

# Pregnancy chances on an IVF/ICSI waiting list: a national prospective cohort study

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**BACKGROUND:** The effectiveness of IVF over expectant management has been proven only for bilateral tubal occlusion. We aimed to estimate the chance of pregnancy without treatment for IVF patients, using data on the waiting period before the start of IVF. **METHODS:** A prospective cohort study included all couples eligible for IVF or ICSI treatment, registered in a national waiting list in The Netherlands. The cumulative probability of treatment-free ongoing pregnancy on the IVF waiting list was assessed and the predictive effect of female age, duration of infertility, primary or secondary infertility and diagnostic category was estimated using Cox regression. **RESULTS:** We included 5962 couples on the waiting list. The cumulative probability of treatment-free ongoing pregnancy was 9% at 12 months. In multivariable Cox regression, hazard ratios were: 0.95 ( $P < 0.001$ ) per year of the woman's age, 0.85 ( $P < 0.001$ ) per year of duration of infertility, 0.71 ( $P = 0.005$ ) for primary versus secondary infertility. Diagnostic category showed hazard ratios of 0.7, 1.6, 1.2, 1.7 and 2.6 for endometriosis, male factor, hormonal, immunological and unexplained infertility, respectively, compared with 'tubal infertility' ( $P < 0.001$ ). The 12-months predicted probabilities ranged from 0% to 25%. **CONCLUSIONS:** The chance of an ongoing pregnancy without treatment while waiting for an IVF or ICSI is below 10% but may be as high as 25% within 1 year for selected patient groups. Timing of IVF should take predictive factors into consideration.

**Keywords:** IVF; ICSI; spontaneous pregnancy; infertility

## Introduction

The indications for IVF have been widened considerably since its introduction in 1978. Whereas in earlier days, bilateral tubal occlusion was seen as the only reason to perform IVF, nowadays IVF is used for virtually any diagnostic category of infertility. Yet, it is only for the tubal indication group that convincing evidence from a RCT is available (Soliman *et al.*, 1993). For patients with patent tubes, another RCT showed that IVF was superior to expectant management (Hughes *et al.*, 2004) over a 3 month time horizon. Combining these studies, Pandian *et al.* (2005) found a significant advantage for IVF over expectant management for unexplained infertility, but numbers were low and the duration of follow-up was considered to be inadequate. The evidence base for other diagnostic categories is entirely lacking.

The alternative treatment options for the other categories are not many: for tubal pathology, endometriosis and for severe male infertility, the choice is between waiting for a pregnancy or start IVF or ICSI. For idiopathic, mild male or

cervical subfertility, intrauterine insemination (IUI) is the only treatment option prior to IVF. The usefulness of IUI is, however, being debated (Pashayan *et al.*, 2006) and instead, a waiting time before IVF treatment could be indicated to profit from a remaining pregnancy chance. Therefore, an evidence-based comparison of expectant management versus IVF is needed for all diagnostic categories. Within the current practice, a randomized comparison would not be feasible. Instead, the waiting period before the actual start of IVF could be used to estimate the treatment-free pregnancy chances of couples who are going to start IVF. A study in this direction has been published, but not on a large scale, nor in a prospective cohort manner (Evers *et al.*, 1998).

In the Netherlands, a nation-wide prospective cohort study has been performed of all couples who were indicated for IVF. The global aim was to determine the cost-effectiveness of IVF compared with waiting for a longer period. The aim of the current study was to assess the remaining chances of pregnancy without treatment of couples who are being

indicated for IVF according to national guidelines and to assess the predictive effects of female age, duration of infertility, type of infertility and diagnostic category on these chances.

## Materials and Methods

### Patients

A national cohort study was started in 2002 that prospectively registered all patients in IVF clinics in the Netherlands at the moment of indication for IVF by their gynaecologist according to the Dutch IVF guideline (Dutch Society for Obstetrics and Gynaecology, 1998), from 1 January 2002 to 31 December 2003. In this way, a national waiting list for IVF was established. During 2004, the waiting list data were cross-checked with the IVF treatment registries of the IVF clinics, to find out whether the patients had actually started IVF or not. Patients who could not be identified in the IVF registries were traced by hand searching the patient files: detailed patient data were collected, and the reason for not starting IVF was registered, including the occurrence of a pregnancy without treatment.

The primary outcome of the study was an ongoing pregnancy without treatment, defined as an ongoing pregnancy occurring after inclusion on the waiting list, but before treatment was started. Criteria for ongoing pregnancy were fetal heart activity on ultrasound after at least 8 weeks gestation. Some patients on the waiting list received other forms of fertility treatment, such as IUI or hormone injections. Pregnancies resulting from these treatments were not included in the primary outcome.

### Indication

Whether couples are indicated to start IVF or ICSI treatment according to the Dutch 'IVF Guideline' has been described previously (Lintsen *et al.*, 2007). In brief, for tubal blockage (1) or severe endometriosis (2), IVF can be offered directly. In case of relative tubal pathology, the subfertility should be at least of 1 or 2 years duration. In case of unexplained subfertility (3) or minimal endometriosis, IVF is only indicated after a duration of subfertility of at least 3 years and should be preceded by IUI. In case of ovulation disorders (4), at least 12 cycles of ovulation induction should precede IVF. When there is a disturbance in the interaction between semen and mucus (cervical hostility or immunological subfertility) (5), IVF is offered after a subfertility of at least 2 years and is preceded by IUI. An identical advice applies for mild male subfertility (6): if the multiplication of the volume, concentration and motility (VCM) of the semen analyses is between 1 and 10 million. For severe male subfertility (VCM < 1 million), there is a direct indication for ICSI. For all diagnostic categories, IVF can be offered 1 or 2 years earlier if women are over 36 or 38 years, respectively.

### Data analysis

The analysis of the chance of treatment-free ongoing pregnancy was carried out by the Kaplan–Meier method and Cox regression. The time variable in these analyses was the time from admission to the waiting list until the date of the last menstruation before pregnancy. If no treatment-free pregnancy occurred, the couple was censored at the end of follow-up, which was defined as the date of the start of the first IVF cycle or the last known date for couples who neither became pregnant, nor started IVF.

Multivariable Cox regression was used to analyse the impact of prognostic factors on the chance of treatment-free pregnancy. Factors considered were the age of the woman, the duration of infertility, the diagnostic category mentioned as the indication for IVF and whether infertility of the couple was primary or secondary.

The internal validity of the resulting model, i.e. how well does the model predict pregnancy chances, cannot be assessed on the same data that were used to construct the model. Instead, validity was assessed by taking samples with replacement from the original data (i.e. bootstrapping) 200 times, mimicking the situation that the study had been repeated multiple times. In each bootstrap sample, the model development was repeated and the resulting model was subsequently tested in the original data set. From this procedure, the amount of over-fitting of the model may be assessed and a 'shrinkage' factor may be derived; for optimal prediction in future patients, the hazard ratios of the model should be adjusted with this shrinkage factor (van Houwelingen and Le Cessie, 1990). The discriminative ability of the model was measured by the *c*-statistic, and a correction for optimism was applied, determined from the bootstrap procedure. The *c*-statistic measures the proportion of cases in which the model can correctly separate a high-chance couple from a low-chance couple (Harrell *et al.*, 1996).

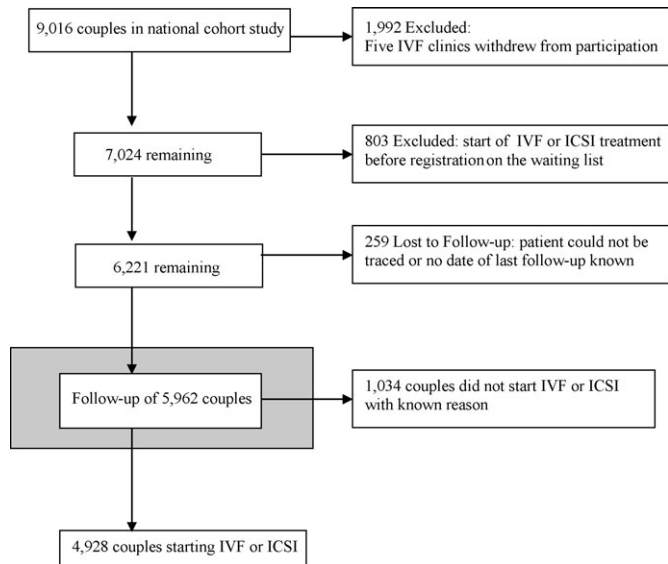
The outcome of a pregnancy (whether it was ongoing or not) was not in all pregnant cases available from the patient files. Therefore, for some cases, the primary outcome of the study was not known, although we know that the couples had become pregnant. Leaving these patients out of the analysis would lead to a biased estimate of the ongoing pregnancy chances. Therefore, we used an imputation method to fill in the missing values (Little and Rubin, 1987; Schafer, 1997), the 'aRegImpute' function (Splus 7.0, 2005 Insightful Corp.) with single imputation. Missing values in patient characteristics were imputed in the same manner. The amount of missing data was as follows: 1.5% of patients had a missing follow-up time or missing pregnancy outcome and 16% of patients had missing values in one or more characteristics. The overall number of missing values relative to the total number of data points was 4.3%, justifying the use of single imputation (Schafer and Graham, 2002).

## Results

There were 7024 patients included on the waiting list. Of 803 patients, IVF data were found, but with starting dates that were partly before the date of inclusion on the waiting list. These patients were therefore removed from the waiting list. For 259 patients, no data could be found in the IVF centre, and these patients were considered lost to follow-up (Lintsen *et al.*, 2007). For 5962 patients, the follow-up could be established, and they form the basis of analysis (Fig. 1). Their characteristics are shown in Table I, overall and subdivided by diagnostic category.

Of these women, 4928 started IVF and 316 became pregnant in the waiting period before IVF, resulting in an ongoing pregnancy in 282 cases (89.2% of pregnancies). The remaining 718 women had not started IVF and had not become pregnant at the date of last follow-up. The time on the waiting list before starting IVF is shown in Fig. 2. The total treatment-free follow-up of the whole group was 33 813 months (median 4.6 months), with a median duration of follow-up of 2.5 months for the pregnant patients, 4.5 months for the patients who started IVF and 6.2 months for the patient who neither started treatment nor became pregnant. The overall (Kaplan–Meier) 1 year cumulative ongoing pregnancy rate was 9.1% (95% confidence interval: 7.5–10.7%), as shown in Fig. 3.

The ongoing pregnancy chances differed markedly between diagnostic categories (Fig. 4): chances with tubal infertility and



**Figure 1:** Description of the recruitment of couples for IVF or ICSI treatment in the Netherlands from January 2002 to December 2004. In grey area: study population, 5962 couples admitted to the waiting list, with known follow-up.

endometriosis were lowest, whereas male factor and immunological infertility had double these chances. For unexplained infertility, chances were more than tripled compared with tubal infertility. The multivariable Cox regression confirmed these results (Table II), although the differences between diagnostic categories are less extreme than in the univariable case. As expected, pregnancy chances are lower with higher age of the woman [a hazard ratio (HR) of 0.95, i.e. a 5% relative decrease in monthly chances with each year older], longer duration of infertility (HR = 0.85, a 15% relative reduction per additional year) and for primary compared with secondary infertility (HR = 0.71, a 29% relative reduction). The 12 months chances of pregnancy without treatment predicted by the Cox regression model are shown in Fig. 5. Predictions range from 0% to ~25%, with 8.3% of patients having a predicted chance of 15% or higher. The discriminative index of the model (*c*-statistic) in these data was equal to 0.66, and 0.65 when corrected for optimism, indicating that the model will be able to separate a high-chance couple from a low-chance couple in 65% of cases. The shrinkage factor determined by the internal validation procedure was 0.91, showing only slight overfitting.

## Discussion

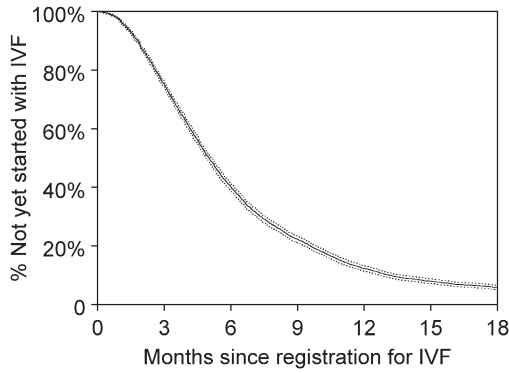
We conducted a large-scale cohort study in patients on the waiting list for IVF and found that on average 9.1% of the couples would have an ongoing treatment-free pregnancy within 1 year. Further, we found that ongoing pregnancy chances were higher than average with younger female age, shorter duration of infertility, secondary versus primary infertility and for couples with unexplained, male or immunological infertility compared with other diagnostic categories. A multivariable prediction model was able to identify couples with a 1 year chance up to 25%.

The level of the ongoing pregnancy chance within 1 year is lower than in other studies on infertile couples (Eimers *et al.*, 1994; Collins *et al.*, 1995; Snick *et al.*, 1997; Hunault *et al.*, 2004). Since most of the studies excluded 'poor prognosis' diagnostic groups, such as azoospermia, tubal pathology or ovulation disorders, and were conducted in a non-IVF setting, we might expect to find a lower pregnancy chance in our data. Nevertheless, even the Collins study, which included all diagnostic groups and which was based on patients in a tertiary care setting comparable with a modern IVF setting, found on average almost twice the pregnancy chance within 1 year that we found: 16.1%.

As far as we know, apart from Denmark (Danish Fertility Society, [www.fertilitetsselskab.dk](http://www.fertilitetsselskab.dk)), the Netherlands is the only country that has a central guideline for the indication for IVF, with a recommendation for each diagnostic category, depending on the duration of subfertility. For instance, in case of unexplained or mild male subfertility, it is advised to perform 3–6 cycles of IUI. This might explain for a part the low chances on the IVF waiting list: patients who did not become pregnant with the forgoing treatment and who thus turned to IVF are probably a 'low chance' selection with respect to treatment-free pregnancy chances. Nevertheless, the overall pregnancy rate in our study was higher than in the waiting list study of Evers *et al.* (1998), and in contrast to that study we did not find a higher pregnancy rate during the first 3 months of the waiting period. In a 5 year follow-up study from Denmark (Pinborg *et al.*, 2007) comprising 818 couples starting with assisted reproduction treatment (ART), 156 (19.1%) had delivered from a spontaneous pregnancy, mostly after start of treatment (134 women). Very few pregnancies occurred before the start of treatment, mainly due to the fact that patients were included only at the start of treatment. Nevertheless, this study shows that considerable spontaneous pregnancy potential may be present in a population starting ART.

**Table I.** Characteristics of 5962 couples on a national waiting list for IVF during 2002–2004 in the Netherlands.

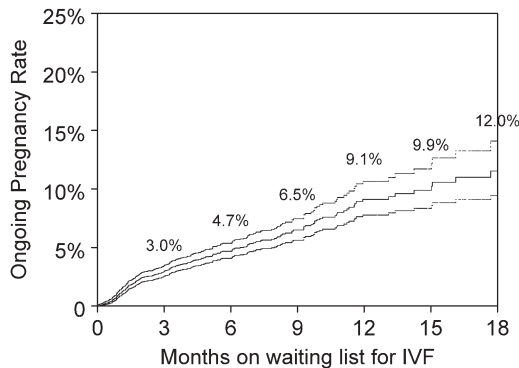
Diagnostic category	N	Age of the woman, years		Duration of infertility		% Primary infertility
		Mean	(SD)	Mean	(SD)	
Tubal pathology	1059	34.0	(4.0)	3.2	(2.5)	49
Endometriosis	500	32.4	(3.8)	3.0	(2.0)	70
Male	2545	32.3	(4.4)	2.9	(2.1)	66
Hormonal	462	32.7	(4.0)	3.3	(2.3)	59
Unexplained	1236	34.5	(4.0)	3.6	(2.1)	58
Immunological	160	34.2	(4.0)	3.4	(2.3)	61
Total	5962	33.1	(4.3)	3.2	(2.2)	61



**Figure 2:** Number of couples on the waiting list for IVF or ICSI, who have not yet started treatment, against time since registration on the waiting list.

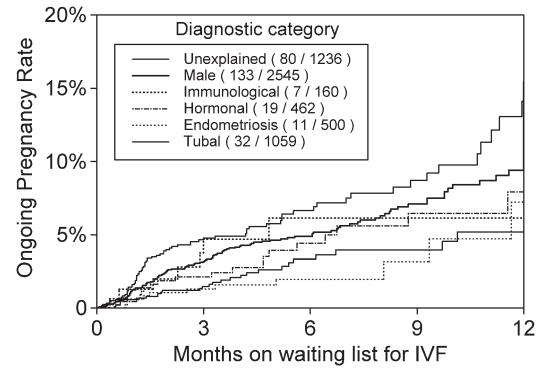
Kaplan–Meier estimates, censoring for treatment-free pregnancy and for termination of the active childwish.

The prognostic effects of the factors in our data are comparable with those found in the other studies on infertile couples. Further, the discriminative ability of our model,  $c = 0.65$ , is very similar to that found by others (Eimers *et al.*, 1994; Collins *et al.*, 1995; Snick *et al.*, 1997; Hunault *et al.*, 2004). Such a low discriminative ability appears frequently in the reproductive medicine literature and indicates that it is very hard to determine for individual patients who will become pregnant and who will not, based on the age, duration, type of infertility and the diagnostic category. Perhaps additional predictive ability may come from markers of ovarian reserve such as the basal (FSH and the antral follicle count) or from the treatment history of the patients, as stated above. Unfortunately, we were unable to collect data on any of these factors, and we recommend that future studies take these factors into consideration. Despite these facts, the model was able to identify a subgroup of patients with relatively high chances for whom postponing IVF might be a realistic option: a recent RCT (Steures *et al.*, 2006) showed that, after the initial fertility work-up, expectant management was the best option for ‘average-to-good prognosis’ patients, who were selected by a



**Figure 3:** Cumulative chance of an ongoing treatment-free pregnancy, against time since registration on the waiting list for IVF or ICSI.

Kaplan–Meier estimates, censoring for start of treatment and for termination of the active childwish.



**Figure 4:** Cumulative chance of an ongoing treatment-free pregnancy, against time since registration on the waiting list for IVF or ICSI, separately for diagnostic categories.

Kaplan–Meier estimates, censoring for start of treatment and for termination of the active childwish.

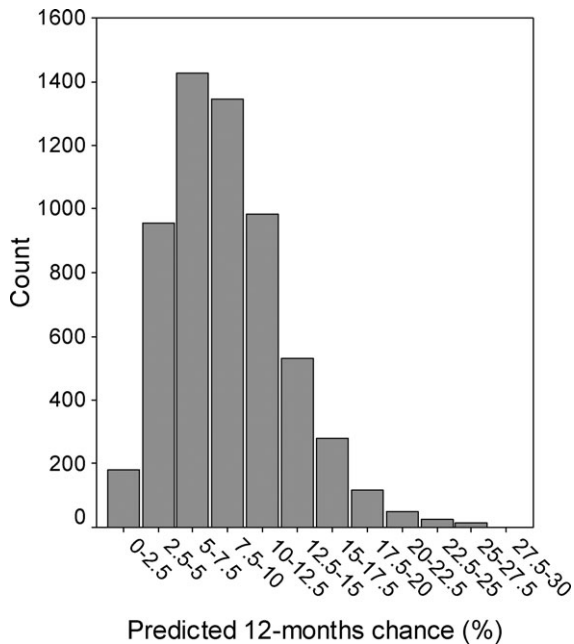
prediction model with even less discriminative power (Hunault *et al.*, 2004).

The main research question of this study was: what are the pregnancy chances of couples who are indicated for IVF in a usual care setting using guidelines and clinical judgement? If there are patient groups whose chances of pregnancy without treatment are sufficiently high, it might be cost-effective to postpone treatment for them, e.g. by 1 year. An important issue is whether the current study design can give representative data to answer this question; the loss to follow-up, inherent to this type of study, was limited (259 out of 5962 = 4%), and is considered not to be a threat to validity. However, the waiting list design may be questioned: are the pregnancy chances of couples who get an indication for IVF, but who have to wait because of a waiting list, comparable with couples who would have been asked to wait longer before being indicated for IVF? An issue of concern here could be that patients who get the indication for IVF might experience stress relieve that could positively influence their pregnancy chances. On the other hand, couples might feel that they do not have to try themselves to become pregnant anymore, because IVF will take care of it. We have collected data on psychological questionnaires during the study that could be used to test these hypotheses.

**Table II.** HR for ongoing pregnancy without treatment of 5962 patients on the waiting list for IVF.

	HR	95% confidence interval lower–upper
Age (per year)	0.95	0.93–0.98
Duration of infertility (per year)	0.85	0.79–0.91
Indication		
Tubal pathology	1*	—
Endometriosis	0.73	0.37–1.46
Male	1.57	1.06–2.32
Hormonal	1.19	0.67–2.11
Unexplained	2.64	1.75–3.98
Immunological	1.69	0.75–3.84
Primary versus secondary infertility	0.71	0.56–0.90

\*Reference group.



**Figure 5:** Histogram of the predicted 12 months chances of a treatment-free pregnancy, as determined by the prognostic model based on female age, duration and type of infertility and diagnostic category.

Our findings may have implications for the indication for IVF. Depending on the prognosis with IVF and on treatment costs, we could determine the duration of infertility at which waiting is no longer justified based on cost-effectiveness considerations (Mol *et al.*, 2000). That duration may differ between diagnostic categories, between age groups and between primary and secondary infertility. As an example, in case of unexplained infertility, the treatment-free prognosis may be so good, particularly in young women, that IVF might be postponed for a longer time than in the case of tubal infertility.

We conclude that the chances of ongoing pregnancy without treatment are on average low for subfertile couples who are waiting for IVF. Nevertheless, prognostic factors may identify ‘high chance’ groups for which it might be cost-effective to postpone IVF and take advantage of pregnancy chances without the costs and burden of treatment.

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