Why do couples drop-out from IVF treatment? A prospective cohort study

M.F.G. Verberg1,4, M.J.C. Eijkemans1,2, E.M.E.W. Heijnen1, F.J. Broekmans1, C. de Klerk3, B.C.J.M. Fauser1 and N.S. Macklon1

1Department of Reproductive Medicine and Gynaecology, University Medical Centre Utrecht, Heidelberglaan 100, 3584 CS Utrecht, The Netherlands; 2Department of Public Health, Erasmus Medical Centre Rotterdam, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands; 3Department of Medical Psychology and Psychotherapy, Erasmus Medical Centre Rotterdam, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

4Correspondence address. E-mail: m.f.g.verberg@umcutrecht.nl

BACKGROUND: Cumulative IVF pregnancy rates are compromised by the large number of couples who drop-out of treatment before achieving pregnancy. The aim of this study was to identify the role of the treatment strategy applied, and potential other factors that influence the decision of couples to discontinue treatment. METHODS: The incidence of drop-out from IVF treatment and factors related to drop-out were studied in a cohort of IVF patients aged <38 years embarking on IVF treatment either with a mild or a standard treatment strategy for a planned maximum number of treatment cycles. RESULTS: Of the 384 couples studied, 17% dropped out of IVF treatment. The physical or psychological burden of treatment was the most frequent cause of drop-out (28%). The application of a mild treatment strategy (mild ovarian stimulation along with the transfer of a single embryo) significantly reduced the chance of drop-out (hazard ratio (HR) 0.55; 95% confidence interval (CI), 0.31–0.96). When a mild IVF strategy was employed, the association between the baseline anxiety score and drop-out was reduced by >50%. The presence of severe male subfertility (HR 4.80; 95% CI, 1.63–14.13) and the failure to achieve embryo transfer (odds ratio 0.41; 95% CI, 0.24–0.72) were also related to drop-out. CONCLUSIONS: Reducing drop-out rate is crucial to further improve the efficacy and cost-effectiveness of IVF treatment. An important factor determining the risk of drop-out is the burden of the treatment strategy. The application of a mild treatment strategy and managing patient’s expectations might reduce drop-out rates.

Keywords: drop-out; discontinuation; IVF; mild ovarian stimulation; stress

Introduction

The ovarian stimulation regimens applied for in vitro fertilization (IVF) and intracytoplasmatic sperm injection (ICSI) treatment are expensive, complex and associated with significant side-effects and stress (Fauser et al., 2005; Macklon et al., 2006). High rates of drop-out are therefore frequently encountered in IVF and ICSI treatment. Drop-out from IVF treatment should be considered an adverse treatment outcome since early cessation of treatment deprives the couple an optimal cumulative chance of achieving pregnancy, and therefore impacts on the overall success of the IVF program. The importance of drop-out from IVF treatment has been highlighted by the increasing trend towards reporting IVF outcomes in terms of cumulative success rates per complete treatment or per period of time (instead of per cycle) (Johnson et al., 2003; Heijnen et al., 2004). Average drop-out rates well above 50% have frequently been reported in literature (Callan et al., 1988; Land et al., 1997; Tan et al., 1992; Olivius et al., 2002; Schroder et al., 2004).

It is often assumed that patients withdraw from IVF treatment for only two reasons: the withholding of further treatment because of a poor prognosis (active censoring) and inability to pay for further treatment (Cousineau and Domar, 2007). Although some studies observe a high incidence of patients with a poor prognostic profile among those who elect to discontinue treatment (Stolwijk et al., 1996; Sharma et al., 2002) other studies have not confirmed this (Haan et al., 1991; Roest et al., 1998; de Vries et al., 1999). Furthermore, studies from countries where the costs of IVF are reimbursed indicate that actively censored patients constitute a minority of drop-outs (Land et al., 1997; Olivius et al., 2004). An important reason why many patients drop-out from IVF treatment before they have received all reimbursed treatment cycles appears to be psychological distress associated with IVF treatment (Olivius et al., 2004). As previously published, additional factors involved in drop-out include the age of the male partner, previously successful IVF treatment, parity of...
of couples to discontinue treatment.

There are also indications that the nature of the ovarian stimulation protocol applied might determine the extent of psychological stress and drop-out rates from IVF treatment. A study by Høggaard et al. (2001) showed that the patients receiving minimal ovarian stimulation IVF (unstimulated or Clomiphene Citrate stimulated cycles) reported fewer side-effects and stress related to hormone treatment and cycle cancellation compared with conventional stimulation. A recent publication by our group showed that the drop-out rate following two cycles of a mild ovarian treatment strategy was significantly lower than following a similar number of cycles using a conventional approach (Heijnen et al., 2007).

Insight into the factors that influence the decision of couples to discontinue treatment and their reasons for dropping-out may allow early identification of women at risk and the tailored interventions to improve treatment compliance, and as a result, improve cumulative pregnancy rates and the cost-effectiveness of IVF programs. The aim of this study was to prospectively assess the incidence of drop-out from fully reimbursed IVF treatment and to identify the role of the treatment strategy applied and potential other factors that influence the decision of couples to discontinue treatment.

Materials and Methods

Subjects and study design

The subjects of this study were participants in a randomized controlled trial comparing the efficacy of a mild treatment strategy with a conventional treatment strategy (Heijnen et al., 2007). Detailed information on the design and clinical outcomes and preliminary findings regarding the effect of each protocol on the drop-out rate of this study has been described previously (de Klerk et al., 2006; Heijnen et al., 2007). The study was approved by the local ethics review boards of both participating centers, and written informed consent was obtained from each participant.

Infertile patients with a regular indication for IVF or ICSI who attended the Erasmus Medical Center (Rotterdam, the Netherlands) and the University Medical Center Utrecht (Utrecht, the Netherlands) were invited to participate. Participants were <38 years of age, had a regular menstrual cycle (25–35 days) and a body mass index between 18 and 28 kg/m². Only couples with no previous IVF treatment or a healthy born child after a previous IVF treatment were included. Data of all patients that actually started treatment were included in the present study.

IVF treatment protocol

The mild treatment strategy consisted of ovarian stimulation with a fixed daily-dose of 150 IU recombinant follicle stimulating hormone (rFSH) (Gonal-F®: serono Benelux B.V., Amsterdam, the Netherlands; or Puregon™: N.V. Organon, Oss, the Netherlands) subcutaneously (s.c.) per day, initiated on cycle day 5 as previously published (Heijnen et al., 2007). In order to prevent premature luteinization, a gonadotrophin-releasing hormone (GnRH) antagonist (ganirelix, Orgalutran®: N.V. Organon, 0.25 mg/day; or cetorelix, Cetrootide®: Serono Benelux, 0.25 mg/day) was administered s.c. when at least one follicle ≥14 mm was observed. In cycles resulting in the development of less than three pre-ovulatory follicles no oocyte retrieval was performed. Human choriocgonadotrophin (hCG) (Profasi®, Serono Benelux B.V.; or Pregnyl®; N.V. Organon) 10 000 IU s.c. was administered for the triggering of final oocyte maturation. Oocyte retrieval and fertilization were performed according to standard procedures, as described previously (Kastrop et al., 1999; Huisman et al., 2000). The single best-quality embryo was transferred. The luteal phase was supported with progesterone, 600 mg/day, intravaginally. Excess embryos of sufficient quality were cryopreserved and transferred in a subsequent unstimulated cycle according to standard procedures. The maximum planned number of mild strategy IVF cycles was four.

The conventional IVF approach included pituitary down-regulation with a GnRH agonist initiated during the mid-luteal phase of the pre-treatment cycle (Leuproline, Lucrin®; Abbott B.V., Amstelveen, the Netherlands, 0.2 mg/day s.c.; or triptoreline, Decapeptyl®; Ferring B.V., Hoofddorp, the Netherlands, 0.1 mg/day s.c.). After 2 weeks of GnRH agonist administration, ovarian stimulation was started with a daily-dose of 150 IU/day rFSH s.c. Similar criteria applied for cancellation, hCG, oocyte retrieval and fertilization procedures as in the mild strategy group. In the conventional approach, a maximum of two embryos were transferred. Luteal phase support and criteria to cryopreserve embryos were applied as in the mild strategy. The maximum planned number of conventional strategy IVF cycles was three. In both arms of the study, the costs of all treatment cycles were reimbursed to the patient.

Patients were considered as treatment drop-outs when they did not return for a further IVF cycle within 1 year after the failure of the previous cycle, before they had completed the planned number of treatment cycles. The drop-out cycle was defined as the treatment cycle preceding discontinuation of treatment. Cancelled cycles were considered as treatment cycles, frozen embryo transfer cycles were not. A cycle not resulting in an ongoing pregnancy was considered to be a failed cycle. Patients who did not complete the total number of cycles offered because they became pregnant (either spontaneously or following treatment) were not considered drop-outs. Owing to the difference in the maximum number of treatment cycles offered per treatment protocol, patients treated by the conventional strategy could drop-out following the first or second treatment cycle while patients in the mild strategy arm of the study could also drop-out following a third treatment cycle.

Surveys were sent out to couples who did not return for further treatment within 6 months following a failed attempt (including frozen embryo transfers). Patients were asked whether they intended to return for further treatment and if not what was their primary reason for drop-out. Some couples received medical advice to discontinue treatment because of a poor ovarian response or poor embryo quality. However, this advice was not binding, patients were allowed to finish the full number treatment cycles according to the randomized protocol if they wished to.

Non-cycle-related explanatory variables analyzed for drop-out included the age of the male and female partner, cause and duration of infertility, delay before the start of the first treatment cycle, previous pregnancy and previous live birth. In addition, previous fertility treatment (intra-uterine insemination or ovulation induction) prior to the IVF treatment and the education level of the female partner were considered as potential factors. Also, pre-existing symptoms of depression and anxiety as were measured on the Hospital Anxiety and Depression Scale (HADS) were considered. The HADS was developed as a screening tool to measure symptoms of anxiety (HADA) and depression (HADD) experienced by medical patients in the week prior to screening (Zigmond and Snaith, 1983). Both subscales (range 0–21) of the HADS consist of seven items, which are scored on a four-point-Likert scale from 0 to 3. Higher scores imply the presence of more symptoms. Cut-off scores for possible and...
probable depressive and anxiety disorder are 7/8 and 10/11, respectively. The Dutch version of the HADS has shown good test–retest reliability, homogeneity and internal consistency (Spinhoven et al., 1997).

In addition to non-cycle-related factors, the role of events occurring during the drop-out cycle was also investigated. This analysis included voluntary delay before the start of the cycle, the number of treatment days, whether or not the cycle was cancelled, the number of oocytes retrieved and, whether the cycle resulted in an embryo transfer and the quality of the embryo(s) transferred. In addition, the incidence of complications such as ovarian hyperstimulation syndrome or infection, whether the treatment included transfer of cryopreserved embryos, the occurrence of early pregnancy loss and the number of visits patients paid to a physician after the failed treatment were analyzed.

Statistical methods
To compare the drop-out rate between the two treatment strategies applied, Kaplan–Meier survival analysis was performed with the discrete time-variable being the cycle number and censoring (losses from the sample before the final outcome is observed) for patients who achieved an ongoing pregnancy during the period of the study (both spontaneous and following embryo transfer).

To analyze the influence of other potential risk factors on the chance of drop-out, Cox’s proportional hazards analysis was performed with correction for the treatment strategy employed. HRs for the risk of dropping-out of further IVF treatment were calculated (including 95% CI). Logistic regression with correction for the treatment strategy applied was used to evaluate the effect of cycle characteristics on the cycle-specific chance of drop-out. To allow for the pooling of data from different treatment cycles within the same patients, logistic regression was performed with correction for cycle number.

A chi-square test was performed to analyze the difference in reasons for drop-out between both treatment protocols. A value of \( P < 0.05 \) was considered to be statistically significant. Analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA, 1999) and S-plus 7.0 (Insightful Corp., Seattle, WA, USA).

Results
Subjects and distribution of drop-outs
A total of 384 patients underwent treatment. Table I shows the number of participants per cycle in each treatment protocol. Fig. 1 shows the number of patients that underwent treatment and the final outcome after completing the treatment. Thirty-five patients elected to discontinue treatment following mild stimulation; eight (23%) after the first cycle, 12 (34%) after the second cycle and 15 (43%) following the third cycle. In those undergoing conventional stimulation, 30 patients dropped-out; 13 (43%) following cycle 1 and 17 (57%) following cycle 2. Although the cumulative number of drop-outs was similar in both treatment groups, the drop-out rate per cycle was lower in the mild strategy group (7.7 versus 10.0%); Cox analysis of the difference in cumulative drop-out rates between the two treatment strategies applied showed a significant difference (HR 0.55; 95% CI, 0.31–0.96; \( P = 0.034 \)) in favor of patients treated in the mild stimulation arm of the study (Fig. 2).

The causes of drop-out are summarized in Fig. 3; the principal reason for dropping-out was the physical or psychological burden of treatment (28%). Twenty-five percent of patients did not provide a reason for not returning for treatment. In 14% of drop-out patients, the primary reason for stopping treatment was a poor prognosis identified by a physician (actively censored). Seventy-six percent of the drop-outs were voluntary (passively censored). There were no significant differences in the distribution of reasons for dropping-out between the treatment groups (\( P = 0.44 \)).

Characteristics of drop-out patients
The HR and 95% CI for cycle independent risk factors after correction for the treatment strategy applied are depicted in Table II. The indication for IVF was significantly related to the chance of discontinuing treatment (\( P = 0.040 \)). Patients with severe male subfertility (and therefore treated by ICSI) had a significantly higher risk of dropping-out of treatment (HR 4.80; 95% CI, 1.63–14.13). Additionally, there was a tendency towards a significant effect for female age (HR 0.94; Table I. The number of participants per cycle for both treatment protocols.

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Standard</th>
<th>Mild</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>189</td>
<td>195</td>
<td>384</td>
</tr>
<tr>
<td>2</td>
<td>112</td>
<td>153</td>
<td>265</td>
</tr>
<tr>
<td>3</td>
<td>107</td>
<td>107</td>
<td>214</td>
</tr>
<tr>
<td></td>
<td>301</td>
<td>455</td>
<td>756</td>
</tr>
</tbody>
</table>
In other words, given the same increase in the level of relieve, relative reduction in hazard: 0.84; 95% CI, 0.72–0.99).

HADA scale point in the conventional and mild group, respectively, relative reduction in hazard: 0.84; 95% CI, 0.72–0.99). In other words, given the same increase in the level of measured symptoms of anxiety, couples undergoing the mild strategy were half as likely to discontinue treatment as those undergoing conventional stimulation. None of the other studied risk factors showed significant interaction with the stimulation protocol applied.

**Discussion**

The aim of the present study was to prospectively assess the rate of drop-out after a complete course of IVF treatment and identify the role of the treatment strategy applied and potential other factors which increase the risk of a couple electing to discontinue reimbursed IVF treatment. The use of a mild treatment strategy was found to be associated with a reduction in drop-out rate. In particular, patients considered to be at an increased risk of giving up treatment due to high pre-existing levels of anxiety symptoms were found to be less prone to drop-out when a mild stimulation protocol was applied. After correction for the treatment strategy applied, the chance of drop-out was observed to be significantly increased when severe male subfertility was the treatment indication and when embryo transfer had not been performed.

The positive effect of a mild treatment strategy on the chance of discontinuing treatment was previously observed in a subgroup of the current studied population (Heijnen et al., 2007). In our previous preliminary analysis (restricted to data from the first two cycles), the drop-out rate per cycle was also significantly lower in the mild treatment group compared with the conventional group (OR 0.53; 95% CI, 0.28–0.98). The positive effect of the mild treatment strategy appears to be related to a reduction of anxiety and treatment-related stress, as mild ovarian stimulation provides a shorter and more patient friendly treatment and reduces the risk of complications (Fauser et al., 1999; Hohmann et al., 2001). Consistent with this, a recent study concluded that the failure of IVF treatment after a mild treatment strategy resulted in fewer symptoms of depression as compared with failure after a conventional treatment strategy (de Klerk et al., 2007). The fact that patients knew they had four instead of three treatment cycles might also have positively influenced the drop-out rate.

### Table II. Hazard ratios for the chance of dropping-out of IVF treatment after correction for treatment strategy applied (384 couples with 756 treatment cycles).

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age woman</td>
<td>0.94 (0.87–1.01)</td>
<td>0.088</td>
</tr>
<tr>
<td>Age man</td>
<td>1.00 (0.95–1.05)</td>
<td>1.0</td>
</tr>
<tr>
<td>Duration of infertility</td>
<td>1.01 (0.90–1.13)</td>
<td>0.8</td>
</tr>
<tr>
<td>Category of infertility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometriosis</td>
<td>0.82 (0.11–6.39)</td>
<td>0.8</td>
</tr>
<tr>
<td>Male</td>
<td>0.94 (0.46–1.94)</td>
<td>0.9</td>
</tr>
<tr>
<td>Severe male</td>
<td>4.81 (1.63–14.14)</td>
<td>0.004</td>
</tr>
<tr>
<td>Unknown</td>
<td>1.32 (0.60–2.89)</td>
<td>0.5</td>
</tr>
<tr>
<td>Immunological</td>
<td>1.34 (0.29–6.14)</td>
<td>0.7</td>
</tr>
<tr>
<td>Tubal*</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Delay before the initiation of the first treatment cycle</td>
<td>1.00 (1.00–1.01)</td>
<td>0.4</td>
</tr>
<tr>
<td>Previous pregnancy</td>
<td>0.94 (0.49–1.80)</td>
<td>0.9</td>
</tr>
<tr>
<td>Previous childbirth</td>
<td>1.19 (0.70–2.01)</td>
<td>0.5</td>
</tr>
<tr>
<td>Previous fertility treatment</td>
<td>0.78 (0.48–1.27)</td>
<td>0.3</td>
</tr>
<tr>
<td>Pre-existing depression</td>
<td>1.06 (0.95–1.17)</td>
<td>0.3</td>
</tr>
<tr>
<td>Pre-existing symptoms of anxiety</td>
<td>1.05 (0.97–1.14)</td>
<td>0.21</td>
</tr>
<tr>
<td>Educational level of the woman</td>
<td>**</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Intra-uterine insemination or ovulation induction. 2 Measured on the hospital anxiety and depression scale (HADS). **Reference category. **Hazard ratios for the individual education levels were not given because there was no significant correlation with the chance of drop-out.

95% CI, 0.87–1.01), indicating a higher chance of discontinuing treatment with lower female age at the start of the treatment.

Of the risk factors associated with events during the drop-out cycle only the failure to achieve embryo transfer was found to be significantly related to the chance of discontinuing treatment (odds ratio (OR) 0.41; 95% CI, 0.24–0.72;  P = 0.002) (Table III).

The association between the baseline score on HADA and the chance of drop-out was found to be significantly dependent on the treatment strategy applied (HR 1.38 versus 1.16 per HADA scale point in the conventional and mild group, respectively, relative reduction in hazard: 0.84; 95% CI, 0.72–0.99). In other words, given the same increase in the level of anxiety and depression scale (HADS). *Reference category. **Hazard ratios for the individual education levels were not given because there was no significant correlation with the chance of drop-out.
in the mild treatment group. Taken together, these data suggest that a mild treatment strategy constitutes a more patient-friendly treatment protocol and the decrease in drop-out rate can itself compensate for a slightly lower pregnancy rate per cycle observed with the mild approach. The overall low drop-out rate in our study compared with the drop-out rate reported in observational studies may reflect the study context. Participants in this study were necessarily more closely observed and may have responded positively to the additional attention they received.

The chance of dropping-out was observed to be increased when severe male subfertility was the indication for IVF treatment. It has been previously shown that male infertility is associated with greater levels of psychological morbidity than other indications for IVF (Connolly et al., 1992), although recently others could not confirm this finding (Holter et al., 2007). Additionally, in our study population, couples with severe male subfertility were less likely to have had pretreatment with IUI or ovulation induction ($P = 0.006$) compared with those undergoing IVF for other indications. Having not previously faced the disappointment of treatment failure, this group may have relatively high expectations with regard to their chance of conceiving following IVF treatment. Consequently, these patients might be less able to cope with the disappointment of a failed IVF cycle, and may be more likely to drop-out of treatment.

Patients whose treatment did not result in embryo transfer were also found to be more prone to discontinue treatment. This could be the result of distress caused by disappointment and loss of hope in a successful outcome. Previous studies have shown that a perceived poor prognosis was strongly associated with stress and was an important reason for drop-out (Sharma et al., 2002; Malcolm and Cumming, 2004; Rajkhowa et al., 2006). Couples were found to have a poor understanding of cumulative live birth rates with three or more attempts despite good awareness of the chance of success per IVF treatment cycles (Rajkhowa et al., 2006). These findings highlight the importance of managing expectations in IVF treatment. If couples are counseled to focus less on the chance of an individual cycle resulting in pregnancy, and encouraged to think in terms of a course of treatment aimed at achieving a live birth, they may be less likely to drop-out of treatment (Fauser et al., 2005).

There is an increasing trend towards the use of milder stimulation approaches for IVF, aiming to achieve a cost-effective and more patient friendly regimen (Nargund and Frydman, 2007). The efficacy of such treatment programs is dependent on the outcome following successive treatment cycles instead of the pregnancy rate per cycle (Fauser et al., 2005; Heijnen et al., 2007). Crucial to the success of these programs is a reduction in drop-out rates. Until now, most research in this area has focussed on psychological interventions to reduce treatment-related stress (Boivin, 2003). However, the beneficial effect on drop-out rates has never been shown and many patient couples consider such counseling unnecessary (de Klerk et al., 2005). Additionally, randomized studies of counseling interventions on treatment-related stress have shown no significant effect (de Klerk et al., 2005). This study shows that the use of a mild strategy reduces drop-out rates, and that patients at increased risk of discontinuing treatment can be specifically identified. Recognition of the factors which cause couples to drop-out of IVF treatment allows interventions to be designed aimed at reducing drop-out rates and to further improve the efficacy and cost-effectiveness of IVF treatment.

**Author roles**

M.F.G.V.—Substantial contributions to conception and design, analysis and interpretation of data, drafting the article and final approval of the version to be published.

M.I.C.E.—Substantial contributions to conception and design, analysis and interpretation of data, drafting the article and final approval of the version to be published.

E.M.E.W.H.—Substantial contributions to acquisition of data, revising the article critically for important intellectual content and final approval of the version to be published.

F.J.B.—Substantial contributions to conception and design, revising the article critically for important intellectual content and final approval of the version to be published.

C.de—Substantial contributions to acquisition of data, revising the article critically for important intellectual content and final approval of the version to be published.

B.C.J.M.F.—Substantial contributions to conception and design, revising the article critically for important intellectual content and final approval of the version to be published.

N.S.M.—Substantial contributions to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.

**Funding**

This study was funded by ZonMw (The Netherlands), program Doelmatigheidsonderzoek (Grant no. 945-12-010).

**References**


Submitted on January 4, 2008; resubmitted on May 1, 2008; accepted on May 7, 2008.