Intrauterine insemination: Fine-tuning a treatment
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Couples dropping out of a reimbursed intrauterine insemination program: what is their prognostic profile and why do they drop out?

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ABSTRACT

Objective: To evaluate whether baseline characteristics and prognostic profiles differed between couples who drop-out from IUI and couples that continue IUI, and the reasons for couples dropping-out from IUI programs.

Design: Retrospective observational cohort study

Setting: Three fertility centres in the Netherlands

Patients: Consecutive subfertile couples undergoing IUI.

Interventions: None

Main Outcome Measure: Characteristics and prognosis on ongoing pregnancy after IUI, calculated by the model of Steures et al., at the start of treatment, of couples that dropped-out compared to couples that continued treatment or achieved an ongoing pregnancy.

Results: We studied 803 couples who underwent 3,579 IUI cycles of whom 221 couples dropped-out (28%). Couples dropping-out completed 2.8(SD±1.4) cycles per couple compared to 4.5(SD±2.3) cycles per couple for those continuing treatment. Couples dropping-out had a higher female age, longer subfertility duration and higher basal FSH. Mean prognosis to achieve an ongoing pregnancy after IUI at start of treatment was 7.9% (SD±2.4) per cycle for couples who dropped-out, and 8.5%(SD±2.5) per cycle for couples continuing treatment. Of the dropouts, 100 couples (45%) were actively censored from the IUI-programme of whom 87 couples (39%) because of poor prognosis. 121 Couples (55%) were passively censored from the program of whom 62 (28%) dropped-out due to personal reasons. 59 Couples (27%) were lost-to-follow-up.

Conclusions: We found significant differences in prognostic profile between couples continuing treatment and couples dropping-out, although these differences seem limited from a clinical perspective. We conclude that overestimation of ongoing pregnancy rates after IUI due to couples dropping-out is limited.
INTRODUCTION

The majority of couples that face involuntarily childlessness seek medical help. Although most couples are very motivated in achieving their ultimate goal of parenthood at the start of their fertility treatment, many couples -up to 60% - stop treatment before an ongoing pregnancy is achieved. Even in countries where fertility treatment is completely reimbursed, dropout is a well known phenomenon.

Studies on couples who drop out from fertility treatment have so far almost solely focused on couples receiving IVF. Reasons why many couples withdraw from IVF appear to be a poor prognosis for achieving a pregnancy after the actual treatment, psychological distress associated with IVF or financial reasons. Thus far, only a few studies focused on drop out during the entire period of fertility work-up and subsequent treatment. Until now, no single study has addressed drop out in a population undergoing intra-uterine inseminations (IUI) as a first line treatment.

Since couples who drop out from an IUI program typically disappear from our sight, they usually are not included in analyses of success of IUI programs. This is worrisome, because selective dropout of poor prognostic couples might lead to over-estimation of cumulative pregnancy rates and this hampers us to counsel couples realistically on their chances of ongoing pregnancy after intra-uterine insemination.

The aim of this cohort study was therefore to evaluate in retrospect, whether baseline characteristics and prognostic profiles differed between couples who drop out from IUI and couples that continue IUI, and to register the reasons for couples dropping out from IUI programs.

MATERIALS AND METHODS

Patients and procedures
Consecutive subfertile couples undergoing IUI between January 2000 and January 2008 were included in the study. For these patients, IUI treatments as well as the use of necessary medication was covered by their reimbursement programme. Data were collected from three fertility centres in the Netherlands: Academic Medical Center, Amsterdam; TweeSteden Hospital, Tilburg and Onze Lieve Vrouwe Gasthuis, Amsterdam. All couples had been trying to conceive for at least 12 months and underwent a basic fertility workup according to the guidelines of the Dutch Society of Obstetrics and Gynaecology (http://nvog-documenten.nl).

Couples had not been pre-selected by the use of a prognostic model. IUI was offered for the diagnoses male subfertility, cervical factor subfertility, unexplained subfertility or one-sided tubal pathology according to National guidelines and local protocols. Male subfertility was defined as a Total Motile Count (TMC) < 10*10^6 /mL. Cervical factor subfertility was diagnosed by means of at least one well-timed post coital test (PCT) in which no...
progressive motile spermatozoa were seen in five high-power fields at a magnification of 400 (TMC at least 10 million). For each treated couple, female age, duration of subfertility, primary or secondary subfertility, total motile semen count, type of controlled ovarian stimulation (COS), basal FSH level and diagnosis was registered.

For couples dropping out from treatment as well as for couples continuing treatment, the baseline characteristics were recorded and with these variables the prognosis on an ongoing pregnancy after IUI at the start of the first cycle was retrospectively calculated by a validated prediction model for IUI by Steures et al., 200421 (formula see appendix). In case the type of COS (Clomiphene citrate or gonadotropins) was not registered, we assumed gonadotropins had been used, since this is the most widely used protocol in the Netherlands.

A couple was considered a dropout if they had not utilized six completed cycles of IUI, which are reimbursed by Dutch healthcare companies or achieved an ongoing pregnancy. Pregnancies were divided in treatment related pregnancies and spontaneous pregnancies in between treatment cycles. A treatment cycle was considered complete if processed semen was inseminated; all other cycles were registered as started cycles. Couples who intended to proceed to in vitro fertilization were also registered. If a couple dropped out, their record was assessed for the reason for dropping out, at least 6 months after their last visit. All outcomes of basic fertility work-up and treatment had been registered in an electronic database at the time of treatment of the couple as well conventional written charts.

Reasons for dropping out were divided in four categories: poor prognosis as estimated by the treating physician, technical IUI related problems, personal reasons (burden of treatment, no confidence in IUI, health problems not IUI related, relational problems, moving house or adoption), or unknown reasons (lost to follow up).

We defined couples that were advised to stop treatment by their doctor because of poor prognosis or IUI related, technical problems as actively censored drop outs. Couples that dropped out by their own choice due to personal reasons, or couples lost to follow up were defined as passively censored drop outs.

Because the study is a retrospective observational cohort study, Institutional Review Board approval was not required.

Statistics

Differences in baseline characteristics, including prognostic profiles between couples dropping out of treatment and couples continuing treatment, as well as subgroups, were calculated with ANOVA or Mann-Whitney test as appropriate using Spss 18.
RESULTS

We studied 803 couples who started 3,579 IUI cycles, of which 3,237 were completed cycles. There were 221 (28%) couples that stopped treatment before finishing six completed cycles of IUI and did not achieve an ongoing pregnancy. 152 Couples (69% of all dropouts) had stopped treatment after the third insemination. Of the remaining 582 couples that continued treatment, 307 had an ongoing pregnancy (38% of all couples) of which 264 were IUI related and 43 occurred spontaneously between treatment cycles (Figure 1).

Figure 1. Flowcharts of couples continuing IUI and couples dropping out during intra-uterine insemination
Baseline characteristics of couples that dropped out and couples that continued IUI are summarized in table 1. Mean female age (SD) was higher in the group of dropouts (34.2 ± 4.2 versus 33.5 ± 3.9 years; p 0.04) as well as the duration of subfertility (3.4 ± 2.1 versus 3.0 ± 1.7 years; p 0.00) and baseline FSH (7.5 ± 6.5 versus 6.7 ± 4.3 U/l; p 0.02). We found no significant differences in all other characteristics. The overall prognosis (SD), calculated retrospectively by the model of Steures et al., at start of treatment on an ongoing pregnancy was 7.9% (2.4) per cycle for couples dropping out and 8.5% (2.2) per cycle for couples continuing treatment (p=<0.001) (Table 1).

The mean number (SD) of started cycles was 3.2 (1.4) for couples that dropped out versus 4.9 (2.6) for couples continuing IUI. The mean number (SD) of completed treatment cycles was 2.8 (1.4) versus 4.5 (2.3) (Table 2).

Of the 221 couples that dropped out, 100 couples (45%) were actively censored from the programme (table 3). From these 100 couples 87 (39%) were advised to stop because

### Table 1 Baseline characteristics dropouts versus couples continuing treatment

<table>
<thead>
<tr>
<th></th>
<th>Drop outs (n=221)</th>
<th>Patients continuing (n=582)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female age in years, mean (SD)</td>
<td>34.2 (4.2)</td>
<td>33.5 (3.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Duration subfertility in years, mean (SD) median</td>
<td>3.4 (2.1) 2.9</td>
<td>3.0 (1.7) 2.6</td>
<td>0.00</td>
</tr>
<tr>
<td>Primairy subfertility(%)</td>
<td>192 (87)</td>
<td>538 (92)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical (%)</td>
<td>48 (22)</td>
<td>141 (24)</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>45 (20)</td>
<td>109 (19)</td>
<td></td>
</tr>
<tr>
<td>Unexplained (%)</td>
<td>94 (43)</td>
<td>241 (41)</td>
<td></td>
</tr>
<tr>
<td>Tubal pathology (%)</td>
<td>26 (12)</td>
<td>66 (11)</td>
<td></td>
</tr>
<tr>
<td>Multiple diagnoses (%)</td>
<td>8 (4)</td>
<td>25 (4)</td>
<td></td>
</tr>
<tr>
<td>TMC mean (SD) median</td>
<td>78.8 (126)</td>
<td>88.8 (117)</td>
<td>0.18</td>
</tr>
<tr>
<td>FSH U/l, mean (SD) median</td>
<td>7.5 (6.5)</td>
<td>6.7 (4.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Chance ongoing pregnancy/ cycle at start treatment (SD)</td>
<td>7.9 (2.4)</td>
<td>8.5 (2.2)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

### Table 2 Treatment characteristics dropouts versus patients continuing treatment

<table>
<thead>
<tr>
<th></th>
<th>Dropouts (n=221)</th>
<th>Patients continuing (n=582)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number started cycles</td>
<td>713</td>
<td>2866</td>
</tr>
<tr>
<td>Total number completed cycles</td>
<td>625</td>
<td>2612</td>
</tr>
<tr>
<td>Total number unfinished or cancelled cycles (%/ started)</td>
<td>88 (12)</td>
<td>254 (8.9)</td>
</tr>
<tr>
<td>Mean number started cycles (SD)</td>
<td>3.2 (1.4)</td>
<td>4.9 (2.6)</td>
</tr>
<tr>
<td>Mean number completed treatments (SD)</td>
<td>2.8 (1.4)</td>
<td>4.5 (2.3)</td>
</tr>
</tbody>
</table>
A poor prognosis was expected in case of advanced female age, long duration of subfertility or unexpected poor semen quality during treatment. The retrospectively calculated prognosis with the IUI prediction model of Steures et al., in these couples was an ongoing pregnancy chance of 7.6% per cycle at the start of their treatment which was only slightly lower than the overall prognosis for the total group of couples that dropped out (7.9%). Thirteen couples (5.9%) were advised to stop IUI because of treatment related technical problems, such as repeatedly premature ovulation, repeated cycle-cancellation due to risk of a high-order multiple pregnancy or failure to monitor the cycle due to poor visibility of the ovaries. All of these 100 actively censored couples that dropped out were planned to continue with in vitro fertilization after stopping IUI.

Passive censoring occurred in 121 couples (55%). Of these couples, 62 couples (28%) dropped out because of personal reasons. Fifty-nine couples (27%) were lost to follow up: 54 did not return for treatment without further notice and five couples had a spontaneous pregnancy in between treatment cycles of which four women miscarried. Of one couple we were not able to find out if the pregnancy was ongoing or not.

**DISCUSSION**

The present cohort study in couples that underwent IUI showed that couples dropping out of an IUI program have a significantly different prognostic profile as compared to couples that continue IUI. Women were significantly older, duration of subfertility was longer and the prognosis for an ongoing pregnancy at the start of IUI treatment was significantly lower for couples that dropped out. Although statistically significant, the absolute difference of
this prognosis for an ongoing pregnancy at the start of treatment was very small (only 0.6%; 7.9% and 8.5% respectively) and therefore seems to be clinically irrelevant. Assuming that pregnancy chances only declined at increasing cycle number and all couples would continue treatment until six cycles, we calculated that the cumulative ongoing pregnancy rate after 6 cycles in the entire population would add up to 41%, in patients who dropped out of treatment 39% and in patients who continued treatment 42%. The observed ongoing pregnancy rate was 38% (307 ongoing pregnancies in 803 couples), which corresponds exactly with these calculations based on the prediction model of Steures et al.

The subgroup of couples who were advised to stop treatment because of alleged poor prognosis would reach an estimated cumulative ongoing pregnancy rate of 37%. It is possible that other considerations such as patients preference or relative efficacy of IVF for the individual couple also played a role in decision making to stop IUI-treatment, but it is likely that doctors are not effective in estimating the patients’ prognosis if they do not use a prediction model. This is in line with a previous study that found that gynaecologists differed widely in their estimation of prognosis on a spontaneous pregnancy of subfertile couples.22 This emphasizes that the use of prediction models in counselling couples to stop or continue treatment is essential; it might prevent premature referral to more invasive treatments as IVF.

In our cohort, the treatment cycles were completely reimbursed. Decision making by couples and physicians to stop or continue treatment was therefore not influenced by direct costs through treatment. Indirect costs by foregone wages were not mentioned by any of the couples as a reason to stop treatment.

We could not differentiate between the commitments of couples using clomiphene or gonadotropins as the vast majority had used gonadotropins which was the standard protocol at the time of the study. Furthermore, psychological distress did not appear to be a main reason for dropping out of treatment: dropping-out due to the “burden of the treatment” and “no confidence in treatment” occurred in 16% of the couples. However, 27% of the couples that did not return for further treatment were lost to follow-up. It is possible that in this group a portion of the couples found the treatment too burdensome. An important issue and possible shortcoming of the present study is that “burden of the treatment” and no “confidence in treatment”, classified as psychological distress, was interpreted by the treating physician and not by standard interviews or a questionnaire because of the retrospective nature of the study.

In IVF poor prognosis and psychological distress are the main reasons for dropping out.5,16,17 It is possible that the main reasons for dropping out differs between IUI and IVF because after IUI there are still alternative options to achieve pregnancy, whereas IVF might be considered as “last resort”.


In conclusion, we found that the observed pregnancy rates after IUI are overestimated due to patient drop out. This overestimation however is limited and it is therefore unlikely that we counsel our patients too optimistically.

Appendix:

The formula for prediction of an ongoing pregnancy is as follows:

\[ \text{Probability} = \frac{1}{1+\exp(-\beta)} \]

Where \( \beta = -1.41 + (\text{maternal age} \times -0.03) + (\text{duration of subfertility} \times -0.03) + (\text{cervical factor} \times 0.27) + (\text{male factor} \times -0.14) + (\text{one-sided tubal pathology} \times -0.15) + (\text{uterine anomaly} \times -0.98) + (\text{endometriosis} \times -0.34) + (\text{use of clomiphene citrate} \times 0.21) + (\text{use of HMG or FSH} \times 0.23) + (\text{cycle number [up to six]} \times -0.09). \]
REFERENCES


