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Original article

Comfort, ease of use and practicality of the pen injector for follitropin α for assisted reproduction: an observational post-marketing study in Egypt

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Abstract

Objective:
We evaluated the ease of use of a pen injector for follitropin α (recombinant human follicle-stimulating hormone [r-hFSH]) during assisted reproduction technologies (ARTs) in Egypt.

Methods:
One hundred women undergoing ART completed a questionnaire in a non-interventional, observational study. The primary endpoint was patients' rating of the comfort associated with the injector. The main limitations of the study were the design and lack of knowledge regarding any impact of failure of ART on perceptions of treatment for a minority of patients.

Results:
Patients rated the follitropin α pen injector as 'very comfortable' (61%), 'comfortable' (29%), or 'somewhat comfortable' (10%). Understanding instructions and using it were 'very easy' or 'easy' for 97–99%; 94% reported 'no' or 'minimal' difficulty with injections, 83% were 'very confident' about altering doses, 77% reported no interference with normal daily activities and 94% reported 'no' or 'minimal' stress using the device. Women with previous experience of ART rated the device as more practical than their previous injection system. Overall, 96% were 'very satisfied' or 'satisfied' with the device and 99% would recommend its use to others. Pregnancy rates were consistent with previous clinical experience. Injection site reactions occurred in 10% (all of mild severity except one moderate event).

Conclusions:
Positive perceptions of the follitropin α pen injector identify this device as suitable for use for Middle Eastern women undergoing ART.

Introduction

Administration of follicle-stimulating hormone (FSH) is performed to induce multiple follicular development concomitant to GnRH analogue administration to prevent luteinising hormone (LH) surges within assisted reproduction technology (ART) protocols, such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI)[1]. Follitropin α is a commercial preparation of r-hFSH used to induce multi-follicular development in ART[2,3]. Formerly, this preparation of FSH was supplied as lyophilized powder in glass vials, to be reconstituted by the patient and injected using a syringe[2], while a newer formulation provides the product in liquid form in three dosage strengths in a pre-filled injection pen which dispenses doses with a high degree of accuracy[3,4]. We

evaluated the ease of use of the injector pen for follitropin α in the usual care setting in women undergoing IVF or ICSI in Egypt.

Patients and methods

Study design and objectives

This was a non-interventional, observational, post-marketing (Phase IV) study (EMR 700623-525) conducted between December 2010 and October 2011. The principal objective was to investigate the ease of use of a follitropin α pen injector device (Gonal-F, Merck Serono) in women undergoing follicular stimulation within an ART protocol conducted in the routine care setting, and to assess the efficacy of this treatment when used in conjunction with a gonadotrophin releasing hormone antagonist (cetrorelix) to promote recruitment and development of follicles.

Patients

Eligible patients were pre-menopausal women (18–39 years), with FSH <10 IU/mL on the second day of the menstrual cycle, with a clinical indication for controlled ovarian hyperstimulation (COS) with FSH for IVF or ICSI. Principal exclusion criteria were pregnancy; lactation; known allergy to any component of study treatment; enlarged ovaries or cysts unrelated to polycystic ovary syndrome; gynecological bleeding of unknown origin; cancer of the ovary, uterus, breast, hypothalamus or the pituitary gland; and hyperprolactinemia.

Study procedures

A blood sample was drawn on the second day of a spontaneous menstrual cycle for assessment of the basal FSH level. A pregnancy test was performed within 1 week prior to the start of follitropin α treatment, to rule out pre-existing pregnancy (see exclusion criteria, above). All treatment was conducted according to the standard practice of the investigators. Patients began self-injection of follitropin α subcutaneously at a dose of 150–375 IU/day, having received education on injection techniques from physicians and/or nurses. Each patient's response to COS was determined by transvaginal ultrasound scan and/or serum estradiol levels. After 5 days of COS, the dose of follitropin α was adjusted according to the results of the patient assessment. Follicular development was monitored until investigators' criteria for maturity were met (typically at least two follicles >14 mm and one follicle >17 mm), at which time the subject received human chorionic gonadotrophin (hCG) to induce final oocyte maturation. Oocytes were recovered by ultrasound-guided aspiration. Fertilization and embryo transfer were also carried out according to local practice. Cetrorelix 0.25 mg (Cetrotide, Merck Serono) was administered subcutaneously once daily, alternately on each side of the abdomen according to investigators' standard practice until follicles were recruited and developed (no dose adjustment was permitted).

Study endpoints

The primary endpoint was the comfort associated with use of the follitropin α pen injection device, measured using a questionnaire administered by physicians either on the day of administration of hCG or at the final study visit for patients for whom the cycle was cancelled without receipt of hCG (see Results). The questionnaire was in Arabic, translated from the original English version by a certified medical translator in Egypt.

Secondary endpoints were other aspects of ease of use; total dose of r-hFSH; the number of days of COS; adverse events (AE), including ovarian hyperstimulation syndrome (OHSS); rate of premature LH rise with the GnRH antagonist protocol; the number and size of follicles on the day of administration of hCG, the total number of oocytes retrieved; the cycle cancellation rate and the pregnancy rate.

An AE was any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerged or worsened relative to the initial study visit, regardless of causal relationship. A serious AE was any AE that resulted in death, was life-threatening, required or prolonged subject hospitalization, was a congenital anomaly or birth defect, resulted in persistent or significant disability or incapacity, or was a medically important condition.

The interpretation of endpoints was based on clinical factors alone and thus no formal power calculations were carried out (approximately 100 subjects were considered sufficient to explore the study end points). Data were analyzed using descriptive statistics (means and SD, except where stated) and without statistical testing. Rates of cancellation of cycles, pregnancy rate and safety/tolerability outcomes were analyzed according to an intention-to-treat analysis in all subjects.

Ethics

This study was performed in accordance with the Declaration of Helsinki, the requirements of Good Clinical Practice, and all applicable regulatory requirements. The study protocol was approved before initiation of the study by local Ethics Committees at the two participating centers (Cairo University, Egypt, and Ain Shams University, Egypt). All subjects gave written, informed consent before participating in the study.

Table 1. Patients at baseline.

Age, y	29.7 (4.2)
Body mass index, kg/m^2	30.6 (5.6)
Caucasian, %	98
Primary/secondary infertility, %/%	66/34
Duration of infertility, y	5.2 (3.4)
Type of infertility, %	
Female and male infertility	12
Female infertility only	32
Male infertility only	39
Unexplained	17
Cause of female infertility, %[a]	
Tubal factor	24
Endometriosis	1
Ovulatory dysfunction	22
Other	55
No. previous pregnancies/live births, %/%	
0	68/92
1	17/6
2	10/2
≥2	5/0

Means (SD) unless stated.
[a]More than one response allowed.

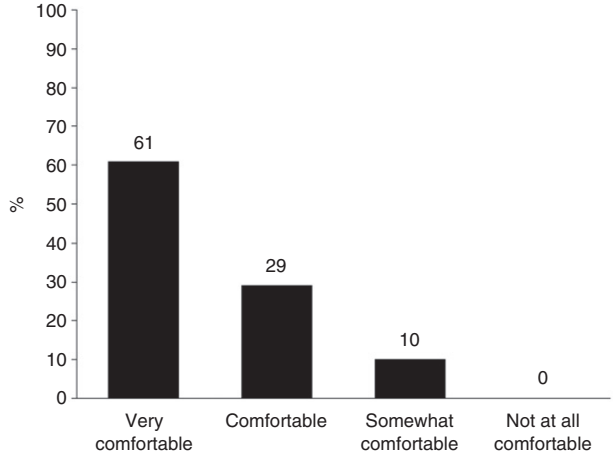

Figure 1. Primary endpoint: overall comfort of using the follitropin α pen injector. Subjects were asked 'Overall, how would you rate the comfort of the follitropin α pen?' (NB: the trade name for the preparation was used in the questionnaire, see Patients and methods).

Results

Patients

Of 100 patients enrolled, 99 filled in the questionnaire and 90 completed the study. Reasons for discontinuation were cancellation of the cycle (no hCG injection for 8 patients [8%] and protocol violation for 2 patients [2%]). No oocytes were retrieved for a further 3 patients (3%) and no sperm was collected for 2 patients (2%); these 5 patients received hCG and are counted among the cohort who completed the study protocol. Almost all patients were Caucasian, and 66% had primary infertility (Table 1). Levels of hormones at baseline were: median LH 4.5 IU/mL (interquartile range [IQR] 0.96, 12.2); mean FSH 6.23 mIU/mL (SD 1.75); mean prolactin 12.41 ng/mL (SD 4.80); median estrogen 44.6 pg/mL (IQR 18.60, 127.80); and median progesterone 0.77 ng/mL (IQR 0.10, 15.0).

All but one patient (99%) had a normal gynecological examination. The population was generally healthy with one case each of hypertension, diabetes and mitral valve disease. Five abnormal uterine ultrasound scans were reported: four fibroids, and one retroversion–flexion (RVF) uterus.

About half of the study population (51.5%) had previous experience of self-injection during ART treatment. Of these, 56.8% had used a pen injector, with the remaining subjects using a syringe. The majority (68.9%) self-administered injections, with 11.3% given injections by a partner or other non-medical person, and 19.8% receiving injections from a healthcare professional.

Ease of use of the injection pen

Figure 1 shows the findings for the primary endpoint of the study, the overall comfort of using the pen injector. The majority of patients (61%) found the device 'very comfortable' to use, and no patient reported that it was 'not at all comfortable'.

In addition, patients found the device easy to use (Table 2), with regard to understanding the instructions, learning to use it, and the ease of administration of r-hFSH (only 2–4% found these aspects of the injector 'somewhat' or 'moderately' difficult). Accordingly, 99% found the device 'easy' or 'very easy' to use, and a large majority (95%) felt 'very' or 'somewhat' confident in changing their daily dose of r-hFSH. More than half of the patients (56%) used the device in less than 15 seconds, and the majority (83%) required less than 30 seconds for the injection.

The majority of patients (97%) rated the device as 'practical' or 'very practical to use', with little impact on daily life (25% reported any degree of interference with normal daily activities), and 94% reported 'no' or 'minimal' stress associated with its use (Table 3 shows responses to questions concerned with the practicality of the device). The ease of reading doses and administering drug were the aspects of practicability most often cited. All patients who indicated that they had used a different injection system during a previous experience of ART rated the current injection pen as being more practical than their previous injection system. Rates of satisfaction with the follitropin α injector pen were also high (Table 4), with 95% 'satisfied' or 'very satisfied' with the device. Almost all (99%) would recommend the device to another woman undergoing ART.

Table 2. Questionnaire items relating to the ease of use of the injector pen.

Questions	%
Were the instructions for administering follitropin α pen easy to understand? ($n=99$)	
Very easy	73 (73.7)
Easy	26 (26.3)
Somewhat difficult	0 (0.0)
Very difficult	0 (0.0)
Altogether, how would you rate the ease of learning to use follitropin α pen? ($n=98$)	
Very easy	66 (67.4)
Easy	30 (30.6)
Somewhat difficult	2 (2.0)
Very difficult	0 (0.0)
Altogether, did you find that follitropin α pen enabled you to inject yourself with... ($n=98$)	
No difficulty	75 (76.5)
Minimal difficulty	17 (17.4)
Moderate difficulty	4 (4.1)
Great difficulty	2 (2.0)
Altogether, how would you rate the ease of using follitropin α pen? ($n=98$)	
Very easy	67 (67.4)
Easy	30 (30.6)
Somewhat difficult	1 (1.0)
Very difficult	0 (0.0)
How confident did you feel about accurately changing your daily dose using follitropin α pen? ($n=40$ [a])	
Very confident	33 (82.5)
Somewhat confident	5 (12.5)
Not confident	2 (5.0)
On average, how much time did it take to perform the follitropin α pen?	
<15 seconds	55 (55.7)
15 to 30 seconds	28 (28.3)
1 to 2 minutes	14 (14.1)
>2 minutes	2 (2.0)

[a]Responses of 40/62 women who women changed their follitropin α dose during the study; '*n*' in this and later tables refers to numbers answering individual questions. The questionnaire completed by patients used the trade name for the follitropin α preparation (see Patients and methods).

Secondary endpoints

Endpoints relating to the delivery of ART and to pregnancy outcomes are shown in Table 5. The total dose of r-hFSH administered ranged from 675–5625 IU, and treatment duration was between 3 and 16 days. Premature LH rise was uncommon, and the majority of follicles were at least 14 mm in diameter. On average, about 10 oocytes per patient were retrieved (range 0–32). There were 33 pregnancies, according to a β-hCG test, and 29 of these women received an ultrasound scan. The scan confirmed that most were carrying a single fetus, with three sets of twins and one of triplets. There was no significant difference (*t*-test) in the total r-hFSH dose between women with a clinical pregnancy (2461 IU [SD 883]), compared with non-pregnant women (2762 IU [SD 937]).

Table 3. Questionnaire items relating to the practicality of the injector pen and its impact on daily life.

Questions	%
In your current treatment cycle, did the use of follitropin α pen interfere with your normal daily activities? ($n=98$)	
Substantially interfered with my normal daily activities	6 (6.1)
Moderately interfered with my normal daily activities	6 (6.1)
Slightly interfered with my normal daily activities	11 (11.2)
Did not interfere at all with my normal daily activities	75 (76.5)
How practical did you find this follitropin α prefilled pen? ($n=97$)	
Very practical	69 (71.1)
Practical	25 (25.8)
Somewhat practical	3 (3.1)
Not practical	0 (0.0)
In what aspect do you find this follitropin α prefilled pen practical? ($n=99$)[a]	
Dose selection	35 (35.4)
Ease of dose reading	45 (45.5)
Administration of the drug	49 (49.5)
Easy to carry	22 (22.2)
Easy to store	20 (20.2)
In your current treatment cycle, was the use of the follitropin α pen to deliver your medication associated with... ($n=98$)?	
No stress	60 (61.2)
Minimal stress	32 (32.7)
Moderate stress	5 (5.1)
Great stress	1 (1.0)
If you have previously had a stimulation cycle and used a different device to perform the injections, how did you feel about this follitropin α prefilled pen? ($n=51$)	
Lot more practical	37 (72.6)
More practical	14 (27.5)
Same	0 (0.0)
Less practical	0 (0.0)

[a]More than one response was allowed. The questionnaire completed by patients used the trade name for the follitropin α preparation (see Patients and methods).

Tolerability and safety

Ten patients in total (10%) reported at least one local injection site reaction, described as itching, pain, swelling, redness, or bruising, each by 1–4% of patients. All injection site reactions were mild in severity, except one case of moderately severe itching. Three (3%) patients each reported a single systemic AE: colic (two patients) and drowsiness one patient. All AE were rated as being mild in severity. There were no SAE and no women developed OHSS or withdrew due to AE.

Discussion

The follitropin α injection pen evaluated in this study was well tolerated by patients, and the majority of patients found it comfortable and practical to use, without important adverse impact on their daily lives during treatment.

Table 4. Questionnaire items relating to treatment satisfaction and patient preferences.

Questions	*n* (%)
Overall, how would you rate the level of satisfaction when using the follitropin α pen? (*n* = 98)	
Very satisfied	71 (72.5)
Satisfied	22 (22.5)
Somewhat satisfied	4 (4.1)
Not at all satisfied	1 (1.0)
Based on this experience, would you recommend the follitropin α pen to another woman considering infertility treatment? (*n* = 94)	
Yes	93 (98.9)
No	1 (1.1)
How would you best characterize your experience with the follitropin α pen compared to your selection above: (*n* = 88)	
I preferred the follitropin α pen over my previous treatment medication	80 (90.9)
Follitropin α pen was as easy to learn and use as my previous treatment medication	6 (6.8)
Follitropin α pen was not as easy to learn and use as my prior treatment medication	2 (2.3)

The questionnaire completed by patients used the trade name for the follitropin α preparation (see Patients and methods).

Table 5. Endpoints relating to assisted reproduction technologies and pregnancy outcomes.

Mean total dose of r-hFSH (IU)	2592 (910)
Mean days of stimulation treatment	10.4 (2.1)
Premature LH rise (%)[a]	3.4
Mean number of follicles[a]	
≥14 mm	12.3 (8.2)
13–14 mm	1.0 (1.7)
15–16 mm	2.6 (4.0)
17 mm	2.7 (3.6)
≥18 mm	7.0 (4.2)
Mean number of oocytes retrieved	10.4 (6.2)
Cycles cancelled (%)	8
Pregnancy (%)	
Chemical pregnancy (% β-hCG-positive)[b]	33
Clinical pregnancy (% with fetus visualized on ultrasound)[c]	29
Rates of single and multiple pregnancy, number (%)[c,d]	
1 (singleton pregnancy)	25 (86)
2 (twins)	3 (10)
3 (triplets)	1 (3)

Means (SD) except where stated. Based on an intention-to-treat analysis in the overall study population (*n* = 100). Figures in parentheses are SD.
[a]Measured on the day of hCG administration.
[b]15 patients (15%) did not have β-hCG measured.
[c]Of patients who had an ultrasound scan (four β-hCG-positive patients had no ultrasound).
[d]Based on the number of fetal hearts visible on ultrasound.
IU: international unit(s); r-hFSH: recombinant human follicle stimulating hormone; LH: luteinising hormone; β-hCG: beta-human chorionic gonadotrophin.

In previous studies, patients in the USA[5], Iran[6] and Germany[7] preferred an injection pen for follitropin α to previous methods of injecting r-hFSH and also found the device to be convenient and practical in daily use. An observational study in Northern Europe also supported the ease of use of injector pens pre-filled with follitropin α[8]. Studies in Germany and Australia reported higher ratings for an injector pen containing follitropin α compared with a pen dispensing follitropin β[9], and a comparative study in the USA showed that patients preferred the pre-filled follitropin α pen to a follitropin β pen or another product administered by syringe[10]. Importantly, the current pen design studied here was not associated with an increased risk of errors in dosing, compared with the previous version[11]. Other previous studies have also documented improved local tolerability at the injection site with a pen injector for follitropin α or β, compared with use of a syringe[6,12,13]. The findings of our study are therefore concordant with previous clinical experience with the follitropin α injection device.

Endpoints relating to ART and pregnancy outcomes were also typical of previous clinical experience. The incidence in the present study of positive β-hCG tests (33%) was within the range of previous large observational studies conducted in northern Europe (38%)[8]. The rate of cycle cancellation was also similar in the present study and the French study (8% vs. 11%, respectively).

Patient-reported outcomes are an important determinant of the success of therapeutic interventions, and a change in the method of delivery of any injectable treatment clearly has the potential to influence its therapeutic use by patients[14,15]. In addition, cultural factors can influence the ways in which patients view and use therapies, especially in Middle-Eastern countries, where sociocultural values impact strongly on reproductive health[16,17]. The high ratings for convenience and ease of use of the follitropin α pen injector confirm and extend previous findings in Iranian women[6], and indicate the suitability of this device for use in Middle Eastern women undergoing ART.

The lack of a control group represents an important limitation of this study, as it precludes direct comparison with other injection methods. However, the majority of women in the present study who had undergone previous ART stated a preference for the current device. We also do not know to what extent disappointment over failed IVF may have influenced perceptions of some patients to aspects of their treatment; however, only 9/99 who completed questionnaires did not complete the study.

Conclusions

The follitropin α injection pen evaluated in this study was well tolerated by patients, and the majority of patients

found it comfortable and practical to use, without important adverse impact on their daily lives during treatment. Positive perceptions of the follitropin α pen injector by this Egyptian patient population identify this device as suitable for use for Middle Eastern women undergoing ART.

Transparency

Declaration of funding

The study was funded by an educational grant from Merck Ltd Egypt, an affiliate of Merck KGaA, Darmstadt, Germany. No payment was made to patients, although the follitropin α pens were provided free of charge as part of the study protocol.

Declaration of financial/other relationships

M.Y., W.E.-K., A.K., A.H.M., A.A.A.K., A.A. and S.K. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

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