Male subfertility and assisted reproduction: the quest for the ultimate treatment strategy
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Citation for published version (APA):
Patients’ preferences for intrauterine insemination or in vitro fertilization.

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Abstract

The aim of this study was to assess patients’ preferences for IUI relative to IVF using trade-off interviews and to assess the number of IUI cycles they would endure before they want to convert to IVF. A total of 73 couples undergoing IUI with a total of 111 interviews were included. We offered these couples scenarios in which the pregnancy chance after IUI with COH was varied against a fixed pregnancy rate after IVF. The probability of an ongoing pregnancy after one year of IUI was reduced or increased until the couple switched their preference. We also investigated the impact of the risk on a multiple pregnancy on the couple’s preference. The interviews were held before the start of IUI (baseline-group), after three or four IUI cycles (mid-group) and after six IUI cycles (end-group). With a decreasing probability of an ongoing pregnancy after IUI with COH, an increasing number of couples switched their preference from IUI to IVF. This switch occurred in the end-group at a statistically significant higher mean cumulative pregnancy rate (53%) as compared to the baseline- and mid-group (31%). With an increasing risk on a multiple pregnancy the preference for IUI declined only slightly in the baseline- and mid-group, with a mean risk of 73% and 78% on a multiple pregnancy, respectively. This percentage was statistically significantly higher in the end-group (83%). In conclusion, at baseline and after three cycles of IUI a majority of couples undergoing IUI preferred continuation of IUI over IVF. After six cycles there was a clear shift in preference towards IVF. The risk on a multiple pregnancy did not affect the preference for IUI with COH.

Key words: intrauterine insemination, in vitro fertilisation, preference, subfertility.
Patients’ preferences

Introduction

Intrauterine insemination (IUI) with or without controlled ovarian hyperstimulation (COH) is frequently used in the treatment of couples suffering from subfertility. Indications for IUI are mild male subfertility, cervical hostility or unexplained subfertility \(^1-4\). The overall pregnancy rates for IUI with COH vary between 9% and 36% per cycle \(^5,6\). When IUI fails, the next step usually is in vitro fertilisation (IVF). The pregnancy rates after IVF vary from 12% to 33% per cycle \(^7-9\). At present, it is unclear how many cycles of IUI should be given before proceeding to IVF. Some authors advocate that after four to six cycles of IUI the pregnancy rates decline \(^2,4,5,10,11\) while others suggested that there are still acceptable pregnancy rates achievable until the 10\(^{th}\) cycle \(^12,13\).

In the decision when to proceed to IVF after IUI there are some important medical and non-medical issues to consider. The priority of the clinician is obviously to select the proper patients for IUI to achieve acceptable pregnancy rates. This selection should ideally be based on the subfertility diagnosis followed by the use of prediction models \(^14,15\).

Although both IUI with controlled ovarian hyperstimulation (COH) and IVF are associated with the risk of multiple pregnancies \(^16\), IVF bears the risk of ovarian hyperstimulation syndrome (OHSS), which is virtually absent in IUI.

The non-medical issues concern the higher costs of IVF and the more intensive treatment strategy with a higher drop out rate relative to IUI \(^6,17\).

Nowadays, it is generally acknowledged that patients’ preferences should also be incorporated into medical decision making \(^18\). Several studies have shown that patients’ perspectives on the burden and benefits of therapy can differ from those of the health professionals \(^19,20\). Therefore, the decision when to start and how long to continue IUI or proceeding to IVF should not only be based on the expected success rates of these treatments, but should also be based on the preferences of couples for either IUI or IVF. Patients’ preferences in Reproductive Medicine can be studied by a trade-off interview \(^20,21,22\).

In a previous study on patient preferences for expectant management versus IUI in unexplained subfertility, we found that couples prefer IUI with or without COH when the probability of a treatment-independent pregnancy in the next 12 months is \(<50\%\) and \(<40\%\), respectively. The risk of a multiple pregnancy did not affect their preference for IUI \(^20\).
The aim of the present study was to assess in patients undergoing IUI their preferences for IUI versus IVF and their valuation of the risk of a multiple pregnancy, at different times during their IUI treatment and using the same trade-off design.

**Material and methods**

**Interviews**

The study was performed between July 2003 and September 2004 at the Academic Medical Centre (AMC) and the Onze Lieve Vrouwe Gasthuis (OLVG) in Amsterdam, The Netherlands. We used the same methodology as in a previous study on patients’ preferences for either expectant management or IUI. Couples with unexplained subfertility, mild male subfertility or cervical hostility who were starting or undergoing IUI, were invited to participate in this study, as these are the indications for IUI in our clinic. In case of additional anovulation, ovulation induction was performed prior to IUI. All women received mild ovarian hyperstimulation during IUI treatment with 75U of follicle stimulating hormone. A language barrier was a reason for exclusion, but as all couples entering a treatment programme in our clinic should master either Dutch or English this did not lead to any exclusions.

The selection of couples depended upon the presence of the interviewer on non-fixed scheduled days. The interviewer was a recently graduated doctor with experience in the field of subfertility. Prior to the interview, baseline characteristics of these couples were abstracted from their medical files. These included female age, fertility treatment in the past, cycle history and presence and outcome of earlier pregnancies. The interviews took place at three different stages, i.e. when couples started IUI (baseline-group), after the third or fourth cycle (mid-group), and after the sixth IUI cycle (end-group). Couples were followed during their IUI cycles and if possible, they were asked for a second and/or third interview. A structured interview was designed to assess patients’ preference for IUI relative to IVF conditional on the probability of a pregnancy after IUI. The interviews were conducted by the same person in a standardized manner with the aid of a standardized information sheet on IVF en IUI. Most interviews took place with both partners present. The aim of the interviewer was to elicit agreement upon the responses of both partners.

Firstly, in all interviews detailed information was given about IVF. Ovarian hyperstimulation during IVF, oocyte retrieval and embryo transfer were explained.
The pregnancy rate per IVF cycle in the interview was set at 20% per cycle. It was explained that one in two couples would be pregnant after three cycles. The possibility of single embryo transfer was not discussed. Subsequently, the interviewer provided structural information about the adverse effects of IVF. The risks and consequences of ovarian hyperstimulation syndrome (OHSS) were explained with its diverse expressions such as nausea, pain, ascites, hospitalisation, thrombo-embolism and, as an ultimate consequence, death. The possibility of severe OHSS in this interview was set at 2% per cycle. Furthermore, possible cancellation of an IVF cycle was discussed, e.g. in case of threatening OHSS or in case of poor follicle development. Additionally, information on the risk of a multiple pregnancy and its possible implications such as premature birth and its implications for future development of the child, hospitalisation (incubator), a lower birth weight and maternal complications like pre-eclampsia, were given. The possibility of a multiple pregnancy after IVF in this interview was set at 25% per ongoing pregnancy.

Secondly, the interviewer provided information about IUI with COH i.e. controlled ovarian hyperstimulation, follicular growth monitoring, ovulation induction and insemination procedure. As the chance on an ongoing pregnancy after IUI was the variable in the trade-off interviews, no set pregnancy rate was mentioned. Furthermore, structural information was given on the adverse effects of IUI with COH. The possible cancellation of IUI was discussed, and the virtual absence of OHSS in our clinic was mentioned. Additionally, it was stated that, similarly to IVF, the risk of a multiple pregnancy and its possible consequences existed. The chance of a multiple pregnancy after IUI with COH in this interview was set at 30% per ongoing pregnancy. The information given by the interviewer was similar to the counselling before the start of IUI in our clinic. IVF is in the Netherlands not an alternative for these couples but a second line therapy, so an extensive explanation of IVF was not part of the counselling process before the start of IUI.

The interviewer asked the couple whether IUI with COH or IVF was preferred in a scenario with a 50% probability of a pregnancy after one year of IUI with COH. Depending on the preference of the couple, the probability of a pregnancy after IUI was subsequently de- or increased with 5% steps until they switched their initial preference.

To determine the impact of the risk of a multiple pregnancy on their preference, couples were asked if they would continue IUI with COH in a
scenario with 0% chance of having a multiple pregnancy after IUI with COH or would prefer IVF. If a couple chose IUI with COH, we systematically increased the probability of a multiple pregnancy with steps of 5% until the couple did prefer not to continue IUI with COH and switched to IVF.

**Data analysis**

Since one couple could have been interviewed more than once, each interview was analysed as a separate unit. We calculated the mean probability of a pregnancy after IUI with COH, at which couples switched in their decision from IUI to IVF. These calculations were performed in three subgroup analyses i.e. the baseline-group, the mid-group and the end-group. Furthermore, differences in the mean thresholds between the groups were analysed using a one-way analysis of variance. To visualize the thresholds of the patients, we plotted the percentage of couples that preferred IVF for each respective probability of a pregnancy after IUI with COH.

To evaluate the impact of multiple pregnancies, we calculated the mean thresholds at which couples would switch from IUI with COH to IVF and compared the mean thresholds between the groups in a one-way analysis of variance.

We anticipated that the couples' preferences might be influenced by their baseline characteristics. Therefore, we assessed the association between baseline characteristics on one hand and the threshold-preference for each couple on the other hand. The continuous baseline characteristics (female age and duration of subfertility) were assessed using Spearman correlation coefficients, whereas preference thresholds of categorical baseline characteristics, i.e. subfertility being primary or secondary, fertility treatments, having a child or not and having a regular or irregular cycle, where compared using Student’s T-tests.
Results

We interviewed 73 couples, of which 41 were interviewed once, 26 were interviewed twice and six couples were interviewed three times. In total 111 interviews were taken, 33 interviews in the baseline-group, 45 interviews in the mid-group (after 3-4 cycles), and 33 interviews in the end-group (after 6 cycles).

Preferences related to probability of pregnancy

The baseline characteristics are listed in Table 1.

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>All couples (n=73)</th>
<th>Baseline group (n=33)</th>
<th>Mid-group (n=45)</th>
<th>End-group (n=33)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)*</td>
<td>34.4 (26.4-40.6)</td>
<td>33.8 (26.4-39.8)</td>
<td>34.1 (27.0-40.5)</td>
<td>34.5 (27.5-40.6)</td>
<td>0.69</td>
</tr>
<tr>
<td>Duration of subfertility (years)*</td>
<td>3.7 (0.4-9.9)</td>
<td>3.0 (0.4-7.1)</td>
<td>4.2 (1.0-9.9)</td>
<td>4.35 (1.11-9.5)</td>
<td>0.09</td>
</tr>
<tr>
<td>Anovulation*</td>
<td>7 (10%)</td>
<td>4 (12%)</td>
<td>4 (9%)</td>
<td>1 (3%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Secondary subfertility*</td>
<td>31 (42%)</td>
<td>16 (48%)</td>
<td>18 (40%)</td>
<td>12 (36%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Live born*</td>
<td>15 (21%)</td>
<td>8 (24%)</td>
<td>8 (18%)</td>
<td>6 (18%)</td>
<td>0.75</td>
</tr>
<tr>
<td>History of IUI*</td>
<td>15 (21%)</td>
<td>6 (18%)</td>
<td>10 (22%)</td>
<td>7 (21%)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

* Ranges are given in parentheses. \* Percentages are given in parentheses. \* Number of live-born children born to couples with secondary subfertility.

Baseline group= before the start of IUI; mid-group=after three or four cycles; end group=after six cycles. There were no statistically significant differences between the groups.

Overall, the mean female age was 34.4 years, the mean duration of subfertility was 3.7 years and anovulation was present in seven (10%) women. In total 31 couples (42%) suffered from secondary subfertility. From these couples 15 (21%) had at least one live born child. A total of 15 (21%) couples had a history of IUI in a previous episode of subfertility. The baseline characteristics of the three groups showed no statistical differences.

With decreasing probability of an ongoing pregnancy after IUI with COH, an increasing number of couples switched their preference from IUI to IVF (Figure 1).
Figure 1. Patients’ preferences for intrauterine insemination with ovarian hyperstimulation as expressed as a function of the probability of a pregnancy after IUI with ovarian stimulation. COH=controlled ovarian hyperstimulation.

In the end-group couples switched their preference to IVF at higher pregnancy rates of IUI with COH as compared to the baseline-group and mid-group. In the baseline-group 97% of couples opted for IUI with COH if the pregnancy rate with IUI in the next 12 months was set at 100%. In the mid-group this percentage was 98% and end-group all but two couples (94%) would opt for IUI with COH with this scenario. In the baseline- and mid-group three couples refused treatment with IVF (9% and 7%, respectively), even if they had no chance to conceive with IUI. In the end-group this was only one couple (3%). The mean threshold for a pregnancy in the next 12 months with IUI at which couples switched their preference from IUI to IVF was 31% at baseline, 31% in the mid-group and 53% in the end-group.

Analysis of variance showed a significant difference in the means of the thresholds between all groups with an overall difference of 11% (p=0.01). When analyzing the groups separately, there was no statistical difference between the baseline group and the mid-group (difference 0.6% p= 0.91), whereas a
significant difference was found between the mean of the thresholds in the baseline group and the end-group (difference 21%, p=0.002) and the mid-group and the mean of the threshold in end-group (difference 21%, p<0.01).

Preferences related to probability of multiple pregnancy

With an increasing probability of a multiple pregnancy after IUI with COH an increasing number of couples would switch their preference from IUI to IVF in the baseline- and mid-group (Figure 2).

![Figure 2. Patients’ preferences for IUI with ovarian stimulation as a function of the probability of a multiple pregnancy](image)

In the end-group, few couples were influenced in their preference for either IUI or IVF based on the probability of a multiple pregnancy. The majority of couples that would continue IUI with COH even at a probability of a multiple pregnancy of 50% would still do so even at a 100% probability of a multiple pregnancy. If the risk of a multiple pregnancy after IUI was set at 0%, 82% (27 couples) of the baseline group, 69% (31 couples) of the mid-group, and 42% (14 couples) of the end-group would continue IUI. In the baseline group, 16 (59%) couples that had initially preferred IUI would continue IUI even at a 100% certainty of achieving a multiple pregnancy. In the mid-group and in
the end-group this was the case for 19 couples (61%) and ten couples (71%), respectively. The mean threshold at which the couples in the baseline group with an initial preference for IUI switched their preference to IVF was at a risk of 73% on a multiple pregnancy, 78% in the mid-group, and 83% in the end-group.

Analysis of variance showed a significant difference in the means of the thresholds between all groups with an overall difference of 12% (p=0.02). When analyzing the groups separately, there was no statistical difference between the baseline group and the mid-group (difference 5% p=0.63), whereas a significant difference was found between the mean of the thresholds in the baseline group and the end-group (difference 12%, p=0.03) and a borderline significant difference between the mid-group and the mean of the threshold in end-group (difference 20%, p=0.05).

No significant correlation was found between female age and duration of the subfertility and the thresholds of the couples. We also did not find any statistically significant differences in the mean of the thresholds of couples when divided in groups for primary or secondary subfertility, presence of anovulation or history of IUI or not.

Discussion

The provision of information before treatment is an essential aspect of fertility care in terms of patient satisfaction, preparation and anxiety reduction. It can lead to a marked reduction in non-attendance at clinic appointments for IVF.

This study shows that the valuation of IUI was different at different stages of a treatment programme. At the start and after three or four cycles of IUI, couples would on average expect a cumulative pregnancy rate of 31% in a year to continue with IUI. After six cycles of IUI couples would on average expect a statistically significant higher cumulative pregnancy rate of 53% in a year to continue this treatment. Since a cumulative pregnancy rate of 53% after six unsuccessful IUI cycles seems unrealistic, we concluded that very few couples would be inclined to continue IUI after six cycles in daily practice.

Another notable finding was that more than 70% of couples that initially preferred IUI over IVF would continue this treatment at a 100% certainty of getting a multiple pregnancy, with 83% of couples after six cycles of IUI. The lack of a negative attitude towards multiple pregnancies in subfertile couples has been described before. One could argue that these couples lack knowledge...
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about the risks of a multiple pregnancy and are therefore not capable of making a reasoned decision for one or the other treatment. Most couples with subfertility are however well informed about these risks, and, even if these risks are systematically emphasised, were more concerned about perceived treatment failure than about iatrogenic complications, such as a multiple pregnancy. In our study, we performed structured interviews in which the potential disadvantages of multiple pregnancies were emphasized systematically.

In spite of these efforts, patients preferred treatment even at a considerable risk of a multiple pregnancy. Our study clearly demonstrates that structured information on the potential hazards of multiple pregnancies has little impact on patients’ preferences. Considering the fact that the association between pregnancy chance and risk of multiple pregnancy was not discussed with the couples, the impact of the potential hazards of a multiple pregnancy might be even lower on patient preferences.

This study and our previous study on patients preferences for expectant management versus IUI unambiguously show that the valuation of a multiple pregnancy by subfertile couples is independent of whether they have just finished the basic fertility work up or undergoing fertility treatment.

There are some methodological issues to consider. Preference studies are prone to interpretation bias of patient and interviewer. First of all, preference measurements are subject to instability over time because patients acquire more information on the treatment side effects and effectiveness during their course of treatment. We interviewed patients on different moments in their treatment course to give more insight into this instability. Not all couples were interviewed at baseline but as we used the interview (at baseline, after three cycles and after six cycles) rather than the couples as separate units in the analysis, this has not led to selection bias.

Secondly, there are instrument related biases such as the presentation and interpretation of the mentioned risks. For instance, in a face-to-face interview there are more tools to inform the patient in a manner that fits her intelligence and background knowledge but at the same time such an intervention is prone to a subjective presentation of the facts by the interviewer. Possibly, this bias is present in our study because the instrument we used was a face-to-face interview by a single interviewer.

Thirdly, one could argue that the patients entered in this study had
already been counselled to undergo IUI in the first place and would have been informed about the risks and success rates of IUI by the clinician entering them in IUI program. Couples undergoing IUI could therefore only be couples that chose IUI over IVF anyway. This is however not the case in the Netherlands, where most patients can as a rule only undergo those treatments that have been advised by their clinician, using Dutch guidelines and indications.

Fourthly, patient preferences are undoubtedly influenced by social and cultural differences. Specifically, the differences in reimbursement policy concerning artificial reproductive therapies between different countries make the results of this preference study not applicable to for instance a subfertility population in the United States. In the Netherlands most patients are adequately insured and will be reimbursed for most of their fertility treatments. This study portrays the preferences of patients without the influence of financial issues.

Finally, confounding factors like multiparity and female age did not have a statistically significant impact on patient’s preferences but this could be due to the number of patients included. To reach definitive conclusions about the impact of confounding factors a larger study is needed.

It was found that a few couples had a pre-set preference for either IUI or IVF (four couples for IUI and three couples for IVF). They showed little confidence in the other treatment option even when risks on side effects and complications were significantly in or decreased. This was despite the fact that couples had received thorough information about these potential risks of treatments.

The IUI success rate in the Netherlands is 9% per cycle and the contribution made by IUI to the number of multiple pregnancies in the Netherlands was much smaller than the contribution made by IVF. These data were not used in the counselling of couples, as these data had not been published yet. If we combine the results of this national survey with the results of our preference study, we could argue that if patient preferences were taken into account after counselling with these data, almost no one would prefer IUI over IVF (lower success rate, lower multiple pregnancy rate)!

In summary, at the start of IUI with COH and after three to four cycles the majority of our patients wanted to continue this treatment. After six cycles most couples demanded such high cumulative pregnancy rates with IUI that continuation of IUI became unrealistic and IVF would be preferred. The risk on a multiple pregnancy hardly affected the preference for IUI with COH in relation to IVF. These data should be incorporated into clinical guidelines on IUI and IVF.
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References


