropin alfa administration in IVF. Dose finding studies comparing dosages of 120, 180 and 240  $\mu$ g corifollitropin alfa revealed no significant dose–response relationship either in terms of the total dose of FSH required from Day 8 onwards or in the number of oocytes retrieved. While this indicated that the lowest effective dose might be even lower, it also confirmed that a single injection of corifollitropin alfa could induce and sustain multi-follicular development for a week and thus could replace the first seven injections of daily FSH. With a half-life was 60–75 h FSH-CTP levels may decline below the threshold after a few days, causing FSH-sensitive follicles to cease development and become atretic. This has been shown to be prevented by administration of daily recFSH injections at the appropriate juncture.

Recently, a large multicentre trial compared FSH-CTP 150 mcg to 200 IU rec FSH (follitropin beta). 1500 patients were randomized to receive either corifollitropin alfa 150 mcg or a daily dose of 200 IU recombinant FSH, followed by recombinant FSH (maximum 200 IU/day) from stimulation day 8 onward. The ongoing pregnancy rate obtained in each group was the same (38 vs 39%), and the number of oocytes retrieved was not significantly different. These data confirm the efficacy of this long acting FSH preparation, which represents an important step forward in rendering stimulation regimens more patient friendly.

What about the safety of long acting FSH preparations? Their longer half life and activity could increase the risk of developing OHSS as a result of extended stimulation of the development of multiple follicles. Once the initial corifollitropin alfa dose has been given, it is not possible—as in daily injections—to reduce the dose in case signs of ovarian stimulation are observed during the mid-follicular phase. One week after the initial injection, daily FSH doses can be either reduced or withheld. In a dose finding study, signs and symptoms of OHSS were reported in 15 out of 307 patients treated for IVF or ICSI with 60–240  $\mu$ g corifollitropin alfa, 6 of whom (2%) required hospitalization. This was similar to the incidence of OHSS reported in the rFSH group.

As the trend to more patient friendly and milder stimulation protocols continues, there would appear to be an important place for long acting FSH in the IVF protocols of the future. Recent studies have demonstrated the efficacy and safety of this novel preparation.

Further reading:

B.C.J.M. Fauser, B.M.J.L. Mannaerts, P. Devroey, A. Leader, I. Boime and D.T. Baird. Advances in recombinant DNA technology: corifollitropin alfa, a hybrid molecule with sustained follicle-stimulating activity and reduced injection frequency. Hum Reprod Update 2009 Jan 30. [Epub ahead of print].

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