Article

Use of a fully automated injector for self-administration of follitropin α in an IVF/ICSI programme

Ermanno Greco is the scientific director at the European Hospital Reproductive Medicine Unit in Rome, Italy. He graduated from the Medical School of the University of Rome in 1982. He became Researcher in Andrology at the University of Rome in 1985 and then Professor in Andrology there. Subsequently he has also been appointed Professor in Andrology at the University of Pisa. His current areas of interest include male infertility, azoospermia treatment, sperm DNA fragmentation, impotence and drug delivery devices.

Dr Ermanno Greco

E Greco[1], P Polonio-Balbi[1], S Ferrero[1], E Baroni[1], F Ubaldi[1], L Rienzi[1], J Tesarik[2,3]
[1]Centre for Reproductive Medicine, European Hospital, Via Portuense 700, 00149 Rome, Italy; [2]MAR and Gen, Molecular Assisted Reproduction and Genetics, Gracia 36, 18002 Granada, Spain
[3]Correspondence: Fax: +34 958 089909; e-mail: cmendoza@ugr.es

Abstract

Recombinant FSH (r-FSH) used for ovarian stimulation can currently be self-administered either by a conventional syringe or by a pen device. This randomized controlled trial compares the efficacy and convenience of a new, more sophisticated and fully automated injection device (Softinject™) with the conventional syringe for r-FSH self-administration. A total of 300 women needing ovarian stimulation for IVF/intracytoplasmic sperm injection were randomized to the automated injector or the conventional syringe group. Patients of both groups had ovarian stimulation with follitropin α after pituitary desensitization with a gonadotrophin-releasing hormone agonist. State anxiety score, overall pain score and pregnancy rate were chosen as the main outcome measures. Patients in the automated injector group showed lower state anxiety ($P < 0.01$) and overall pain ($P < 0.01$) scores and a comparable pregnancy rate per started cycle as compared with the conventional syringe group. They needed lower doses of r-FSH ($P < 0.05$) and their stimulation was shorter ($P < 0.05$). It is concluded that the use of a fully automated injector for r-FSH self-administration reduces pain and stress as compared with the conventional syringe. This device can be used for any subcutaneously administered drug employed in ovarian stimulation.

Keywords: *anxiety, automated injector, follitropin α, ovarian stimulation, pregnancy rate, recombinant FSH, self-administration*

Introduction

Until recently, pharmaceutical presentation of FSH preparations used for ovarian stimulation was a freeze-dried lyosphere which had to be dissolved before administration. The advent of recombinant human FSH (r-FSH) available as a ready-to-use solution was accompanied by the development of a new presentation of both commercially available r-FSH preparations (follitropin α and follitropin β), which are now available not only in vials but also in cartridges for administration with a pen device. Several studies have suggested that the use of a pen device enables easier, safer, less painful and more convenient r-FSH self-administration than the conventional syringe, although no improvement in success rates has been reported (Craenmehr *et al*., 2001; Platteau *et al*., 2003). In a previous study, 100% of subjects using a preloaded pen device for r-FSH self-administration rated the overall experience of self-administering as 'very good' to 'good' (Kettel *et al*., 2004). However, this device does not eliminate the manual needle insertion. It has been shown previously that non-compliance in children receiving chronic growth hormone treatment can be alleviated by automatic needle insertion (Main *et al*., 1995), and an automated self-injection system has been shown to decrease the drop-out rate in impotent males undergoing intracavernous vasoactive pharmacotherapy (Montorsi *et al*., 1993). This study was undertaken to evaluate the efficacy and convenience of a fully automated (including automatic needle insertion) injector for r-FSH self administration as compared with the conventional syringe.

Materials and methods

Participants

This study involved 300 women treated by IVF/intracytoplasmic sperm injection (ICSI) at the Centre for Reproductive Medicine of the European Hospital in Rome from May 2000 to February 2003. Inclusion criteria were age <36 years, willingness to self-inject r-FSH medication, body mass index between 18 and 29 kg/m^2, presence of both ovaries, basal FSH concentrations <12 IU/l, and the absence of polycystic ovaries and pelvic endometriosis detectable by ultrasound.

Sample-size calculation was based on the same considerations as those previously published in a study comparing a pen device with conventional syringe, and involving patients with similar demographic and clinical characteristics (Platteau *et al.*, 2003). Accordingly, 200 infertile women (100 in each group) for whom conventional IVF or ICSI was indicated and who fulfilled the inclusion criteria (see above) were initially enrolled. When the study was in progress, it was decided to add an additional 50 women in each group in order to confirm the observed trend towards a higher pregnancy rate in the fully automated injector group.

Study design

All patients were programmed for a long protocol of pituitary down-regulation with a gonadotrophin-releasing hormone (GnRH) agonist before the beginning of ovarian stimulation with r-FSH. Before the beginning of GnRH agonist administration, the patients were randomized by using a computer-generated randomization list to self-inject r-FSH either with a fully automated injector or with a conventional syringe.

Description of the fully automated injector

The Softinject™ (Androsystems, Rome, Italy) (**Figure 1**) is a fully automated injector which can be pre-loaded with a conventional 1-ml insulin syringe (B-D Plastipak) in advance. This makes it possible to keep the protective cap of the needle in place while loading. The syringe can be easily pre-filled at the prescribed dosage. A safety catch prevents the injector from accidental discharge.

The distance of needle penetration can be adjusted by turning a special cylinder at the tip of the injector, so adapting the depth of injection to the local thickness of subcutaneous tissue. Immediately before injection, the protective cap is removed without opening the device, while the needle is retained inside the device and thus remains hidden. This makes it possible to avoid the rather common 'needle-phobia'.

Unlike other injectors used to administer r-FSH up to date, the Softinject™ is capable of operating needle penetration to subcutaneous tissue and drug discharge at the same time and in a fully automated way. This action is triggered by simply pushing the trigger button after releasing the safety catch. Through a small window on the side of the device, the completeness of drug discharge can be controlled before removing the needle from the skin.

Ovarian stimulation and assisted reproduction techniques

Ovarian stimulation was performed as described (Greco *et al.*, 2005). Briefly, pituitary activity was down-regulated by subcutaneous administration of a GnRH agonist (Suprefact; Hoechst, Milan, Italy) administered twice daily. Once down-regulation was achieved, as shown by vaginal bleeding and serum oestradiol concentrations <45 pg/ml ovarian stimulation was started. Daily injections of follitropin α (Gonal F; Serono Rome, Italy) were self-administered with the use of either the fully automated injector or a conventional syringe according to the study design. The starting dose of follitropin α was chosen individually and adapted during the stimulation according to changes in serum oestradiol concentration and the number and size of ovarian follicles determined by vaginal ultrasound.

Oocyte recovery, ICSI, and embryo culture and uterine transfer were performed as described previously (Greco *et al.*, 2005). Two or three embryos were transferred at a time. All embryo transfers were performed 3 days after IVF/ICSI.

Primary and secondary outcome measures

Primary outcome measures were state anxiety score, overall pain score, and pregnancy rate. State anxiety score, together with trait anxiety score, was determined with the use of a State and Trait Anxiety Inventory (STAI) questionnaire (Spielberger *et al.*, 1970) as described (Sanders and Bruce, 1999). To evaluate overall pain related to self-injection patients were asked to rate on a visual analogue scale (VAS) a score ranging from 0 (no pain, very convenient) to 10 (severe pain, not convenient). Pregnancy rate was calculated from the number of patients who had embryo transfer.

Secondary outcome measures were the total dose of r-FSH, the duration of stimulation and the number of oocytes retrieved. For continuous parameters values indicated in the text are means ± SD.

Statistics

Differences between groups were assessed by two-tailed chi-squared test with Yates' correction or Fisher's exact test for categorical variables, and by Mann–Whitney *U*-test for continuous variables.

Results

Study population and patient flow through the randomized study

A total of 300 patients were randomly allocated to the automated injector or to the conventional syringe group

(**Figure 2**). Both groups were comparable with respect to the patients' demographic characteristics (**Table 1**). The contribution of different causes of infertility was also similar in both groups, male factor being the most frequent cause (**Table 1**). The proportion of patients in whom ICSI was indicated in the fully automated injector and the conventional syringe group was 85 and 84% respectively (**Table 1**). All of the subjects who were randomized achieved pituitary down-regulation and started r-FSH administration. Out of the 148 patients enrolled to the fully automated injector group, no patient stopped treatment before ovarian puncture for oocyte recovery. In the conventional syringe group, in which 152 patients were enrolled, six patients stopped treatment before ovarian puncture (**Figure 2**). All of the remaining patients had embryo transfer. One patient in each group was lost from analysis after embryo transfer. The remaining patients were followed until the pregnancy test (**Figure 2**).

Pain and anxiety

Pain at the injection site was limited to the first minutes after injection in both the fully automated injector and the conventional syringe group. When subjectively rated by the patients by VAS score, the pain perception was significantly lower in the fully automated injector group than in the conventional syringe group (1.1 ± 0.6 versus 3.5 ± 1.4; $P < 0.01$).

Trait anxiety scores did not differ between patients of the fully automated injector and the conventional syringe groups (37.0 ± 6.4 versus 36.5 ± 6.3). However, state anxiety score, determined during r-FSH treatment, was significantly lower in the fully automated injector group than in the conventional syringe group (37.3 ± 7.1 versus 44.8 ± 7.6; $P < 0.01$).

Clinical efficacy

No difference in serum LH, oestradiol and progesterone concentration, number of oocytes retrieved and fertilization rate was found between the fully automated and the conventional syringe group at the outset of r-FSH treatment (**Table 2**). However, patients in the fully automated injector group showed a slightly but significantly reduced total r-FSH dose and the duration of stimulation as compared with the conventional syringe group ($P < 0.05$; **Table 2**). The number of embryos and pregnancy rate per embryo transfer were comparable in both groups (**Table 2**).

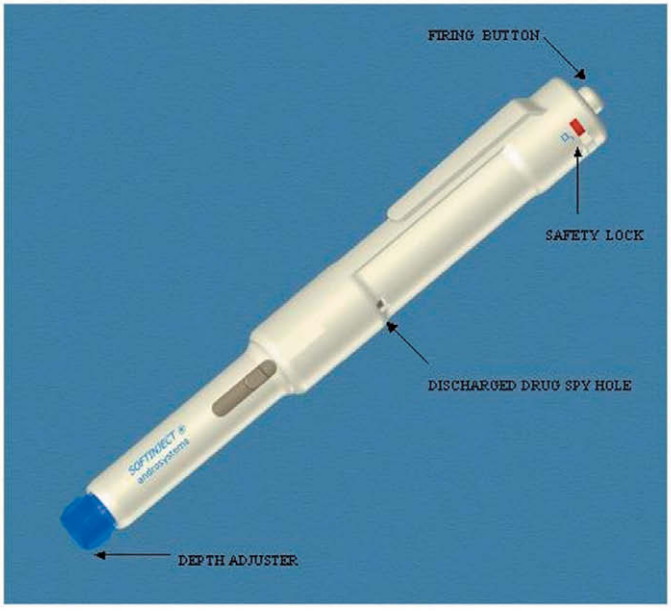

Figure 1. Softinject™ fully automated injection device.

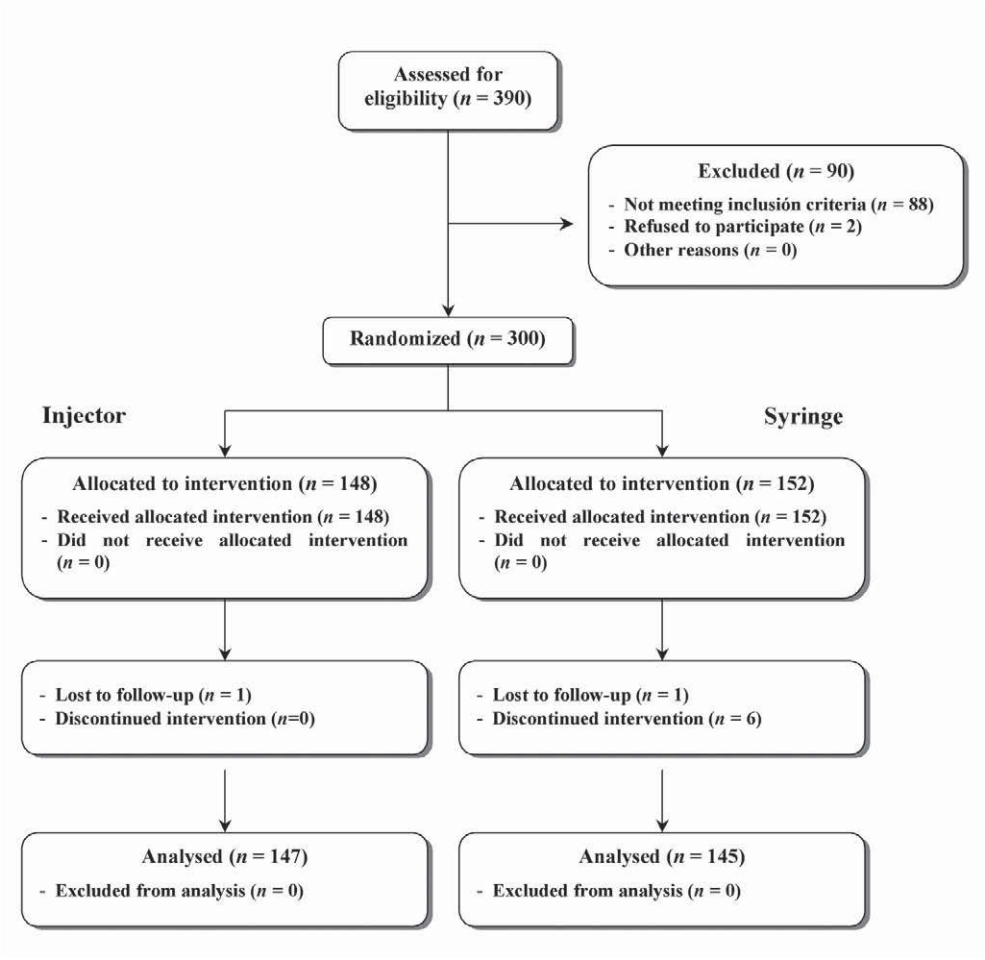

Figure 2. Flow chart of participants through each stage of the randomized trial.

Table 1. Patients' demographics and infertility baseline characteristics (continuous values are means ± SD).

	Fully automated injector	*Conventional syringe*
Age (years)	30.5 ± 3.9	30.9 ± 3.6
Body mass index (kg/m^2)	22.2 ± 1.7	22.3 ± 1.8
Duration of infertility (years)	4.3 ± 2.5	4.4 ± 2.5
Subjects with primary infertility (%)	54	56
Main cause of infertility (%)		
Male	68	70
Tubal	13	11
Unexplained	15	14
Other	4	5
Cases treated by ICSI (%)	85	84

ICSI = intracytoplasmic sperm injection.

Table 2. Efficacy parameters and clinical outcomes.

	Fully automated injector	*Conventional syringe*
Serum concentrations at outset of stimulation		
LH (IU/l)	2.5 ± 1.3	2.8 ± 1.4
Oestradiol (pg/ml)	30.5 ± 4.0	31.3 ± 3.5
Progesterone (ng/ml)	0.73 ± 0.19	0.78 ± 0.26
Total r-FSH dose (IU)	1902 ± 641[a]	2238 ± 769
Duration of stimulation (days)	11.2 ± 3.4[a]	12.4 ± 2.7
No. oocytes retrieved	15.6 ± 9.5	13.5 ± 8.9
Fertilization rate (%)	68.5	67.8
Pregnancy rate (%)	44.8	40.2

[a]Significantly different from the conventional syringe group ($P < 0.05$). r = recombinant.

Discussion

This study clearly demonstrates that the use of a fully automated injector for r-FSH self-administration during ovarian stimulation for IVF/intracytoplasmic sperm injection (ICSI) reduces pain and patient discomfort as compared with the conventional syringe. Moreover, with the use of the automated injector, the total r-FSH dose required for adequate follicular development was lower and the duration of stimulation was shorter than with the use of the syringe. Similar improvements have also been reported with the use of a semi-automated pen device instead of the conventional syringe for r-FSH self-administration (Craenmehr *et al*., 2001; Platteau *et al*., 2003). The reduction of r-FSH dose and the shortening of stimulation duration with the pen device can be explained by a better economy of drug administration because of a finer dose adjustment and the avoidance of losses owing to void volumes which are common with the use of the conventional syringe (Platteau *et al*., 2003). The reduction in pain and discomfort when using a pen device instead of the syringe is attributable to the smaller needle size and injected volume (Craenmehr *et al*., 2001). With respect to these qualities, the fully automated injector evaluated in this study is similar to the previously used pen devices, and the observed improvement in tolerance and drug economy as compared with the syringe is thus not surprising.

However, unlike previous studies testing the pen device, the present study also shows an improvement in state anxiety and overall pain scores in the fully automated injector group as compared with the conventional syringe group. Previous studies have shown that anxiety and depression are common reactions during IVF (Eugster and Vingerhoets, 1999) and that stress and anxiety can influence treatment outcomes (Csemiczky *et al*., 2000; Klonoff-Cohen *et al*., 2001), although other studies failed to confirm a similar relationship (Boivin and Takefman, 1995; Slade *et al*., 1997). In the present study, it is shown clearly that in addition to experiencing less pain, patients using the fully automated injector for r-FSH self-administration also have lower state anxiety during the treatment as compared with those using the conventional syringe. This observation can be explained by the fully automated mode of r-FSH delivery with the injector, which does not require patient's action or attention for either the insertion of the needle to the subcutaneous tissue or drug expulsion at the injection site. Together with the fact that the needle of the device remains completely hidden throughout the procedure, thus avoiding any kind of 'needle-phobia', these features make the use of the fully automated injector maximally easy and patient-friendly. Further study is needed to determine whether the use of the fully automated injector has a beneficial effect on the drop-out rate.

Even though the fully automated injector was only tested for r-FSH administration in this study, the versatility of this device and the ease of filling its cartridge with differently conditioned drugs make it a suitable tool for other subcutaneous administrations related to IVF/ICSI protocols also. This is particularly so for daily injections of GnRH agonists or antagonists. However, if compared with ready-to-use, preloaded pen devices, such as that commercially available for Gonal-F, the workload to use the non-preloaded injector, described in this study, may be slightly higher. A study is under way, to compare the fully automated injector with a semi-automated, preloaded pen device.

In conclusion, this is the first study evaluating a fully automated injector for r-FSH self-administration. It is shown that the use of the injector reduced pain and anxiety in an IVF/ICSI programme as compared with the conventional syringe. A larger scale evaluation of the fully automated injector in assisted reproduction, including the use for GnRH agonist and antagonist administration, is warranted.

References

Boivin J, Takefman J 1995 Stress level across stages of in vitro fertilization in subsequently pregnant and nonpregnant women. *Fertility and Sterility* **64**, 802–810.

Craenmehr E, Bontje PM, Hoomans E *et al*. 2001 Follitropin-α administered by pen device has superior local tolerance compared with follitropin-α administered by conventional syringe. *Reproductive BioMedicine Online* **3**, 185–189.

Csemiczky G, Landgren BM, Collins A 2000 The influence of stress and state anxiety on the outcome of IVF treatment: psychological and endocrinological assessment of Swedish women entering IVF-treatment. *Acta Obstetrica et Gynecologica Scandinavica* **79**, 113–118.

Eugster A, Vingerhoets AJ 1999 Psychological aspects of in vitro fertilization: a review. *Society for Science and Medicine* **48**, 575–589.

Greco E, Scarselli F, Iacobelli M *et al*. 2005 Efficient treatment of infertility due to sperm DNA damage by ICSI with testicular spermatozoa. *Human Reproduction* **20**, 226–230.

Kettel LM, Scholl G, Bonaventura L *et al*. 2004 Evaluation of a pen device for self-administration of recombinant human FSH in clomiphene citrate-resistant anovulatory women undergoing ovulation induction. *Reproductive BioMedicine Online* **9**, 373–380.

Klonoff-Cohen H, Chu E, Natarajan L, Sieber W 2001 A prospective study of stress among women undergoing in vitro fertilization of gamete intrafallopian transfer. *Fertility and Sterility* **76**, 675–687.

Main KM, Jorgensen JT, Hertel NT *et al*. 1995 Automatic needle insertion diminishes pain during growth hormone injection. *Acta Paediatrica* **84**, 331–334.

Montorsi F, Guazzoni G, Bergamaschi F *et al*. 1993 Intracavernous vasoactive pharmacotherapy: the impact of a self-injection device. *Journal of Urology* **150**, 1829–1832.

Platteau P, Laurent E, Albano C *et al*. 2003 An open, randomized single-centre study to compare the efficacy and convenience of follitropin administered by a pen device with follitropin administered by a conventional syringe in women undergoing ovarian stimulation for IVF/ICSI. *Human Reproduction* **18**, 1200–1204.

Sanders KA, Bruce NW 1999 Psychosocial stress and treatment outcome following assisted reproductive technology. *Human Reproduction* **14**, 1656–1662.

Slade P, Emery J, Lieberman BA 1997 A prospective, longitudinal study of emotions and relationship in in-vitro fertilization treatment. *Human Reproduction* **12**, 183–190.

Spielberger CD, Gorsuch RL, Lushene RE 1970 *STAI Manual for the State–Trait Anxiety Inventory (Self-evaluation Questionnaire)*. Consulting Psychologists Press, Palo Alto, USA.

Received 22 April 2005; refereed 5 May 2005; accepted 13 July 2005.