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Qualitative risk assessment of follicle stimulating hormone injectable products

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ABSTRACT

Background: Gonadotropin injections for fertility treatment regimens are usually self-injected, typically over 8–12 days during the assisted reproductive technology cycle. Parenteral gonadotropins are available in different formulations and administered through various systems. A user experience study and risk assessment were performed to evaluate different product types for risks to the patient when preparing and administering injections.

Methods: Nine women of child-bearing age each prepared and administered injections of six products representing single- and multidose vials of menotropin for reconstitution (Merional® and Menopur®), follicle stimulating hormone (FSH) reusable pen injectors with (Puregon®), and without cartridges (Gonal-f®), and single-use FSH pre-filled pens (Bemfola®). Risk assessments based on user feedback were made with reference to EU regulations for implementing practices for safe use of injectable products.

Results: Products requiring reconstitution with diluent in glass ampoules were associated with medium risk for sharps injury and a lower level of user confidence. Pen injectors were considered easy-to-use, with a low risk of sharps injury. Single-use pens were associated with the lowest risk of dosing errors.

Conclusions: The study identifies differences in the risks for both sharps injuries and dosing errors between FSH delivery options that practitioners should consider when making a treatment choice.

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Risk assessment; needle-stick injury; glass-cut injury; parenteral products; self-administration; follicle stimulating hormone; menotropin; reconstitution; pre-filled pen injector; fertility treatment

1. Introduction

Since the early experimental use of gonadotropins to treat infertile patients in the late 1930s, both the gonadotropins used, particularly follicle stimulating hormone (FSH), and the way they are administered have seen major advancements leading to improvements in efficacy, safety, and ease of use as treatment components of assisted reproductive technologies (ART) [1,2]. Initially FSH was provided as menotropin (human menopausal gonadotropin, HMG) in a glass ampoule that had to be scored prior to snapping for reconstitution with a diluent also provided in glass ampoules. Later, HMG became available in single-dose and multidose vials for preparation with a diluent. More significant developments included the production of recombinant FSH (rFSH) in liquid formulations held in cartridges added to pens by users or in pre-filled pens for patient treatment. Pens initially were multi-use, requiring bacteriostatic agents to reduce risk of infection following multiple injections. Later, a single-use multidose pen was introduced, reducing pen size and avoiding the need for bacteriostatic agents.

Since the introduction of the single-use, self-administered, pre-filled injection pen, several studies have compared this option against available alternatives with respect to use and handling, human factor interactions by patients and nurses, and potential drug wastage [3–7]. Although a diverse range of FSH products including menotropin products with diluents in glass ampoules are still in widespread use throughout Europe, previous studies have not considered the relative risks to the patient when preparing and administering these different alternatives. The European Union Regulations 2014 (Prevention of Sharps Injuries in the Healthcare Sector) requires that employers should carry out a risk assessment for injectable products to ensure safe use of sharps (needles) and minimization of sharps injuries [8,9]. Although written for employers, the principles of these guidelines apply equally to users' (patients') own actions with regard to ensuring the safe administration of treatments. The aim of this study was to assess the different types of parenteral gonadotropin products for risks to the patient when preparing the product for injection and subsequent use, including the potential for dosing errors.

2. Methods

A qualitative assessment of risks of sharps injury with use of gonadotropin injections was conducted according to the principles of the relevant EU Regulations [8,9]. The study was conducted in two parts and evaluations of risk and potential for dosing errors were made by relevant experts.

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2.1. Focus group activity

In the first part of the risk assessment, a focus group activity was conducted at The University of Manchester as a practical test of product usability and to identify potential risks associated with preparation and use of a range of parenteral gonadotropin products.

The focus group participants were women of child-bearing age who worked in the laboratories of the University of Manchester School of Pharmacy, formally trained in risk assessment as a requirement of their employment, and engaged in postgraduate education or research. Participants were invited to participate in the risk assessment and given an opportunity to ask questions about the study prior to consenting to participate. They had not and were not undergoing treatment with any of the products to be evaluated. The test involved preparing the injections and administering them on an artificial piece of skin. Participants were provided with the relevant 'instructions for use' leaflets for each product and were also referred to online instruction videos demonstrating how to use each product, prior to the activity. On the day of the group event, nine participants were asked to prepare each product for administration and provide information on any potential risks they perceived to be associated with each product during preparation and administration.

The activity included commercially available gonadotropin products representing five different types of injectable delivery formulation. These were: (A) single-use pre-filled rFSH pen delivery device (Bemfola®) [10]; (B) multi-use rFSH pen delivery device pre-filled with a rFSH cartridge (Gonal-f®) [11]; (C) multi-use rFSH pen delivery device for use with replaceable rFSH cartridges (Puregon®) [12]; (D) multi-use HMG vial with pre-filled syringe(s) of solvent and needle for reconstitution, and separate syringe and needle for administration (Menopur® multidose) [13]; and (E) single-use HMG vial and solvent ampoule with needles and syringes for preparation, and Autoject-2 auto-injector device for administration (Menopur® and Merional®) [14,15].

The participants were asked to prepare each product for administration according to the 'instructions for use' leaflet provided and other information/notes they had prepared in pre-study activity. Each preparation kit included all of the equipment they would need to safely prepare and administer each product, including a sharps bin for disposal. Each participant prepared and evaluated all six products, in no predefined sequence, and documented positive and negative features of each. They also ranked the products according to ease of use and personal preference ('which product are you most likely to use?'). After the preparation of each product, the participants were asked to report any potential risks or safety issues (e.g. possible sharps injury, glass cuts) associated with each product relating to preparation and administration. Details of the information they were asked to document is shown in Table 1. Reports were collated for each product and aggregated into a table and assessed for risk level by the study authors according to their professional opinions, informed by relevant guidance [8,9].

Table 1. Questions included in structured questionnaire of user experience with the six test products.

Questions
(1) List any good aspects you noticed when you were using the products.
(2) List any bad aspects you noticed when you were using the products.
(3) (a) Rank these products according to ease of use (1- being the easiest to use and 6- being the most difficult). (b) What made you choose this product as the easiest product to use? (c) What made you choose this product as the most difficult product to use?
(4) Which product would you be most likely to use?
(5) Is there any safety issue(s) you have with any of the product(s), and why?

2.2. Evaluation of risks

In the second step of the assessment, the tabulated reports of the focus group participants were qualitatively evaluated using theme analysis by the expert multidisciplinary group of the authors of this paper, reflecting on their extensive clinical experience to provide a likelihood of risk.

Briefly, the risk assessment is a three-step process that involves (i) identifying the hazard, (ii) assessing the risk, and (iii) implementing the appropriate control measures. The principal hazard under assessment in the present study was 'regular self-injection of gonadotropin products by patients'. Specific risks associated with the practice of subjects' self-preparation of the products were identified and quantified as low, medium or high, with consideration of the likelihood and consequence of the event occurring. Based on existing knowledge of risks associated with self-preparing injectable products – e.g. manual recapping of needles has been identified as a particularly hazardous activity – control measures to minimize risk included provision of information on the correct use of the equipment provided to protect against sharps injury. To evaluate the availability and quality of information available to patients undergoing fertility treatment involving gonadotropin injections, an internet search was conducted to identify online patient information leaflets, online support groups, and videos. This information was used to develop the product evaluation activity, provide some online training on the product preparation for the activity, and to inform questions after the activity about risk in the preparation of the products. In addition, expert information was collected from healthcare professionals (HCPs) at the Department of Reproductive Medicine at Saint Mary's Hospital (Manchester University Foundation Trust, UK). All the information was collated for presentation to the participants so that they understood the preparation of the injectable products.

Institutional Review Board or Independent Ethics Committee approval was not required as this was a simulated-use study with no injections administered. All participants gave informed consent prior to taking part in the study.

3. Results

3.1. Experiences of product usability

Participants' positive and negative experiences of the usability of each product are presented in Table 2. The

Table 2. Participants' feedback on product usability – themes reported by two or more participants. *Comments in quotation marks represent direct quotes from individual participants.*

POSITIVE themes	NEGATIVE themes
A. Bemfola® pre-filled pen	
(1) Easy to use (2) Fine needles (3) No need to recap the pen if sharp bin to hand as could be disposed of directly[1] (4) Minimize needle related injuries (5) Single use device and disposable (6) Clear dose bar (7) Clear instructions (8) Pre-filled pen	No common negative themes among participants Individual comments included: *'Need to be sure of the dose'* *'Multiple doses possible'* *'Step needed to exclude bubble'* *'Feels a bit flimsy; feels like a pen'*
B. Gonal-F® pre-filled pen	
(1) Easy to use (2) Needle risk is low (3) Dose can be rectified easily (4) Premixed preparation (5) Finding appropriate dose is simple (6) Minimal packaging	(1) Risk of needle injury when recapping needle to remove it (2) Need to keep a record of previous doses (3) Need to calculate how much dose is left Individual comments included: *'Bulkier storage'*
C. Puregon® pen	
(1) Fine needle (2) Low risk of needle-stick injury (3) Easy to use (4) Clear dose marking (5) Compact packaging (6) Discreet	(1) Cannot rectify the dose easily; *'If you dial up the wrong dosage, you cannot go back, you need to restart'* (2) Have to keep a record of doses administered and calculate subsequent doses Individual comments included: *'Have to put the cartridges in pen'* (might get it wrong); *'Recapping the needle to remove it could cause needle injury'*
D. Menopur® multidose vials	
(1) Easy to prepare (2) Easily explained leaflet (3) Pre-filled syringes are safer than solvent vials used in Menopur® and Merional® (4) Less equipment needed (5) There is no need for daily preparation	(1) Preparation involves multiple steps and is complicated; *'A lot of clinical looking components which may overwhelm or "scare" users who are not used to being in a clinical setting' ; 'Multiple steps increase the risk of error in mixing or drawing up the dose'* (2) Needle-stick injury risk (3) Need to calculate remaining dose Individual comments included: *'Leaving the needle in the powder bottle to attach the new syringe may be a little tricky'* (one needle is used for the two pre-filled syringes provided)
E (i) Menopur® vials	
No common positive themes among participants Individual comments included: Safety device for opening ampoule can be used to reduce glass-cut related injuries Can still be used without the auto-injector	(1) Mixing needles are long and off putting (2) High risk of injury when breaking glass vials; *'Ampoules are dangerous' ; 'This one is very stressful [to use]'* (3) High risk of needle-stick injury (4) Too many steps, causing confusion Individual comments included: *'Lots of places to go wrong' ; 'Dose has to be made up daily' ; 'Risk of confusion' ; 'A lot of clinical looking components which may overwhelm or "scare" users who are not used to being in a clinical setting'*
E (ii) Merional® vials	
(1) Easily explained leaflet Individual comments included: Can be used without auto-injector *'Not too intimidating'*	(1) Risk of needle injury (2) Prolonged needle handling (3) Too many steps – risk of confusion (4) Vials are fragile and pose a risk of injury (5) Risk of spillage
Auto-injector (with Menopur and Merional vials) (No positive comments made)	Individual comments included: 1. Auto-injector is complicated, counter-intuitive, and pointless; *'Any risk that is reduced by [the] needle guard [on the] auto injector is lost by the complicated assembly steps and extra needle handling'* 2. Fear of not injecting properly or wasting the dose; *'Cannot see the needle'*

1. Note although the Bemfola instructions for use do not require the small inner needle cap to be replaced prior to disposal, after the injection the wide outer needle cap is to be replaced onto the needle carefully.

single-dose HMG vial preparations (E) requiring use of a separate needle and syringe for preparation and an optional auto-injector for administration involved multiple steps, were complicated to use, and attracted the highest number of negative comments. Provision of the solvent for reconstitution in pre-filled syringes was a positive feature of the multidose vial (D), but dose calculations and use of multiple syringes were complicating features. Participants reported more advantages than negative features with the pen devices compared to the HMG vials. The injection pens were all assessed as 'easy to use', required minimal preparation, had clear dose-setting features, and required minimal handling of needles.

Overall preference scores were twice as high for the pen delivery devices compared with the single-or multidose vials (Figure 1). The main reason for preferring the pen products

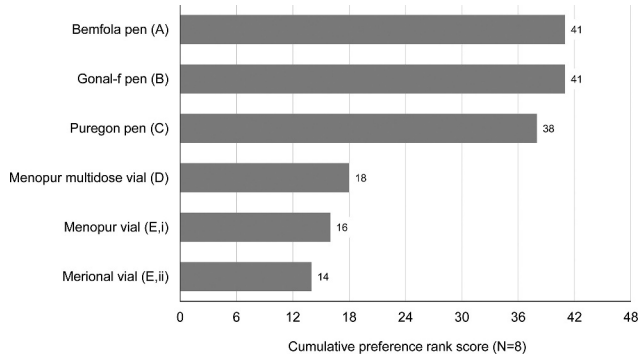

Figure 1. Combined preference ranking scale scores of the six products from eight study participants. One participant did not provide an overall preference ranking. Each participant ranked the products on a scale of 1 to 6, where 1 = least preferred and 6 = most preferred (total maximum score per product = 48).

was the 'ease of use', which was felt to reduce confusion and stress. The pre-filled rFSH pen delivery devices (A, B), were preferred over the rFSH pen delivery device that required a replaceable rFSH cartridge to be loaded prior to use (C).

3.2. Risk assessment analysis

Specific safety issues identified by participants in the product usability activity were: (1) mixing multiple vials of single-use HMG (E) can be confusing and might lead to administering the wrong dose if the user was not concentrating; (2) prolonged handling of needles (especially mixing needle) can increase the risk of needle-stick injury; (3) there is a risk of glass injury when snapping glass solvent ampoules (thus a plastic snapping device was provided with kits E(i) and E(ii) to minimize this risk); (4) the packaging of HMG vials (D, E) can be stressful to inexperienced users; (5) the use of HMG multidose vial (D) can increase the risk of contamination (therefore, it contains a bacteriostatic agent); (6) the auto-injector (used with E) is complicated and can be stressful to use, outweighing its safety benefits. With reference to this safety feedback and to definitions and guidelines laid out in directives for implementing practices for safe use of injectable products [8,9,16], as well as authors' professional judgment, quantification of the likelihood of each risk is summarized in Table 3. For all three types of pen device (A, B, and C), the risk of sharps injury was graded as low; the two pen devices designed for multi-dose use (B, C) were assessed as medium risk for the possibility of dosing errors. The single-dose HMG vial preparations requiring the user to open a glass ampoule of solvent (E) were evaluated as medium risk for causing glass cuts. A medium level of risk for needle-stick injuries was determined in the products that required use of separate syringes and large needles to reconstitute powder for injection and transfer the drug from multiple vials (D, E). With the appropriate user instructions available to follow, none of the products was assessed as having a high risk of causing a sharps injury.

4. Discussion

This study was triggered in response to the risk assessment required by the EU Prevention of Sharps Injuries in the Healthcare Sector Regulations 2014, which should be considered when prescribing gonadotropin products to women. Although these regulations apply specifically to HCPs in the workplace, in situations where the risks extend to patients in their homes, the same principles apply and HCPs have a responsibility to ensure the safe use of treatments that present a potential hazard to the patient.

For the most basic product presentation, the single-dose HMG vials, even with their high level of education, there was some confusion amongst the participants on the appropriate methods of reconstituting and opening the glass solvent ampoules and these products were considered to have a medium risk of needle-stick injuries and glass-cuts. With regard to dosing, use of the single-use vials can require the patient to mix the contents of multiple vials if they have been prescribed a high dose of drug, introducing a potential risk of incorrect dosing or overdose. Not surprisingly, in our product usability group activity, the single-use HMG vial products were considered to have too many components involved in their preparation, take too much time to prepare, and have a higher risk of sharps injury (needle-stick and glass injuries). The auto-injector, which is intended to reduce the risk of sharps injuries with Menopur® and Merional®, was considered complicated to use, hence participants did not consider it useful for improving the product administration experience.

The provision of pre-filled syringes of solvent with the multi-use HMG vial was considered an advantage over the single-use HMG vial products because it avoided the need to snap open a glass ampoule of solvent. The Menopur® multi-dose product comes as a fully prepared kit with all accessories included in the package. However, its preparation and administration still requires multiple needle manipulations and for this reason, similar to single-use HMG vials, the overall risk for sharps injury was assessed as medium. Furthermore, the multi-dose vials could theoretically pose a risk of contamination as a result of multiple uses, even though a bacteriostatic agent is included in the formulation [13]. Importantly, each Menopur® multidose vial is intended for use in a single patient, and infection control guidelines advise against the use of multi-dose vials for multiple patients, as they carry a high risk of contamination and cross-infection [16].

Although HMG delivered in multi-use vials was preferred over single-use vials to reduce the risk of injury, there was no such advantage of multi-use pens over single use pens. The risk of injuries with all pens was considered low. An important finding in a larger product usability study (N = 180) comparing four FSH pen injectors was that handling of multi-use pens resulted in errors if there was an additional step of inserting a rFSH cartridge [7]. Compared with pre-filled rFSH pen devices (Gonal-f® or Bemfola®), Ovaleap® and Rekovelle® injection pens requiring insertion of a rFSH cartridge (similar to the Puregon® pen in our evaluation) were associated with significantly more type 4 handling errors (defined as errors resulting

Table 3. Risks identified by participants were defined with reference to definitions and guidelines laid out in directives for implementing practices for safe use of injectable products [8,9,16]. Likelihood of risks was subjectively quantified based on the professional judgment of the authors of this paper.

Product types	Risks identified	Likelihood of risk
A. Single-use pre-filled FSH pen delivery device For further information see: https://www.medicines.org.uk/emc/product/6835/smpc		
Bemfola® pre-filled pen (Gedeon Richter Plc, formerly Finox Biotech UK & Ireland Ltd)	Risk of sharps injury – Re-sheathing of needle	Low
	Risk of administering the wrong dose, or missing dose	Low – One pen per day with limited dose range and clear markers for precise dosage
B. Multi-use FSH pen with pre-filled FSH cartridge For further information see: https://www.medicines.org.uk/emc/product/71/smpc		
Gonal-f® pre-filled pen (Merck, formerly Merck Serono)	Risk of sharps injury – Re-sheathing of needle	Low
	Risk of administering the wrong dose, or missing dose	Medium • Diary required to record if and how much dose delivered each day • Failure to prime pen when required • Further complication if residual dose in pen is inadequate for intended dose – either waste this residual or perform two injections and ensure correct dose in each injection
C. Multi use FSH pen with replaceable FSH cartridge For further information see: https://www.medicines.org.uk/emc/product/7814/smpc		
Puregon® pen (MSD, formerly Organon)	Risk of sharps injury – Re-sheathing of needle	Low
	Risk of sharps injury – Loading glass cartridge in the pen	Low
	Risk of administering the wrong dose, or missing dose	Medium • Diary required to record if and how much dose delivered each day • Failure to prime pen when required • Further complication if residual dose in pen is inadequate for intended dose – either waste this residual or perform two injections and ensure correct dose in each injection
D. Multi use FSH vial and solvent with needle and syringe For further information see: https://www.medicines.org.uk/emc/product/4594/smpc		
Menopur® multi-dose vials (Ferring)	Risk of sharps injury – Handling and re-sheathing of solvent and injection needles	Medium
	Risk of contamination as a result of reusing vial	Low to medium
	Risk of administering the wrong dose, or missing dose	Medium • Diary required to record if and how much dose delivered each day • Further, as two solvents required for higher 1,200 IU dose, risk of using only one solvent
E. Single use FSH vial and solvent with needle and syringe For further information see: https://www.medicines.org.uk/emc/product/1294/smpc https://www.pharmasure.co.uk/fertility-products/		
Menopur® vial (Ferring) and Merional®/ Meriofert® vial (IBSA)	Risk of sharps injury – Handling and re-sheathing of solvent and injection needles	Medium • Prolonged needle handling required
	Risk of sharps injury – Breakage of solvent glass ampoule	Medium
	Risk of administering the wrong dose, or missing dose	Medium • Reconstitution of multiple vials can cause confusion

in minor injury requiring medical attention, not resolved by the woman herself). The authors concluded that 'Preparation of multi-use pens with cartridges requires an additional step; therefore … specific training should be provided on how to insert and change the cartridge' [7]. In a separate study that evaluated the impact of human factors on usability of the single-use product Bemfola®, no critical errors that could affect the success of the injection process were identified [6].

Although the present study focused on sharps injuries, the risk of dosing errors with FSH was considered of major importance with respect to both patient safety and treatment efficacy. To keep injection volumes small for subcutaneous administration, the single-use vials come with instructions that up to three vials can be reconstituted in the 1 mL of solvent provided [14]. This introduces practical complications in manipulating sequential transfers of

solution from one vial to another, as well as the possibility of confusion with dose volume calculations. Multi-use products present particular challenges to avoid dosing errors, with the requirement for patients to keep a treatment diary in order to record the concentration of reconstituted product and the amount remaining for subsequent doses. The Menopur® multidose vial is available in two sizes – 600 IU and 1,200 IU – and as the larger vial requires addition of two syringes of diluent, there is a risk that only one syringe of diluent might be used by the patient, which would result in double the intended dose being delivered.

Where the residual amount in a multi-use product is insufficient to administer the next full dose, a patient is faced with two options. Either the residual rFSH is discarded or two injections are administered to make up the full dose, introducing an increased risk of incorrect dosing as well as the discomfort of a double injection. Even if patients choose to use the two rFSH pens, a real-world study in the UK of 4,078 IVF cycles with Gonal-f® and 646 IVF cycles with Menopur® suggested FSH wastage would be less if the single-use Bemfola® pen was used, as typical daily wastage with Bemfola would be lower than the terminal wastage in a multi-use option [4].

Other practical considerations can also influence users' confidence with the products. When using the Gonal-f® pen, user judgment is required to determine whether priming is required: if no fluid is observed to appear from the needle tip, then manual priming is required to avoid an air bubble [11]. In contrast, the Bemfola® pen enforces priming by design [10]. Ease of use is likely to contribute to patients' confidence in self-administering injections and might be expected to be a factor in reducing hazards associated with administration as well as other risks such as handling/dosing errors [17,18]. Although the focus group size in this study was only sufficient to assess user preferences between very different products, other larger studies have considered user preferences between the different FSH pens. Longobardi et al. reported a study of 60 fertility nurses and 120 women with infertility, in which the Gonal-f® pen was rated higher in preference before and after simulated injection compared to Bemfola®, Ovaleap®, and Rekovelle® injection pens [7]; however, the study simulated administration of a dose of 65 IU rFSH (or 9.66 µg for the Rekovelle® pen), which is a dose not used in routine IVF practice [4]. In contrast, a study of 65 women and a further study of 460 women, both simulating an intended administration of 225 IU/day followed by a dose increase to 300 IU, found that Bemfola® pen was preferred by treatment-naïve patients to both Puregon® and Gonal-f® pens, particularly with respect to ease of use [3,5]. With a single-use product that requires fewer steps in preparation and is easier to use than others, it is likely that there is less that can go wrong during the preparation and administration process. Further, the single-use Bemfola® pen is available in five dosage strengths, which allows a suitable size to be used as appropriate for the dose prescribed to further reduce risk of administration errors [10].

When considering the use of single-use versus multi-use FSH injection devices, it is notable that no subject identified a potential issue with plastic waste, where single-use devices might be expected to generate more waste than multi-use devices. This is perhaps not surprising, since the exercise focused on the preparation and administration of single doses rather than a whole course of treatment. Furthermore, the subjects in this study worked mainly in laboratories, where the use of single-use plastic items is commonplace, and might therefore not perceive any significantly relevant environmental impact in the relatively small quantity of plastic consumables from FSH preparations administered in an IVF treatment cycle. Indeed, it is more relevant to consider the total plastic usage during a complete IVF cycle, including the contribution of clinical and laboratory procedures in the IVF process. A study in a UK IVF clinic performing approximately 1,000 fresh and 600 frozen cycles per year determined that in the IVF laboratory, an average of 69,488 plastic consumables would be used each year, which broadly equates to 43 pieces per cycle [19]. Accordingly, although a typical course of 10 smaller, single-use rFSH pens may generate slightly more plastic waste than an equivalent course delivered in 3 larger, multi-use rFSH pens, the relative environmental impact is small, and efforts to improve sustainable practices in IVF centers should consider products and equipment used in all procedures involved in the whole IVF cycle.

To our knowledge, this is the first reported comparative assessment of risks specifically associated with the preparation and administration of injection preparations or devices intended for self-administration of gonadotropins as controlled ovarian stimulation during fertility treatment. Although the user study was small and conducted in a single UK center, it provided valuable feedback on product usability and perceived safety and was a component of a thorough evaluation of the products for risk assessment with reference to definitions and guidelines laid out in directives for implementing practices for safe use of injectable products, as well as our expert opinion and experience. For several reasons, it was appropriate to adopt a qualitative rather than quantitative approach to compare the perceptions of risk by potential users of the different FSH injectable products. As FSH injectable products are typically prepared in the homes of the patients, incident reports of a sharps or needle-stick injury are unlikely to be recorded. This under-reporting would make a quantitative analysis unreliable and underestimate the risk. Identifying products that are easy to use and prepare, not alarming in appearance, and simple to handle is difficult by quantitative methods, which might answer the question 'how many', but not the question 'why' as through qualitative methods. Further, the study compared the various product types to one other in a design in which each women prepared all of the products, allowing each subject to provide their comparative opinions of risk. In the real world, women would only receive one product and not experience the various products to enable constructive comparison.

In summary, the findings of the present evaluation of potential risks associated with preparation and self-administration of gonadotropin products in IVF treatment cycles, based on user feedback and formal risk assessment,

define a medium level of risk for sharps injury and a poor level of user confidence with products requiring reconstitution and transfer of product, including both the single-use and multi-use HMG vials. In contrast, all of the pen injectors were considered easy to use, with a low risk of sharps injury, although the multi-dose pen devices were more difficult to dose correctly than the single-use pen, and the need to load a drug cartridge in the Puregon® device was an added complication.

This paper may be used to improve patient experience with injectable products and help guide practice to reduce risk when administering FSH. Firstly, practitioners should reflect on risk when choosing injectable products for patients, drawing on the literature, prior experience and personal judgment. Should glass ampoules be used then safety guards must be provided to snap the ampoules. Education is essential prior to the first patient self-injection and good, multiformat support material should be provided. Once these products are given to the patient for self-administration, HCPs have little control over how well they follow the guidance at home, as unlike many other devices, such as inhalers, technique is not usually reviewed regularly to ensure proper effective use. Thus reinforcement of initial education and assessment of injection technique at home should be considered, for example through videoconferencing. In view of the impact of Covid-19 on ART practice, with recommendations to limit the number of persons simultaneously present in the IVF center [20], easier-to-use FSH administration options may be preferable to shorten the time required for training.

5. Conclusions

Self-administration at home of parenteral gonadotropins has inherent risks, and healthcare teams should choose the safest product for their patients with consideration of the potential for handling errors. Glass-cuts are a significant risk when using diluents in glass ampoules, and disposable injection pens in which the drug is pre-mixed reduce the risk of needle-stick injuries compared to using separate needles and syringes. Ease of use is also important to reduce the risk of dosing errors, which can have adverse consequences during ART treatment. Although there are advantages to multi-use FSH delivery systems, it is inconvenient to track the remaining drug in a diary and there is a risk of dosing errors. The use of a pre-mixed, pre-loaded cartridge, single-dose, disposable injection pen can further simplify the patient experience. This paper presents both the approach to risk assessment and the rationale underlying the conclusions, enabling readers to conduct risk assessments to inform their own practice. Consideration of these risks should inform the choice of FSH treatment to minimize the risk of harm to patients and reduce the risk of dosing errors.

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Declaration of interest

HK has received honoraria to participate in advisory board meetings for Preglem/Gedeon Richter and Theramex. JJ is a paid external advisor for Preglem SA/Gedeon Richter Plc. RM has received honoraria to attend scientific conferences from the following manufacturers of medicines used in fertility treatment: Merck, Ferring, Gedeon Richter, Bessins. Full details can be found at www.whopaysthisdoctor.org. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Author contributions

DT Steinke and OH Zarroug designed and executed the study and assessed the risk of the different products. All authors contributed to the interpretation of data, writing, critical review, and approval of this manuscript for submission to the journal and agree to be accountable for all aspects of the work.

Reviewer disclosures

Peer reviewers on this manuscript have received an honorarium from Expert Opinion on Drug Delivery for their review work, but have no other relevant financial relationships to disclose.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Lunenfeld B. Historical perspectives in gonadotrophin therapy. Hum Reprod Update. 2004;10(6):453–467.
2. Lunenfeld B, Bilger W, Longobardi S, et al. The development of gonadotropins for clinical use in the treatment of infertility. Front Endocrinol (Lausanne). 2019;10:429.
3. Imthurn B, McVeigh E, Stiller R, et al. Evaluation of the use and handling of three different pen systems considered for in vitro fertilization treatment. Expert Opin Drug Deliv. 2014;11(12):1859–1864.
   • **Study provides further findings on user preferences of different FSH pens.**
4. Foxon G, Mitchell P, Turner N, et al. Bemfola® fixed dose pens potentially reduce drug wastage and associated costs of infertility treatment. Hum Fertil (Camb). 2018;21(4):275–280.
5. Quintero LA, Merino VV, de la Fuente Bitaine L, et al. An evaluation by potential IVF/donor oocyte patients of the use and handling of the Bemfola® Pen compared with the Gonal-f® Pen and Puregon Pen®. Rev Iberoam Fert Rep Hum. 2016;33(3):42–51. [cited 2020 Aug 3]. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01602445/full#abstract

- **Study provides further findings on user preferences of different FSH pens.**

6. Saunders H, de la Fuente Bitaine L, Eftekhar C, et al. Functionality of a novel follitropin alfa pen injector: results from human factor interactions by patients and nurses. Expert Opin Drug Deliv. 2018;15(6):549–558.
7. Longobardi S, Seidler A, Martins J, et al. An evaluation of the use and handling errors of currently available recombinant human follicle-stimulating hormone pen injectors by women with infertility and fertility nurses. Expert Opin Drug Deliv. 2019;16(9):1003–1014.
   - **Study provides further findings on user preferences of different FSH pens.**
8. European Agency for Safety and Health at Work. Directive 2010/32/EU - prevention from sharp injuries in the hospital and healthcare sector. 2017. [updated 2017 Oct 4; cited 2019 Aug 3–4]. Available from: https://osha.europa.eu/en/legislation/directives/council-directive-2010-32-eu-prevention-from-sharp-injuries-in-the-hospital-and-healthcare-sector
   - •• **Directive implementing the European Framework Agreement on prevention from sharp injuries in the hospital and healthcare. Provides important background regarding the need for risk assessment for use of injectable products.**
9. Health & Safety Executive. Background to EU Directive Health and Safety (Sharps Instruments in Healthcare) Regulations 2013. [cited 2020 Aug 3]. Available from: https://www.hse.gov.uk/healthservices/needlesticks/eu-directive.htm
   - •• **Important guidance describing regulations to implement the EU Council Directive 2010/32/EU on the prevention of sharps injuries in the hospital and healthcare sector.**
10. BEMFOLA [follitropin alfa] 75 IU/0.125 mL, 150 IU/0.25 ml, 225 IU/0.375 ml, 300 IU/0.50 ml and 450 IU/0.75 ml solution for injection in pre-filled pens. Summary of Product Characteristics. Gedeon Richter (UK) Ltd; 2018 [updated 2018 Nov 12; cited 2020 Aug 3]. Available from: https://www.medicines.org.uk/emc/product/6835/smpc
11. GONAL-f [follitropin alfa] 450 IU/0.75 mL (33 mcg/0.75 mL) solution for injection in pre-filled pen. Summary of product characteristics. Merck Europe B.V.; 2018. [updated 2018 Aug; cited 2020 Aug 3]. Available from: https://www.medicines.org.uk/emc/product/70/smpc
12. PUREGON [follitropin beta] 300 IU/0.36 ml, 600 IU/0.72 ml, 900 IU/1.08 ml Solution for Injection in a multidose cartridge. Package leaflet: information for the user. Merck Sharp & Dohme Limited; 2018 [updated 2018 Jul 6; cited 2020 Aug 3]. Available from: https://www.medicines.org.uk/emc/product/7814/pil
13. MENOPUR [highly purified menotrophin (human menopausal gonadotrophin)] 600 IU multi-dose powder and solvent for solution for injection. Summary of Product Characteristics. Ferring Pharmaceuticals Ltd; 2015. [updated 2015 May; cited 2020 Aug 3]. Available from: https://www.medicines.org.uk/emc/product/4595/smpc
14. MENOPUR [highly purified menotrophin (human menopausal gonadotrophin)] 75 IU powder for injection and solvent for parenteral use. Summary of Product Characteristics. Ferring Pharmaceuticals Ltd; 2015 [updated 2015 Sept; cited 2020 Aug 3]. Available from: https://www.medicines.org.uk/emc/product/1294/smpc
15. UK Medicines & Healthcare products Regulatory Agency (MHRA). Merional sc 75 IU & 150 IU, powder and solvent for solution for injection (menotrophins). UKPAR; 2011 [cited 2020 Aug 3]. Available from: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con131964.pdf
16. Centers for Disease Control and Prevention (CDC). Position statement: protect patients against preventable harm from improper use of single–dose/single–use vials. Atlanta, Georgia, USA: CDC, US Department of Health and Human Services; 2012 [cited 2020 Aug 3]. Available from: http://www.cdc.gov/injectionsafety/CDCposition-SingleUseVial.html
17. Pfützner A. Patients' preferences for insulin injection devices. J Diabetes Sci Technol. 2017;11(2):270–271.
18. Pohlmeier H, Berard L, Brulle-Wohlhueter C, et al. Ease of use of the insulin glargine 300 U/mL pen injector in insulin-naïve people with type 2 diabetes. J Diabetes Sci Technol. 2017;11(2):263–269.
19. Smale D, Wheat S, Campbell A. P041 Plastic use in the IVF laboratory. In: Fertility 2019: Technologies and Controversies in Reproduction, 3–5 January 2019, Birmingham (UK), Abstracts Book. Brentford (UK): Profile Productions Ltd; 2019 [cited 2020 Aug 3]. Available from: https://fertilityconference.org/wp-content/uploads/2018/12/Fertility_2019_abstracts_book-updated.pdf
   - **Discusses the environmental impact of plastic consumables associated with FSH injectable products in the context of total plastic usage during a complete IVF cycle.**
20. ESHRE COVID-19 Working Group. ESHRE guidance on recommencing ART treatments. Grimbergen, Belgium: European Society of Human Reproduction and Embryology; 2020 [updated 2020 May 5; cited 2020 Aug 3]. Available from: https://www.eshre.eu/-/media/sitecore-files/Guidelines/COVID19/ESHRE-Guidance-on-Recommencing-ART-treatments_update-04052020.pdf?la=en&hash=A584F8A306C570BE7648C167CB190F994E21F05A