Pituitary down-regulation in IVF/ICSI: consequences for treatment regimens
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Chapter 3

Patients’ preference for GnRH-agonists or GnRH-antagonists in IVF or ICSI - a discrete choice experiment

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Background

Gonadotrophin-releasing hormone (GnRH) antagonists have proven to be an effective alternative to GnRH agonists in preventing premature LH-surges during controlled ovarian hyperstimulation in IVF or ICSI. There is however evidence that GnRH antagonists result in a lower ongoing pregnancy rate and live birth rate compared to GnRH agonists. Nevertheless, because of the significant shorter treatment duration, the significant lower chances of OHSS and the fewer side effects when using a GnRH antagonist, it is generally assumed that most women would express a preference for the antagonist above the agonist. To date, no patient preference study has been performed.

Method: We investigated patients’ preference for a GnRH agonist or a GnRH antagonist by means of a discrete choice experiment (DCE) by varying attribute-levels. Attributes considered in this study were pregnancy rate, duration of the treatment, OHSS risk and other side effects and whether a forgotten dose would compromise the treatment. Participants were IVF couples who attended an IVF information gathering, in the Academic Medical Centre (AMC) in Amsterdam or the Maxima Medical Centre (MMC) in Veldhoven, from February 2008 until October 2008.

Results: Hundred-fifteen couples participated in this study. At equal pregnancy rates of GnRH agonists and antagonists, most participants (95%) preferred the GnRH antagonist. At a trade of point of 2% in increasing the pregnancy rate of the GnRH agonists, the majority of the participants (82%) switched their preference from a GnRH antagonist to a GnRH agonist. The most important attribute was pregnancy rate, followed by OHSS risk, the presence of adverse side effects, and whether a single forgotten dose would lead to treatment failure. The duration of treatment was valued as the least important attribute.

Conclusion: In the realistic scenario of at least 2% higher pregnancy rate following GnRH agonist downregulated cycles, most IVF patients preferred a GnRH agonist above a GnRH antagonist.

Keywords GnRH antagonists, GnRH agonists, patients’ preference, DCE.
Introduction

Gonadotrophin-releasing hormone (GnRH) antagonists are an effective alternative to GnRH agonists in preventing premature LH-surges during controlled ovarian hyperstimulation in IVF/ICSI. Three systematic reviews and meta-analyses found that GnRH antagonists result in less ovarian hyperstimulation syndrome (OHSS) and other side effects, a shorter duration of treatment time, and a lower amount of gonadotrophin use as compared to GnRH agonists (Kolibianakis et al 2006, Griesinger et al., 2006, Al-Inany et al, 2006). Because of the significantly shorter treatment duration and less side effects when using a GnRH antagonist, it is generally assumed that most women would express a preference for the GnRH antagonist to the GnRH agonist. There is however evidence that GnRH antagonists result in a significant lower ongoing pregnancy rate and live birth rate compared to GnRH agonist; OR 0.82 (95% CI 0.68 to 0.97). (Al-Inany et al, 2006). To date, however, no patient preference study has been performed.

We therefore investigated the preferences of couples that were planned to undergo IVF or ICSI, for either a GnRH agonist or a GnRH antagonist by means of a discrete choice experiment (DCE). A DCE is capable of establishing preferences and to predict uptake in controlled experimental conditions, through responses to realistic and hypothetical scenarios (Ryan et al, 2004). A DCE will optimally lead to a greater understanding of the interaction between risk, benefit and the acceptance by patients, thereby facilitating the process of clinical decision making.

Methods

Participants

The study population comprised couples scheduled for their first IVF or ICSI cycle, who attended an IVF information gathering. These sessions were held at the fertility unit of the Maxima Medical Centre Veldhoven (MMC) and the Amsterdam Medical Center (AMC), between February 2008 and October 2008.

Interview procedure

During the information session, a presentation was held informing the couples in detail about the forthcoming IVF treatment, such as risks and side effects,
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the IVF stimulation protocol and accompanied medication use, oocyte retrieval procedure and success rates per clinic. When the IVF information session was finished, a second presentation for scientific reasons was announced. Attending this presentation was entirely voluntary; couples were allowed to leave. By showing slides, the working mechanisms and the (dis-)advantages of GnRH agonists (labeled as medication A) and GnRH antagonists (labeled as medication B) were explained. This entailed the following characteristics of medication A or B; risk of developing OHSS, adverse side effects (headache, flushes and insomnia), the duration of administration and the risk of treatment failure in case of forgetting a single administration (forgotten dose) (fig.1). These chosen characteristics were determined after reviewing the literature and were selected by gynaecologists and IVF-doctors in the fertility field (MMC Veldhoven and AMC Amsterdam).

Figure 1. Example of presentation slide

Question 1:
What would be your preference: Medication A or B?

Medication A:
- High risk of OHSS
- Adverse side effects like headache, flushes, insomnia
- Forgotten dose not compromises treatment
- Treatment duration long

Medication B:
- Low risk of OHSS
- No adverse side effects
- Forgotten dose compromises treatment
- Treatment duration short

In case of:
0%, 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%
increase in pregnancy rate comparing medication A to B

Subsequently the couples were asked to fill out two questionnaires, a general preference questionnaire and a discrete choice experiment questionnaire.

General preference questionnaire

The general preference questionnaire assessed patients' preference for medication A verses B with its typical characteristics given that pregnancy rates were equal. Subsequently, patients' preferences were asked what there preference was, while the pregnancy rate increased by incremental steps of 0.5 %, until a maximum of 5%, to determine the trade-off point (fig 1).
A discrete choice experiment

Discrete choice experiment, attributes and attribute levels

Preference for GnRH agonist or antagonist in IVF or ICSI was studied by means of a discrete choice experiment (DCE) (Ryan et al, 2001). A DCE assumes that a given treatment can be described by its specific characteristics or ‘attributes’ and that a preference for a treatment is determined by the levels of these attributes. The relative importance of the chosen attributes and trade-offs that patients make between them is assessed by offering a choice between several sets of alternatives with systematically varying combinations of attribute levels (Louviere et al., 2007).

The attribute levels of pregnancy rate during one cycle of IVF varied from 20% to 23% by incremental steps of 1%, the duration of treatment was called long or short, the risk of OHSS was 2.6% or 4.2% (Al Inany et al, 2006), adverse effects were present or not present, accidentally forgetting a single dose compromised the treatment or not.

The questionnaire consisted of choice sets. Each choice set was built up by two alternatives representing hypothetical scenarios of ‘medication A’ and ‘medication B’. The combination of the attribute pregnancy rate with 4 incremental steps of 1% and the other attributes with two levels (present or not present) provided 128 (4²×2⁴) hypothetical alternatives for a treatment. As it is not manageable to include all possible scenarios in the questionnaire, a functional sample of scenarios was generated using an orthogonal design with Orthoplan (SPSS version 16); this design warrants an optimal balance of the levels and attributes with minimal correlation (Louviere et al, 2007). This resulted in 32 orthogonal scenarios which were converted in 16 discrete choices which were presented to the patients. An example of a choice set is shown in figure II.

To assess the understanding of the attributes two control question containing two dominant choices were included (rationality tests) for validation purposes. In these sets one of the two GnRH analogue alternatives was characterised by equal or logically preferable levels on all attributes.
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Figure II. Examples (2) of choice set

**Question 1**

<table>
<thead>
<tr>
<th></th>
<th>Scenario 1</th>
<th>Scenario 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy rate</td>
<td>23%</td>
<td>22%</td>
</tr>
<tr>
<td>Increase OHSS risk</td>
<td>2.6%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Adverse side effects</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>A forgotten dose</td>
<td>has consequences</td>
<td>has consequences</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>Short</td>
<td>Long</td>
</tr>
<tr>
<td>What do you prefer?</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

**Question 8**

<table>
<thead>
<tr>
<th></th>
<th>Scenario 1</th>
<th>Scenario 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy rate</td>
<td>21%</td>
<td>20%</td>
</tr>
<tr>
<td>Increase OHSS risk</td>
<td>4.2%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Adverse side effects</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>A forgotten dose</td>
<td>has consequences</td>
<td>has no consequences</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>Short</td>
<td>Short</td>
</tr>
<tr>
<td>What do you prefer?</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

**Statistical analysis**

According to random utility theory, individuals are assumed to choose the alternative that provides the highest individual benefit or utility (U). In the case of a binary choice between two treatment methods, one would have:

\[
U(\text{medication A or B}) = b_0 + b_1(\text{Pregnancy}) + b_2(\text{OHSS}) + b_3(\text{adverse effects}) + b_4(\text{forgotten dose}) + b_5(\text{duration}) + e
\]

- \(U\) is the observable relative utility (i.e. satisfaction or happiness) that is composed of the preference scores for the individual \(\beta\)-coefficients of the model.
- \(\beta_0\) is the constant term which reflect the preference for medication A relative to medication B.
- \(\beta_1\) to \(\beta_5\) are the individual coefficients of the attributes pregnancy, OHSS, adverse effects, forgotten dose, duration, indicating the relative weight or importance individuals place on a certain attribute.
- \(e\) is error term

A random effects probit regression model (xprobit) was used to analyze the discrete choice data, using Stata 11 (Ryan and Farrar, 2000). To test whether there was heterogeneity in preference between men and women; gender was
A discrete choice experiment

taken as interaction term into the model. Non-significant interaction terms were excluded from the model such that the resulting model included main effects (all attributes) and significant interactions.

To express the relative values, or importance of the different attributes, the ratios of the main effects ($\beta$) were calculated $\beta / \beta_{1.5}$.

Results

94 couples participated in the study (73 heterosexual couples and 21 lesbian couples). All couples had a valid indication for IVF or ICSI according to the Dutch Fertility Guidelines. Of the 188 questionnaires 3 (2%) were not answered properly. Hence there were 185 (98%) questionnaires available for analysis.

General preference questionnaire

When equal pregnancy rates were assumed in both medication A and B, 176 of the 188 participants (95%) preferred the GnRH antagonist and nine participants (5%) preferred GnRH agonist. When a 5% increase in pregnancy rate the agonist group was assumed, 155 participants (82%) preferred the GnRH agonist and 33 participants (18%) kept their preference for the antagonist. At a mean trade off point of 2% (95% CI 1.8 to 2.2) 143 participants (82%) switched their preference from antagonists to antagonist.

There was no difference in trade-off point between women (mean 2.0%, 95% CI 1.7 to 2.3) and men (mean 1.9%, 95% CI 1.6 to 2.3) ($p = 0.86$).

Discrete choice experiment

175 participants (93%) volunteered to contribute to the DCE. Both control questions were answered correctly by all participants. The results of the probit regression model are shown in table 1. All attributes had a statistically significant impact on the individual preference. The most important attribute was pregnancy with a main effect of $+ 1.36$, meaning that an incremental step of 1% in increase in pregnancy rate is valued with a factor of $+ 1.36$. The least important factor was the duration of use with a main effect of - 0.39.
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Table I. Results of the probit regression model

<table>
<thead>
<tr>
<th>Main effect</th>
<th>SE</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy a</td>
<td>+1.36</td>
<td>+1.260 to +1.457</td>
<td>0.000</td>
</tr>
<tr>
<td>OHSS b</td>
<td>-1.18</td>
<td>-1.291 to -1.063</td>
<td>0.000</td>
</tr>
<tr>
<td>Adverse effects c</td>
<td>-1.10</td>
<td>-1.243 to -0.966</td>
<td>0.000</td>
</tr>
<tr>
<td>Forgotten dose d</td>
<td>-0.54</td>
<td>-0.709 to -0.379</td>
<td>0.000</td>
</tr>
<tr>
<td>Duration e</td>
<td>-0.39</td>
<td>-0.603 to -0.173</td>
<td>0.000</td>
</tr>
<tr>
<td>Constant term</td>
<td>-0.18</td>
<td>-0.070 to -0.222</td>
<td>0.070</td>
</tr>
</tbody>
</table>

Participants = 175; number of observations is = 2800. Log likelihood = -773.78; Probability > chi2 = 0.0000

a) Incremental steps of increase of 1%
b) Increase in OHSS risk from 2.6% to 4.2%
c) Present or absent

d) With or without treatment consequences
e) Long or short administration

Table II shows the relative weight or importance of the attributes by calculating the ratio of the main effects. An increase of an incremental step of 1% in pregnancy rate was 3.51 times more important than a longer duration of use, 2.50 times more important than a forgotten dose, 1.23 times more important than adverse effects and 1.15 times more important than OHSS risk. An increase in OHSS risk from 2.6 to 4.2% was valued 3.04 times more important than the duration of use, 2.16 times more important than a forgotten dose, 1.07 more important than adverse effects and 0.87 less important than pregnancy. In comparison to all other attributes, the duration of use was consequently valued as the least important attribute.

Table II. Relative weight of attributes (ratio of main effects)

<table>
<thead>
<tr>
<th></th>
<th>$\beta_j^*$</th>
<th>$\beta_j/\beta_{\text{pregn}}$</th>
<th>$\beta_j/\beta_{\text{ohss}}$</th>
<th>$\beta_j/\beta_{\text{adv-eff}}$</th>
<th>$\beta_j/\beta_{\text{dose}}$</th>
<th>$\beta_j/\beta_{\text{durat.}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy a</td>
<td>1.36</td>
<td>1.00</td>
<td>1.15</td>
<td>1.23</td>
<td>2.50</td>
<td>3.51</td>
</tr>
<tr>
<td>OHSS b</td>
<td>1.18</td>
<td>0.87</td>
<td>1.00</td>
<td>1.07</td>
<td>2.16</td>
<td>3.04</td>
</tr>
<tr>
<td>Adverse effects c</td>
<td>1.10</td>
<td>0.81</td>
<td>1.00</td>
<td>1.07</td>
<td>2.16</td>
<td>2.85</td>
</tr>
<tr>
<td>Forgotten dose d</td>
<td>0.54</td>
<td>0.81</td>
<td>0.94</td>
<td>1.00</td>
<td>2.03</td>
<td>2.16</td>
</tr>
<tr>
<td>Duration e</td>
<td>0.39</td>
<td>0.28</td>
<td>0.330</td>
<td>0.35</td>
<td>0.71</td>
<td>1.00</td>
</tr>
</tbody>
</table>

a) Main effect
b) Incremental steps of increase of 1%
c) Present or absent
d) With or without treatment consequences
e) Long or short administration
Discussion

It is generally considered important to determine which attributes really affect patients’ preference, since patients’ preferences have impact on clinical decision making (Kassirer, 1994; Montgomery and Fahey, 2001). This study evaluated patients’ preferences for GnRH antagonists or GnRH agonists in couples that were planned to undergo IVF or ICSI, using the most significant attributes.

Almost all participants (95%) that had been informed on the (dis-)advantages of GnRH antagonists versus GnRH agonists preferred the GnRH antagonists, provided that both agents result in equal pregnancy rates. However, the majority of participants switched their preference from GnRH antagonists to GnRH agonists when the pregnancy chance was increased in the GnRH agonist group at a trade-off point of 2%.

The most important attribute in the decision making of the participants was pregnancy rate, followed by an increase in OHSS risk. Contrary to our expectation, duration of use of medication was the least important attribute in the decision making of the participants. All the more remarkable since most clinicians assume that the main advantage a GnRH antagonist is its shorter duration of use.

As far as we know this is the first study evaluating the patients’ preference of GnRH analogues in IVF and ICSI, in couples eligible for IVF. The use of discrete choice experiments is a validated tool to elicit these preferences. The study attributes and attribute levels were chosen with the help of an expert panel and data from literature (Gyrd-Hansen and Sogaard, 2001; Sculpher et al, 2004; Marshall et al, 2007, 2009; Bekker-Grob et al., 2010). Our study also has some limitations. To make easy to follow trade-offs we had to limit ourselves in number of attributes and levels of each attribute. For instance, the attribute adverse effects had the option present or not present. Varying the chances of adverse effects would have been more informative, but carried the risk that the scenario would be too difficult to interpret.

Although acknowledging these weaknesses, we feel that the data generated by this patient preference study provide more insight on the relative weight couples place on various aspects of the down-regulation treatments and the treat-offs they make. This will most likely enable clinicians to improve their clinical decision making.

In summary, this preference and DCE study showed that patients’ preferences for GnRH antagonist or GnRH agonist are primarily influenced by
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pregnancy chances and least influenced by duration of administration. In a scenario of at least 2% higher pregnancy rates following GnRH agonist – which seems realistic in view of the data on effectiveness- most IVF patients preferred a GNRH agonist above GnRH antagonists.

Contribution of the authors

L. van den Wijngaard, medical student, manuscript drafting, data entry
M. van Wely, epidemiologist, data analysis, manuscript revising
S. van Voort, gynecologist in training, patient recruitment, executing DCE.
N.M. van Mello, gynecologist in training, comments on DCE design.
B.W.J Mol, trial design, scientific comments.
F. van der Veen, scientific comments, manuscript revising
M.H. Mochtar, data acquisition and interpretation, manuscript revising and corresponding author

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References


