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ORIGINAL ARTICLE *Infertility*

Patient preference for a long-acting recombinant FSH product in ovarian hyperstimulation in IVF: a discrete choice experiment

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STUDY QUESTION: What factors or attributes of a long-acting recombinant FSH (rFSH) or daily-administrated rFSH influence women's preferences IVF?

SUMMARY ANSWER: Patients' preferences for rFSH products are primary influenced by the attribute 'number of injections', but a low 'number of injections' is exchanged for a high 'number of injections' at a 6.2% decrease in 'risk of cycle cancellation due to low response' and at a 4.5% decrease in 'chance of OHSS'.

WHAT IS KNOWN ALREADY: Injections of long-acting rFSH have been claimed to be preferred over daily-administrated rFSH injections, but patient preference studies to underpin this assumption have not been performed.

STUDY DESIGN, SIZE, DURATION: A discrete choice experiment (DCE) was created to assess women's preference for long-acting or daily-administrated rFSH under varying attributes of efficiency, safety and burden. The selected attributes were the 'total number of injections', 'chance of ovarian hyperstimulation syndrome (OHSS)' and the 'risk of cycle cancellation due to low response'. Questionnaires were handed out during information gathering sessions in one academic hospital and two teaching hospitals in The Netherlands between April 2011 and April 2012.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women at the start of their first IVF treatment were asked to participate in this patient preference study. Participation was voluntary. We analysed the data by using mixed logit models to estimate the utility of each attribute.

MAIN RESULTS AND THE ROLE OF CHANCE: Questionnaires (n = 125) were handed out with a response rate of 77% (97/125). Four respondents did not complete the questionnaire. Hence, there were 93 questionnaires available for analysis. All attributes significantly influenced women's preference. Overall, the lower 'number of injections' was preferred above the higher 'number of injections' (mean coefficient 1.25; $P < 0.001$), while an increase of 1% in 'chance of OHSS' or 5% 'risk of cycle cancellation due to low response' was non-preferred (mean coefficients -0.31 and -0.24, respectively, $P < 0.01$). The majority of respondents was willing to trade-off a lower 'number of injections' for a higher 'number of injections' when gaining a 6.2% reduction in 'cycle cancellation due to low response', or a 4.5% reduction in 'chance of OHSS'.

LIMITATIONS, REASONS FOR CAUTION: The generalizability of this DCE is limited in time-span. Women may choose differently when they have previous experience with long-acting rFSH, or when they have to pay for the medication, hospital visits and treatments themselves.

WIDER IMPLICATIONS OF THE FINDINGS: The results of this DCE helps us to understand the trade-off women make in their preference for a long-acting rFSH product or a daily-administrated rFSH product in IVF and may support doctors when counselling patients.

Introduction

IVF is perceived as complex, demanding, invasive and burdensome (Eugster and Vingerhoets, 1999; Rombauts and Talmor, 2012). The mental and psychological distress that accompanies an IVF treatment causes many women to drop out prematurely from their fertility treatment (Olivius et al., 2004; Verberg et al., 2008; Domar et al., 2010). Any refinement that can reduce the dropout rate might result in a higher cumulative chance of achieving a pregnancy (Rombauts and Talmor, 2012).

A major improvement in this respect was the replacement of i.m. injections of gonadotrophins by subcutaneous pen injections (Out et al., 1997; Alviggi et al., 2007). Women were now able to administer FSH products themselves in the privacy of their home, instead of having to visit the hospital to receive the injections by nursing staff.

Recently, a long-acting recombinant FSH (rFSH) product, corifollitropin alpha, became available as another effort to reduce treatment burden. A single subcutaneous pen injection of long-acting rFSH can replace seven daily-administrated rFSH injections during the first week of ovarian stimulation. The long-acting rFSH product thus implies a lower number of injections needed for ovarian stimulation.

Clinical studies have shown that long-acting rFSH and seven daily-administrated rFSH injections are equally effective in terms of pregnancy outcome (Pouwer et al., 2012; Youssef et al., 2012). However, long-acting rFSH causes more ovarian hyperstimulation syndrome (OHSS) (odds ratio (OR) 1.27, 95% confidence interval (CI) 0.72−2.22) and more cycles are cancelled due to either high or low response (OR 1.47, 95% CI 1.08−2.02) (Youssef et al., 2012). So far, all RCTs on long-acting rFSH have been performed with a GnRH antagonist (Pouwer et al., 2012; Youssef et al., 2012) entailing even more reduction in total number of injections needed for ovarian stimulation in IVF.

This long-acting rFSH has been claimed to be preferred over daily-administrated rFSH injections, but patient preference studies by means of a discrete choice experiment (DCE) to underpin this assumption have not been performed (Fauser et al., 2010; Youssef et al., 2012).

This present study aimed to determine women's' preferences for a long-acting rFSH product or standard daily-administrated rFSH injections using a DCE.

Methods

Participant recruitment

The study population consisted of women scheduled for their first IVF cycle who attended an IVF information gathering organized by the assisted conception units of the Maxima Medical Centre in Veldhoven, Onze Lieve Vrouwe Gasthuis and the Academic Medical Centre (AMC) in Amsterdam, The Netherlands. The information gathering sessions were held between April 2011 and April 2012. Subsequently, women were asked to participate and fill out the DCE. Participation was voluntary. The institutional review board of the AMC was informed about this study and approval for this study was not required. Informed consent was presumed by handing back the questionnaires.

DCE, attributes and levels

A DCE is a quantitative technique to elicit patient's preferences. The philosophy of a DCE is based upon two assumptions. First, a given treatment can be described by its characteristics or 'attributes', e.g. chance of developing OHSS and by variants of that characteristic or 'levels' e.g. 1, 2, 3 or 4% chance of developing OHSS (Ryan, 2004). Second, individual preferences for a medical treatment are determined by the levels of those attributes (Ryan, 2004). The relative importance of the attributes and the trade-offs that respondents make between them can be assessed by offering a choice set with several sets of attributes and systematically varying the levels of this attribute (Ryan et al., 2001). This is illustrated in Fig. 1. The selection of the attributes defines the DCE and should be chosen wisely. The choice for attributes and their levels is based on the literature and expert groups. For patients, a DCE is a straightforward task without outside influences (Mangham et al., 2009).

The choice for the attributes and attribute levels in our study was initially based on data from literature (Croxtall and McKeage, 2011; Musters et al., 2011; Verbost et al., 2011; Rombauts and Talmor, 2012; Youssef et al., 2012). Subsequently the input of a focus group consisting of experts in the field was taken into account to finalize the choice for attributes. The chosen attributes for this DCE were 'chance of ovarian hyperstimulation syndrome (OHSS)', which represents safety, the 'total number of injections' which represents efficiency and 'risk of cycle cancellation due to low response', which represent burden.

Since both treatment regimens result in similar pregnancy chances (Pouwer et al., 2012; Youssef et al., 2012), we did not take effectiveness into account, and as the long-acting and the daily-administrated rFSH are completely covered in the Netherlands, and prices of the two products are the same, we decided not to take willingness-to-pay into account. The chosen attribute levels were based on data from the literature and the focus group. The levels were partly hypothetical to make the difference more comprehensible to the respondents.

Per IVF cycle we set the attribute levels for 'chance of OHSS' ranging from 1 to 4%, with incremental steps of 1%. The 'total numbers of injections' per cycle were set at 3 or 9 subcutaneous injections. The attribute level of 'risk of cycle cancellation due to low response' ranged from 5 to 20% with incremental steps of 5% (Table I).

Development of the choice sets

The relative importance of the attributes and trade-offs that respondents make between hypothetical treatment alternatives was assessed by offering a series of 16 choice sets with various combinations of attribute levels.

The combination of two attributes at four levels and one attribute at two levels (Table I) provided 32 ($2^4 \times 2^1 = 32$) hypothetical alternatives for an IVF treatment. These 32 hypothetical treatment alternatives were converted into 16 discrete choice sets.

We used a fractional factorial design to generate a functional sample of these 16 alternative choice sets. The fractional factorial method systematically selects this sample according to an orthogonal design. Orthogonality
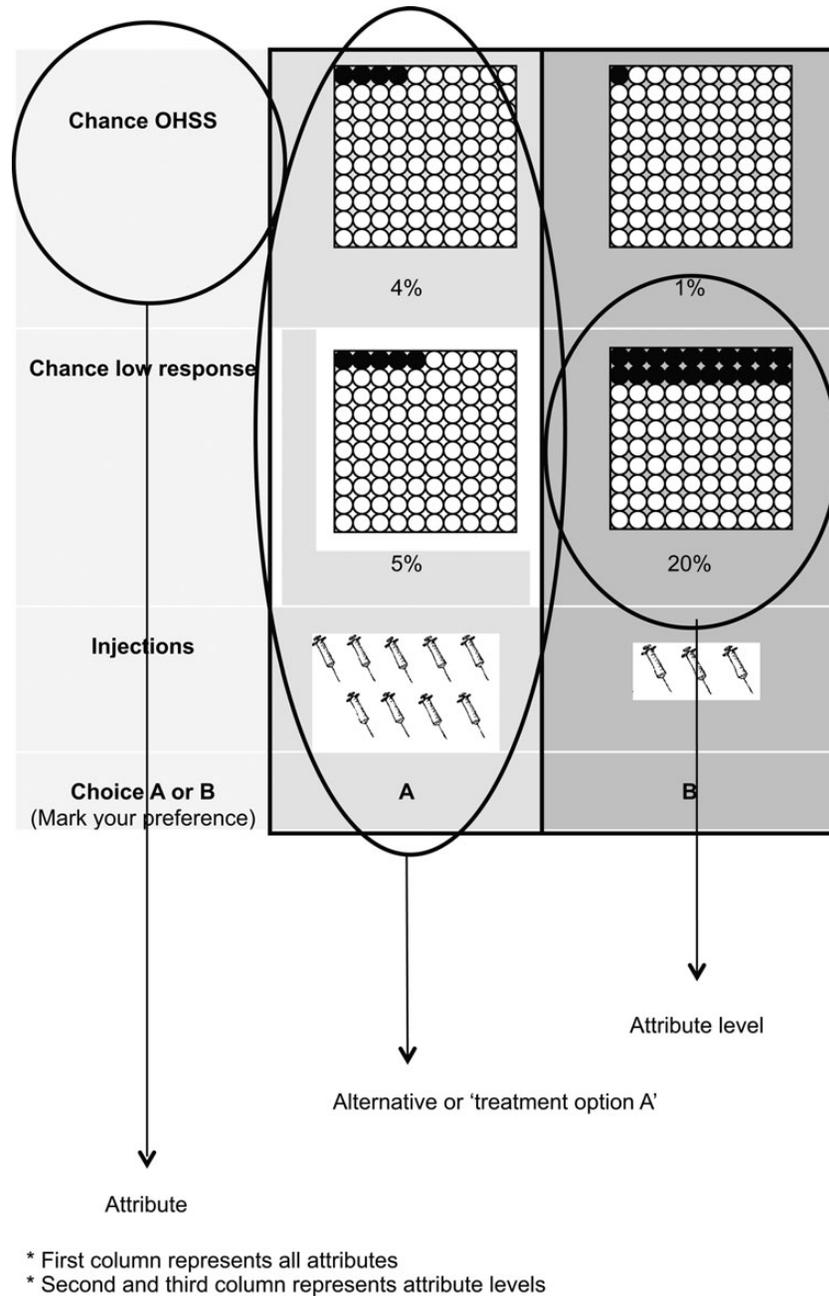
Figure 1 An example of a choice set, representing hypothetical alternatives for an IVF treatment, as presented in the questionnaire.

Sixteen alternative choice sets formed 'treatment A'. To ensure minimal overlap of attribute levels, we created a set of alternatives to form 'treatment B' by means of a syntactical fold over technique, based on the profiles of 'treatment A' (Ryan et al., 2001). This resulted in 16 different choice sets, whereby each choice set consists of two options representing hypothetical alternatives for an IVF treatment. The choice sets were visualized by pictures (Fig. 1). The 16 choice sets for treatment option A and B were considered sufficient to estimate all main effects representing the relative importance of each attribute.

Table I Attributes of treatment options with their corresponding levels.

Attribute	Levels
Total number of injections (per cycle)	'9' or '3'
Chance of OHSS	4, 3, 2, 1%
Risk of cycle cancellation due to low response	20, 15, 10, 5%

OHSS, ovarian hyperstimulation syndrome.

Women had to choose their most preferable option in each choice set, without an 'opt out' alternative (e.g. 'no treatment' option). All women who would like to undergo IVF treatment need a rFSH product, so 'no treatment' was not a realistic option.

The questionnaire contained two dominant choices (rationality tests) as control, in which all attributes were in favour of one of both choices.

The questionnaire provided extra contextual information about the topic and task instructions. Preceding the DCE, women were asked for demographic data, such as age, previous experience with fertility treatment and previous experience with subcutaneous injections. At the end of the DCE women were asked how easy or difficult they would score the DCE using a scale from 1 (extremely difficult) to 10 (extremely easy). The questionnaire was tested by IVF doctors and nurses at the AMC in Amsterdam, the Netherlands, to assess interpretation and validity before starting the study.

Statistical analyses

Data were cleaned (typographical errors corrected, variables recoded when necessary) and transferred to Stata SE 11 (StataCorp LP, College Station, TX, USA). For the demographic and exposure data we calculated means and standard deviations for continuous parameters and number and percentage for dichotomous or nominal data. We analysed the data using a mixed logit model for panel data.

The output of a mixed logit model includes mean coefficients (β) representing the relative utility of each attribute conditional on other attributes and standard deviations of the random coefficients, along with their respective confidence intervals (CIs).

We estimated mixed logit models with DCE attributes as the sole explanatory variables using Stata's mixlogit command (Hole, 2007). To understand how age and other parameters influence attributed preferences, we also estimated models that allowed for these factors to interact with the treatment-related attributes. Non-significant interaction terms were excluded from the model.

Trade-offs that respondents are willing to make between attributes were estimated by calculating the ratios of the coefficients of two attributes where we also accounted for preference heterogeneity. As both the constant and attributes were included as random parameters in the analyses, the trade-offs could not be calculated directly. We calculated importance scores with 95% CI to visualize the relative importance of a given attribute by dividing the difference in utility between highest and lowest level for a single attribute by the sum of the differences of all attributes. A simulation ($n = 1000$) was used to estimate the trade-offs.

Lastly, we repeated the analysis using: (i) a mixed logit model without 'irrational' respondents (respondents selecting the 'inferior' fixed task alternative), (ii) conditional logit (fixed effects only) models.

Results

Respondents

During the information gatherings, questionnaires were handed out to all participating women ($n = 125$) of which a total of 97 were returned. Response rate was 77.6% (97/125). Of these, four respondents did not answer the questionnaire completely. Hence there were 93 questionnaires available for analysis. The two dominant choices questions, which served as control questions, were answered correctly in 85 (91%) cases.

Demographic characteristics

The demographic characteristics of the population are shown in Table II. The mean age of the respondents was 33 years, and 37 years for their

Table II Baseline characteristics of women participating in the discrete choice experiment.

Age of woman ($n = 93$ out of 93 (100%))	*Mean:* 33 years (SD 4.9)
Age of partner ($n = 93$ out of 93 (100%))	*Mean:* 37 years (SD 8.1)
Level of education ($n = 92$ out of 93 (99%))*	
School not finished	2% ($n = 2$)
Secondary school	7% ($n = 7$)
Intermediate vocational education	36% ($n = 33$)
College/University	53% ($n = 49$)
Household income ($n = 90$ out of 93 (97%))**	
Low	9% ($n = 11$)
Moderate	28% ($n = 28$)
High	52% ($n = 51$)
Previous artificial reproductive techniques ($n = 92$ out of 93 (99%))*	
Yes	45% ($n = 41$)
No	55% ($n = 51$)
If Yes, what kind of procedure? ($n = 41$ out of 41 (100%))	
IVF/ICSI	7% ($n = 3$)
Intrauterine insemination	93% ($n = 39$)
If Yes, did the procedure result in a child? ($n = 41$ out of 41 (100%))	
Yes	10% ($n = 4$)
No	90% ($n = 37$)
If Yes, any side effects? ($n = 41$ out of 41 (100%))	
Not any side effects	68% ($n = 28$)
Mild side effects	32% ($n = 13$)
Serious side effects	0% ($n = 0$)
Any experience with subcutaneous injections? ($n = 92$ out of 93 (99%))*	
Yes	34% ($n = 31$)
No	66% ($n = 61$)
If Yes, what for? ($n = 28$ out of 28 (100%))	
Context of IVF/ICSI/IUI	97% ($n = 27$)
Context of different	3% ($n = 1$)
Grade of difficulty of the questionnaire (score 1–10) ($n = 93$)	*Mean:* 8 (SD 1.79)

*One person did not answer these baseline questions.
**Three persons did not answer this baseline question.

partners. Eighty-nine per cent of the respondents were at least educated on an intermediate level. The household income of the majority of the respondents was moderate or high. Forty-one out of 92 respondents (41%) reported a previous treatment with assisted reproductive techniques (ART), which was in 39 cases (93%) an intrauterine insemination procedure. Thirty-one respondents (34%) had previous experiences with subcutaneous injections. Thirteen out of 41 respondents with previous ART experience (32%) had experienced mild side effects (i.e. abdominal pains, headache and irritation on injections site). Twenty-eight respondents experienced 'no side effects' and not one respondent experienced 'severe side effects'. Respondents graded the DCE

questionnaire as 'easy' with an average of 8 points (SD 1.8) on a scale from 1 (extremely difficult) to 10 (extremely easy).

The importance of efficiency in relation to safety and burden of treatment

The results of the panel mixed logit regression model are shown in Table III. The mean coefficient (β) indicated the relative likelihood of choosing a rFSH product with a given attribute-level combination, while holding all other levels constant. The negative signs for 'risk of cycle cancellation due to low response' and 'chance of OHSS' indicated that women preferred the lowest 'risk for cycle cancellation due to low response' and lowest 'chance of OHSS'.

The estimated coefficient for each attribute had the expected sign and was statistically significant. All attributes were statistically significant on the choices of the respondents.

The lower 'number of injections' was preferred above the higher 'number of injections' (mean coefficient 1.25 versus −1.25; $P <$ 0.001). The estimated standard deviations for 'total number of injections' was not significant (SD 0.15 95% CI −0.11 to 0.41). This implies that there was no heterogeneity in preference across the participating women.

An increase of 1% in 'chance of OHSS' or 5% 'risk of cycle cancellation due to low response' was non-preferred (mean coefficients −0.31 and −0.24, respectively, $P < 0.01$). The estimated standard deviations for 'chance of OHSS' and 'risk of cycle cancellation due to low response' were significant (SD 0.26, 95% CI 0.12 to 0.58 and 0.29 CI 0.09 to 0.56, respectively). This implies heterogeneity in preferences across

Table III Results analysis (panel mixed logit regression).

	Coefficient (β)	95% Confidence Interval	P
Number of injections 3 versus 9			
Mean	1.25	1.04 to 1.45	<0.001
SD	0.15	−0.11 to 0.41	ns
Chance of OHSS[a]			
Mean	−0.31	−0.55 to −0.07	<0.01
SD	0.26	0.12 to 0.58	<0.01
Cycle cancellation due to low response[a]			
Mean	−0.24	−0.27 to −0.22	<0.001
SD	0.29	0.09 to 0.56	<0.01
Number of responses	2976		
Number of respondents	93		
Model fits			
Log likelihood	1425.9		
Akaike information criteria	1.91		
Bayesian information criteria	1.93		

[a]Per 1% increase.

the participating women. For some women 'risk of cycle cancellation due to low response' was more important than for other women.

The baseline variables age, previous ART procedures or previous experience with injections did not affect the women's choice. Significant interactions were not found and hence baseline variables and interaction terms were excluded from the model.

Willingness to trade-off efficiency in relation to safety and burden of treatment

Most respondents were willing to make trade-offs between all attributes. A 'low number of injections' would be traded for a 'higher number of injections' in exchange for a decrease of 6.2% (95% CI 2.8 to 9.4) in 'risk of cycle cancellation due to low response' or a decrease of 4.5% (95% CI 1.8 to 7.1) in 'chance of OHSS'.

Sensitivity analysis

We repeated the analysis excluding the eight 'irrational' respondents (respondents selecting at least one of the two 'inferior' fixed task alternatives) and found virtually overlapping mean coefficients and 95% boundaries.

A conditional logit was performed to evaluate whether a fixed model (i.e. a model not accounting for random effects) resulted in comparable outcomes as the primary mixed logit model. Both models were similar in direction of effect. The conditional logit model seemed to result in an overestimation of the differences in main effects when compared with the mixed logit model.

Discussion

The present study used a DCE to evaluate patients' preference for a long-acting rFSH product or daily-administrated rFSH injections. We found 'total number of injections' to be a strong attribute in determining women's preference. More precisely, for a 'lower number of injections' women were willing to accept a 4.5% higher 'change of OHSS' and 6.2% higher 'risk of cycle cancellation due to low response'. Previous 'experience with injections' and 'experiencing side effects' did not have any influence in their choice making.

These findings are somewhat unexpected, as it would seem logical that women would opt for the lowest 'risk of cycle cancellation due to low response' and the lowest 'chance of OHSS' instead of a lower 'number of injections' since a previous preference study showed that women even embrace additional daily injections, provided that it leads to better pregnancy rates (Musters et al., 2011).

The difference between the present and the previous study is that the treatment options did not influence the pregnancy outcome, since in the present study women were informed that both treatment regimens resulted in similar pregnancy chances.

As far as we know, this is the first study evaluating patients' preference for a long-acting rFSH product by means of a DCE. Two systematic reviews evaluated the effectiveness and safety of the products, but none of them involved patients' preferences (Pouwer et al., 2012; Youssef et al., 2012).

The use of a DCE is a validated tool to elicit these preferences and gives us an idea of what patients want. DCEs have become a commonly used instrument in health economics (de Bekker-Grob et al., 2012). Patient preference studies are upcoming in the field of reproductive medicine

and DCE-methodology is increasingly used to replace the time consuming interview used in the past (Nieuwkerk *et al.*, 1998; Bayram *et al.*, 2005; Steures *et al.*, 2005; Twisk *et al.*, 2007; van Weert *et al.*, 2007; van Mello *et al.*, 2010; Musters *et al.*, 2011; van den Wijngaard *et al.*, 2014). Especially when treatments modalities are equal in effectiveness and safety, patients' preference should be taken into account. Although relatively new, DCEs are an important stepping-stone in shared decision-making.

The study attributes and attribute levels were chosen with the help of an expert panel and data from the literature. The expert panel considered attributes as pregnancy rates, the 'chance of developing OHSS', 'cycle cancellation due to low response', daily injections or a few injections, costs, side effects, the duration of administration and the risk of treatment failure in case of omitting a single administration. The attribute 'treatment failure in case of omitting a single administration' was expected to be too insignificant to study. The potential attribute 'duration of administration' was already covered by the attribute 'number of injections', and overlap in attributes is not expedient.

We excluded pregnancy rates, side effects and costs from the present DCE as previous studies showed that use of a long-acting rFSH product results in comparable pregnancy rates and side effects (Pouwer *et al.*, 2012; Youssef *et al.*, 2012). Costs were not included because in the Netherlands the first three IVF treatments and medication are completely re-imbursed and the prices of rFSH products do not differ.

In this study we could rule out a large effect of 'previous experience with injections' and 'previously experiencing side effects' on women's choices, although an earlier study on patients preference comparing long-acting rFSH to daily-administered rFSH, showed that women with previous experience with long-acting rFSH had a tendency to prefer this (Requena *et al.*, 2013).

Our study had some limitations. First, since we did not register the characteristics of non-responders, we cannot exclude that non-responders would have made different choices. On the other hand we do not expect a large effect of non-response on the outcomes as we did not find a significant effect of patient characteristics on women's choices. Second, though the chosen attributes and levels were limited to simplify the DCE, 24% of the respondents found the questionnaire not easy to complete. This could have affected the reliability of the findings.

We had expected a stronger effect of OHSS. Although women were informed on the risks of OHSS they may not have understood the seriousness of the condition like clinicians do. It is also possible that the women considered that rare serious risks are unlikely to happen to them, and it has been shown that understanding risk assessment is difficult for most individuals (Calman, 2002; Slovic *et al.*, 2004).

Acknowledging these strengths and weaknesses, we feel that the data generated by this patient preference study provide more insight in the relative weight patients place on various aspects of a long-acting rFSH product. In our study women would trade-off an increase in 'risk of cycle cancellation due to low response' and 'chance of OHSS' to receive the long-acting rFSH product. A repeat of this experiment in an environment where ART is not re-imbursed is an option for future research, as respondents would perhaps choose differently if they have to pay for the medication, hospital visits and treatments themselves.

In summary, patients' preference for a long-acting rFSH product or a daily-administered rFSH product in IVF is primary influenced by 'total number of injections', followed by the 'risk of cycle cancellations due to low response'. The least important attribute was 'chance of OHSS', if pregnancy chances and side effects were comparable. Understanding the considerations of patients in expressing their preferences regarding rFSH products in IVF can contribute to improvement in patient counselling and shared decision-making.

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Authors' roles

I.C.M.R. L.v.d.W., M.v.W. and M.H.M. designed the study and were responsible for the development of the protocol. I.C.M.R., L.v.d.W., M.H.W.G.-v.E., C.A.M.K., H.R.V. and M.H.M were responsible for the logistical aspects of the study. I.C.M.R. collected all data and managed the database. M.v.W. did all statistical analyses. I.C.M.R., L.v.d.W., M.v.W. and M.H.M. drafted the manuscript. F.v.d.V. and B.W.J.M. commented on the drafted paper. All authors read and approved the final paper.

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Conflict of interest

None declared.

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